Official Title of Study:

A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multiple-dose Phase 2 Study to Evaluate the Efficacy and Safety of BMS-986263 in Adults With Compensated Cirrhosis From Nonalcoholic Steatohepatitis (NASH)

NCT Number: NCT04267393

Document Date (Date in which document was last revised): 13 October 2022

Protocol Number: IM025017
IND Number: 114,517
EUDRACT Number: 2019-003932-22
UTN Number: U1111-1241-4762
Date, Version: 13-Oct-2022

CLINICAL PROTOCOL IM025017

A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multiple-dose Phase 2 Study to Evaluate the Efficacy and Safety of BMS-986263 in Adults with Compensated Cirrhosis from Nonalcoholic Steatohepatitis (NASH)

Protocol Amendment Number 03

Study Director [redacted]

Bristol-Myers Squibb Company
3401 Princeton Pike
Lawrenceville, NJ 08648
USA

Telephone: [redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]

Bristol-Myers Squibb Research and Development
3401 Princeton Pike
Lawrenceville, NJ 08648
USA

1-2-1 Otemachi, Chiyoda-ku,
Tokyo 100-0004, Japan

This document is the confidential and proprietary information of Bristol-Myers Squibb Company (BMS) and its global affiliates. By reviewing this document, you agree to keep it confidential and to use and disclose it solely for the purpose of assessing whether your organization will participate in and/or the performance of the proposed BMS sponsored study. Any permitted disclosures will be made only on a confidential "need to know" basis within your organization or to your independent ethics committee(s). Any other use, copying, disclosure, or dissemination of this information is strictly prohibited unless expressly authorized in writing by BMS. Any supplemental information that may be added to this document is also confidential and proprietary to BMS and must be kept in confidence in the same manner as the contents of this document. Any person who receives this document without due authorization from BMS is requested to return it to BMS or promptly destroy it. All other rights reserved. References to BMS in this protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization.

DOCUMENT HISTORY

Document	Date of Issue	Approvers	Summary of Changes
Protocol Amendment 03 im025017-protamend03	13-Oct-2022	[redacted] Bristol-Myers Squibb	Updates include: change of study director; clarifications of when certain study procedures are required: DXA, liver biopsy, FSH, [redacted]; Stable dose of treatment requirements; study procedures; addition of HbA1c measurement; addition of IM025015 study information; timepoints for endpoints [redacted] updated; removal of Medical Monitor approval for screening extension; updates to inclusion/exclusion criteria (liver biopsy timing, MELD and Child-Pugh scoring criteria, COVID history, AFP and CT/MRI clarification, weight loss timing, vaccines, and HbA1c); [redacted] requirement to seek sponsor's approval for use of alternative brands of fat emulsions for placebo preparation; clarification to premedication administration timing; definition of infusion-related reactions (IRR) added, update to the most common symptoms of IRRs; updates to number and timing of PK sampling; reclassifications to types of [redacted] samples taken and correction of the matrix of [redacted] collected; removal of adiponectin and cluster of differentiation 163 [redacted] addition of a second interim analysis; updates to literature references; update to the serology criteria for diagnosis of hepatitis B infection (HBV) requiring confirmation by HBV DNA testing; and update to countries of country-specific requirements.
Revised Protocol 2 Global im025017-revprot02	25-Nov-2020	[redacted] Bristol-Myers Squibb	Updates include: adjustment of Child-Pugh exclusion criteria, including laboratory exclusion criteria; adding data from Study IM025015; adjustment of step-wise infusion rates/number of steps; addition of an HEDC assay;

Approved v5.0 930147586 4.0

Document	Date of Issue	Approvers	Summary of Changes
			addition of guidance [redacted] related to the COVID-19 pandemic; changing statistical sample size calculation, study stratification factors, and statistical analysis methodology for primary endpoint; excluding participants from the study who are taking anticoagulants; replacing liver ultrasound as screening procedure with liver CT/MRI for detection of HCC; updating exclusion criterion related to history of weight gain/loss and related to history of illegal IV drug use; and adding optionality for treatment of prolonged INR and/or low platelet counts prior to liver biopsy.
Revised Protocol 01 Global im025017-revprot01	27-May-2020	[redacted] Bristol-Myers Squibb	Updates include: clarification of liver disease/biopsy requirements for study inclusion; addition of nintedanib as a concomitant medication restriction; [redacted] addition/clarification of statistical methods for efficacy endpoints; updating of interim analysis; alignment with United States-specific Revised Protocol 00a, Japan-specific Protocol Amendment 01, and Global Original Protocol Administrative Letter 01; alignment with most current protocol template; updating of background clinical study data; addition of recommended stepped infusion rates for study treatment; addition of required pregnancy test prior to DXA scan; referencing Independent Pathology Review Committee; and addition of appendix related to country-specific HIV exclusions.
Protocol Amendment 01 Japan-Specific im025017-amend01-jp-specific	18-Mar-2020	[redacted] Bristol-Myers Squibb	Updates to one of the components of the placebo formula for BMS-986263 and updated to align with Global Original Protocol Administrative Letter 01 and United States-specific Revised Protocol 00a.

Approved v5.0 930147586 4.0

Document	Date of Issue	Approvers	Summary of Changes
Revised Protocol 00a US-Specific im025017-revprot00a-us-specific	21-Feb-2020	[redacted] Bristol-Myers Squibb [redacted] Bristol-Myers Squibb	Updates related to the conduct of the [redacted] to be conducted at select sites in the US, including the addition of actions to be taken in the event of allergic reaction to albumin and criteria for stopping [redacted] testing in the overall study. The Study Director/Medical Monitor contact was also changed, and the Study Acknowledgment/ Disclosure page was removed.
Original Protocol	19-Nov-2019	[redacted] Bristol-Myers Squibb [redacted] Bristol-Myers Squibb	Not Applicable

Approved v5.0 930147586 4.0

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

The primary purpose of this Revised Global Protocol is to add, clarify, or update study assessments, inclusion/exclusion criteria and endpoints, and to implement an additional interim analysis. Key secondary revisions include the following:

- Updating the Study Director
- Addition of study information for the IM025015 study, which is now complete
- Clarifications pertaining to COVID-19 vaccination and interactions with BMS-986263
- Addition of alternative emulsion solutions for placebo preparation
- Updates to timing for administration of premedications
- Addition of definition of infusion-related reactions (IRRs) and updated the most common symptoms of IRRs according to the IB 16.0

All changes applied to the body were applied to the synopsis, as necessary; synopsis changes are not included in the list below.

Only major additions and deletions are provided in this summary; all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications are not included.

The rationale(s) for changes to this Revised Protocol are provided in the summary of key changes table, as shown below:

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Study Director was updated from [redacted] to [redacted]. Contact info was updated accordingly. Address for BMS Belgium was removed and BMS Japan was updated.	Updated with current contact information
Section 1.1: Synopsis	Added the potential for 4 week extension of screening for unavoidable circumstances	Update made to align synopsis with study design in the body.
Table 1: Screening Procedural Outline	It was previously stated that key eligibility criteria had to be evaluated prior to liver biopsy at screening. This was changed to state that it was recommended.	Updated to give the sites more flexibility.
Table 1: Screening Procedural Outline	Clarification that FSH assessment is only required to confirm menopause in women <55 years old.	FSH requirement was listed in Appendix 4. Added in Table 1 to make it convenient for the sites

Approved v5.0 930147586 4.0

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 1: Screening Procedural Outline	HbA1c was added to screening procedures.	HbA1c at Screening is one of the exclusionary laboratory assessments described in Section 9.4.1, Table 8. It has been added to Table 1 (Screening Procedures Outline) for consistency.
Table 2: Treatment Period Procedural Outline	Added that liver biopsy should be performed within ±3 days of the visit window for Wk12 and ETT visits, and that 4 additional days are allowed with Medical Monitor approval.	Updated for clarification.
Table 3: Follow-up Period Procedural Outline	[redacted]	Updated for clarification.
Section 3.2.2: Clinical Studies	Added study results from IM025015 which has been completed.	Updated based on new data available.
Section 3.3.2: Coronavirus Disease 2019-Related and Section 7.7: Concomitant Therapy	Non-live COVID-19 vaccinations are allowed during the study, and should follow local standard practices. Benefit-risk section updated to include the sentence that the efficacy and safety of COVID-19 virus vaccines in patients using BMS-986263 is unknown at the moment.	Updated to align with BMS COVID-19 guidance.
[redacted]		
Section 5.1.1: Screening Period	Medical Monitor approval is no longer required for the extension of screening period.	To decrease the sites burden. the Medical Monitor approval requirement was removed; allowing the sites to extend the screening period up to 4 weeks if necessary, without needing to contact the Medical Monitor.
Section 6.1: Inclusion Criteria and Section 9.1.2: Liver Biopsy Assessments	Liver biopsy performed prior to screening was extended from 6 to 12 months. Additionally NASH criteria could be fulfilled using biopsies of 12 months instead of 6 months.	Updated to allow patients with historical biopsy 6 to 12 months prior to screening to enroll to the study. The study population patients with cirrhosis (Stage 4 fibrosis) have slow disease progression.

Approved v5.0 930147586 4.0

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1: Inclusion Criteria	Language clarified.	Updated to clarify who and how the DXA assessment will be analyzed.
Section 6.1: Inclusion Criteria	Stable dose of treatment requirements was updated to 3 months prior to screening.	Updated due to extension of historical biopsy to 12 months and requirement for stable dose to 15 months prior to screening will be very difficult.
Section 6.2: Exclusion Criteria and Section 8.1: Discontinuation from Study Treatment	Planned liver transplantation changed to planned during the study.	Updated to clarify timeframes of unacceptable liver transplantation.
Section 6.2: Exclusion Criteria	Removed required discussion with Medical Monitor related to MELD and Child-Pugh Score criteria.	Updated to align with local UK amendment, and to provide more objective guidance for investigators to make the eligibility determination of participants with Gilbert syndrome whose MELD and Child-Pugh Scores are elevated due to a benign cause of unconjugated hyperbilirubinemia without requiring consultation with the Medical Monitor.
Section 6.2: Exclusion Criteria	Clarification added that both serum AFP and historical CT/MRI will be required for Screening. and if either of the results meets the criteria the participant will be excluded from study.	Updated for clarification.
Section 6.2: Exclusion Criteria	Updated history of SARS-CoV-2 infection to history of severe COVID-19 disease and added timeframe for screening after mild and moderate infection.	Updated criteria to clarify specific timeframes for screening after COVID depending on the severity of the previous infection.
Section 6.2: Exclusion Criteria	History of significant weight gain/loss relative to the timing of the liver biopsy was removed, and any significant weight changes was updated to within 3 months of screening.	Removed due to extension of historical biopsy to 12 months and requirement for stable weight up to 15 months prior to screening will be very difficult.
Section 6.2: Exclusion Criteria	Exclusion criteria updates so that vaccines approved by regulatory agencies other than the United States Food and Drug Administration may also be considered for inclusion.	Updated to allow vaccines approved by other regulatory agencies.
Section 6.2: Exclusion Criteria	Exclusion criteria for laboratory results were updated that HbA1c could not be ≥ 9.5% instead of 9.0%.	Revised to expand the study population.

Approved v5.0 930147586 4.0

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 6.6.1: Retesting During Screening Period	Language clarified.	Updated to clarify timing of [redacted] DXA scan assessments.
Section 7: Treatment	[redacted]	
Section 7.1.2: Premedication	Timing for administration of premedication before study start was clarified.	Added instruction for the sites.
Section 9.2.9: Infusion-related Reactions	Definition of IRRs was added. Details of IRRs seen with BMS-986263 administration in other studies were added. Clinical symptoms of IRRs aligned with the last IB (v16.0).	Added IRRs definition for the sites to assess the IRRs.
Section 9.5: PK [redacted] Schedule for BMS-986263	[redacted] • The [redacted] PK sampling on [redacted] was removed, and the ±1 day window for the Day 85 sampling was removed. • Timing and timing windows relative to start or end of infusion were updated in footnote C, E, and F. • [redacted] was removed from footnote G.	Updated for the clarification to PK sampling timepoints and to increase window for some timepoints.
[redacted]		
Section 10.4.5: Interim Analysis	Additional interim analysis added for when 30% participants have either completed the Follow-up Week 4 or discontinued prior to the Follow-up Week 4.	Added the additional interim analysis to assess futility.

Approved v5.0 930147586 4.0

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 11: References	IB version number updated. List of reference updated.	Updated based on new IB. Updated to include new references.
Appendix 3: Adverse events and serious adverse events: definitions and procedures for recording, evaluating, follow-up, and reporting	Text modified or added using current template text.	Updated to align with current template language.
Appendix 7: Criteria for diagnosis and exclusion of Participants with hepatitis b virus and chronic Hepatitis c virus infection	Exclusion instructions added based on hepatitis B assessments.	Updated to include the HBV DNA test for HBV natural infection
Appendix 8: Country-specific requirements	Countries listed in country-specific requirements updated.	Updated to align with current country regulation [redacted].

AFP = serum alpha-fetoprotein; BMS = Bristol-Myers Squibb; COVID-19 = coronavirus disease 2019; CT = computed tomography; DNA = deoxyribonucleic acid; DXA = dual-energy X-ray absorptiometry; ETT = Early Treatment Termination; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; IB = investigator's brochure; IRR = infusion-related reaction; MELD = Model for End-stage Liver Disease; [redacted] NASH = nonalcoholic steatohepatitis; PK = pharmacokinetic; [redacted] SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Please provide a copy to your Investigational Review Board/Ethics Committee, unless agreed otherwise with BMS.

Approved v5.0 930147586 4.0

TABLE OF CONTENTS

Approved v5.0 930147586 4.0

Approved v5.0 930147586 4.0

Approved v5.0 930147586 4.0

Approved v5.0 930147586 4.0

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multiple-dose Phase 2 Study to Evaluate the Efficacy and Safety of BMS-986263 in Adults with Compensated Cirrhosis from Nonalcoholic Steatohepatitis (NASH)

Short Title: Efficacy and Safety of BMS-986263 in Adults with Compensated Cirrhosis from NASH

Study Phase: 2

Rationale: Study IM025017 aims to demonstrate the antifibrotic efficacy of BMS-986263, using a liver fibrosis histological endpoint, and the safety and tolerability of BMS-986263, as assessed by adverse events (AEs), serious adverse events (SAEs), laboratory results (including assessment of potential drug-induced liver injury), vital signs, physical examinations, electrocardiograms (ECGs), [redacted] infusion-related reaction monitoring, and bone mineral density (BMD) monitoring, in participants with nonalcoholic steatohepatitis (NASH) and compensated cirrhosis.

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in the world today. NASH, which is the more advanced form of NAFLD, is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning), with or without fibrosis. NASH is associated with increased mortality rates due to cardiovascular-, liver-, and cancer-related deaths. Currently, there are no approved drugs for the treatment of NASH. With the increasing prevalence of obesity and obesity-related diseases, NASH could soon become the leading indication for liver transplantation and the leading cause of hepatocellular carcinoma (HCC) globally.

NASH patients with cirrhosis have a particularly high unmet medical need for effective therapies. Among NASH patients, the stage of fibrosis is the strongest predictor of disease-specific mortality, and patients with cirrhosis are at the greatest risk for disease-related morbidity and mortality. Patients with cirrhosis are particularly at increased risk for poor clinical outcomes, including hepatic decompensation events and the need for liver transplant. It is reasonable to assume that an improvement in fibrosis would be predictive of clinical benefit, and a reduction of fibrosis in patients with compensated cirrhosis, if substantial, could lead to improvements in liver function and long-term clinical outcomes.

Study Population: Study IM025017 will be conducted in adults who have compensated cirrhosis due to NASH. Participants must fully meet all eligibility criteria defined in Section 6 of the protocol; key inclusion and exclusion criteria are summarized as follows:

Approved v5.0 930147586 4.0

Key inclusion criteria

- Male and female participants, ages ≥ 21 years to ≤ 75 years of age, inclusive, at the time of screening
- Liver biopsy performed within 12 months prior to the screening visit or performed during the screening period. A liver biopsy performed prior to informed consent form, if utilized for eligibility, must be available for central pathology reading prior to Randomization.
    i) Liver biopsy consistent with NASH Clinical Research Network (CRN) Fibrosis Score Stage 4, as assessed by central pathology reading.
    ii) Liver biopsy must either be consistent with steatohepatitis, as assessed by central pathology reading, OR, for liver biopsies without definite steatohepatitis, there should be some evidence of steatosis and/or ballooning and the following definition of NASH cirrhosis must be fulfilled:
        1) Absence of other causes of liver disease AND either of the following:
            a) At least 2 of the 3 following criteria:
                (i) History of body mass index [BMI] ≥ 30 kg/m2
                (ii) History of type 2 diabetes mellitus
                (iii)History of hypertension AND/OR history of dyslipidemia

                OR

            b) Previous histologic readings of steatohepatitis (in a past biopsy prior to the one utilized for eligibility) AND either history of BMI ≥ 30 kg/m2 OR history of type 2 diabetes mellitus.

        NOTE: At least 80% of participants will be required to have definite steatohepatitis on the biopsy used to confirm eligibility.

Key exclusion criteria

- Other active causes of liver disease (eg, alcoholic liver disease, hepatitis B virus infection, chronic hepatitis C virus infection, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, drug-induced hepatotoxicity, Wilson disease, homozygous α-1-antitrypsin deficiency, iron overload [with blood iron saturation > 50%], or hemochromatosis)
- Past or current evidence of hepatic decompensation (eg, ascites, variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis)
- Liver transplantation (past or planned during the study)
- Child-Pugh Score > 6 at screening (APPENDIX 5). Exception: Participants with Gilbert Syndrome who have a Child-Pugh Score > 6 with elevated total bilirubin and direct bilirubin ≤ the upper limit of normal (ULN) may be included, provided that total bilirubin is < 4.0 mg/dL
- Model for End-stage Liver Disease (MELD) score > 14 at screening (APPENDIX 6). Exception: Participants with Gilbert Syndrome who have a MELD Score > 14 with elevated total bilirubin, and direct bilirubin ≤ the ULN may be included, provided that total bilirubin is < 4.0 mg/dL

Approved v5.0 930147586 4.0

- Evidence of HCC at screening based on (i) serum alpha-fetoprotein (AFP) > 20 ng/mL (> 16.5 IU/mL) or (ii) Liver Reporting & Data System 3, 4, or 5 as determined by historical computed tomography (CT)/magnetic resonance imaging (MRI) with contrast within 3 months prior to screening or from multiphasic CT/MRI of liver during screening. Both AFP and CT/MRI assessments will be required from all participants to determine eligibility.
- The participant's laboratory test results at screening include any of the following:
  - Albumin < 2.8 g/dL
  - INR > 2.2
  - Alanine aminotransferase value ≥ 5× the ULN
  - Aspartate aminotransferase value ≥ 5× the ULN
  - Total bilirubin > 3.0 mg/dL, unless participant has a documented diagnosis of Gilbert Syndrome, provided that total bilirubin is < 4.0 mg/dL and direct bilirubin is ≤ ULN
  - Platelet count < 85,000/µL
  - Hemoglobin A1c ≥ 9.5%
  - Serum vitamin A (retinol) > ULN
- Inability to safely undergo a liver biopsy in the opinion of the investigator.

[redacted]

Objectives and Endpoints:

The following table summarizes the primary and secondary objectives and endpoints:

Objective	Endpoint
Primary	
• To evaluate the efficacy of BMS-986263 compared with placebo to improve liver fibrosis in participants with compensated cirrhosis due to NASH	• Proportion of participants who achieve ≥ 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score), as determined by liver biopsy after 12 weeks of treatment
Secondary	
• To further assess the efficacy of BMS-986263 compared with placebo to improve liver fibrosis, as determined by liver biopsy, in participants with compensated cirrhosis due to NASH	• Proportion of participants with ≥ 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score), with no worsening of NASH after 12 weeks of treatment (worsening defined as an increase of the NAS by ≥ 1 point)

Approved v5.0 930147586 4.0

Objective	Endpoint
	• Proportion of participants with ≥ 2 stage improvement in liver fibrosis (NASH CRN Fibrosis Score) after 12 weeks of treatment • Proportion of participants with ≥ 1 stage improvement in liver fibrosis (modified Ishak score) after 12 weeks of treatment • Proportion of participants with ≥ 2 stage improvement in liver fibrosis (modified Ishak score) after 12 weeks of treatment • Change from baseline in CPA after 12 weeks of treatment
• To assess the safety and tolerability of BMS-986263 in participants with compensated cirrhosis due to NASH	• Incidences of SAEs, AEs, clinical laboratory values, vital signs, physical examination findings, and ECGs • Change from baseline in BMD, as measured by DXA scan, at Follow-up Week 24
• To assess the PK of BMS-986263 in participants with compensated cirrhosis due to NASH	• Plasma concentrations of siRNA, DPD, HEDC, and S104 (components of BMS-986263 for injection)

AE = adverse event; BMD = bone mineral density; CPA = collagen proportionate area; CRN = Clinical Research Network; DPD = di-retinamide-PEG-di-retinamide; DXA = dual-energy X-ray absorptiometry; ECG = electrocardiogram; HEDC = (Bis[2-(tetradecanoyloxy)ethyl] carbamoylmethyl)-(2-hydroxyethyl)dimethylazanium bromide; NAFLD = nonalcoholic fatty liver disease; NAS = NAFLD Activity Score; NASH = nonalcoholic steatohepatitis; PK = pharmacokinetics; SAE = serious adverse event; SiRNA = small interfering ribonucleic acid

Overall Design: This is a randomized, double-blind, placebo-controlled, parallel-group, multiple-dose Phase 2 study to evaluate the efficacy, safety, and tolerability of BMS-986263 in adults with compensated cirrhosis due to NASH. The primary study endpoint is the proportion of participants who achieve ≥ 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score) on biopsy after 12 weeks of treatment.

The study includes:

- A screening period of up to 8 weeks; may be extended (up to an additional 4 weeks) to accommodate unanticipated delays in obtaining required screening results.
- A 12-week, double-blind treatment period, during which participants will receive 1 of the following 3 treatments by intravenous (IV) infusion: 45 mg BMS-986263 once every week (QW), 90 mg BMS-986263 QW, or placebo QW
- A follow-up period of 24 weeks, during which participants will not receive investigational treatment

Approved v5.0 930147586 4.0

Participants meeting eligibility criteria during the screening period will enter the treatment period and be randomized to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW by IV infusion in a double-blind manner for 12 weeks. Participants will be stratified at Randomization by the presence of definite steatohepatitis on biopsy (yes versus no). At least 80% of participants will be required to have definite steatohepatitis on the biopsy used to confirm eligibility. Participants will receive study treatment via IV administration for a total of 12 weeks. Liver biopsy will be performed at Week 12.

This study will utilize an external Data Monitoring Committee for the duration of the study to assess safety data, and an external Independent Pathology Review Committee to assess liver biopsies for eligibility and efficacy.

Number of Participants: In this study, approximately 270 participants will be randomized via interactive response technology (IRT) in a 1:1:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW in a double-blind manner. The primary endpoint is the proportion of participants with ≥ 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score) as determined by liver biopsy after 12 weeks of treatment.

Assuming a Chi-Square test with an $\alpha = 0.05$ and expected response rates for BMS-986263 90 mg, BMS-986263 45 mg, and placebo of 45%, 40%, and 20%, respectively, this study will have at least 80% power to detect superiority over placebo versus each dose, assuming a minimum difference of 20% from placebo. Accounting for a 6% dropout rate, approximately 90 participants will be randomized per treatment group.

Treatment Arms and Duration: Participants meeting eligibility criteria during the screening period will enter the treatment period. Approximately 270 participants will be randomized via IRT in a 1:1:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW by IV infusion in a double-blind manner for 12 weeks.

After 12 weeks of treatment or after early treatment discontinuation, participants will enter the 24-week follow-up period. After all participants complete the Follow-up Week 4 visit, the study will be unblinded and analyses of the available Week 12 data will be conducted.

Study Treatment:

Study Drug for IM025017		
Medication	**Potency**	**IP/Non-IP**
BMS-986263 for injection	10 mg per vial; 3 mg/mL after reconstitution	IP
Placebo[a] for BMS-986263 for injection/on-site compounded sterile dosage form	NA	IP

IP = investigational product; IV = intravenous; NA = not applicable

[a] [redacted]

Approved v5.0 930147586 4.0

Statistical Methods: Efficacy analyses will be performed using the modified intent-to-treat population. Participants who discontinue early and do not have an Early Treatment Termination liver biopsy or otherwise have the result from the liver biopsy missing will be considered a "nonresponder" for the evaluation of the primary endpoint and other binary endpoints based on liver biopsy.

Primary Endpoint Analysis: To evaluate the effect of BMS-986263 (90 mg QW and 45 mg QW) on NASH CRN Fibrosis Stage at Week 12, a 95.0% confidence interval of response rate for active treatment versus placebo will be used to estimate the difference between the proportions of participants with ≥ 1 stage improvement in fibrosis on liver biopsy. Additionally, the odds ratio will be used to estimate improvement of treatment as compared with placebo for the proportion of participants with ≥ 1 stage improvement in fibrosis on biopsy at Week 12. A logistic regression will be performed with platelet count as independent covariate and stratified by the Randomization strata with a Z-test statistic at a two-sided significance level of α◦=◦0.05 to assess the difference of response rate separately between each BMS-986263 treatment group and placebo. To control for the family-wise (two-sided) Type◦1◦error rate of α◦=◦0.05, the statistical tests will be performed in the following hierarchical order: 1) BMS-986263 90◦mg versus placebo, and 2) BMS-986263 45◦mg versus placebo. If the first comparison is not statistically significant, then the second comparison will be treated as descriptive in nature.

Secondary [redacted] Endpoint Analyses: No adjustment will be made for multiplicity for secondary [redacted] endpoints. Secondary [redacted] endpoints will be analyzed in a similar method as the primary endpoint unless otherwise specified in the statistical analysis plan (SAP).

Selected continuous endpoints will be characterized using descriptive statistics and may be analyzed by analysis of covariance methods and/or by a mixed model for repeated measurements. Treatment differences at prespecified time points will be estimated using least squares means. Full details regarding this model and covariance structure will be provided in the SAP.

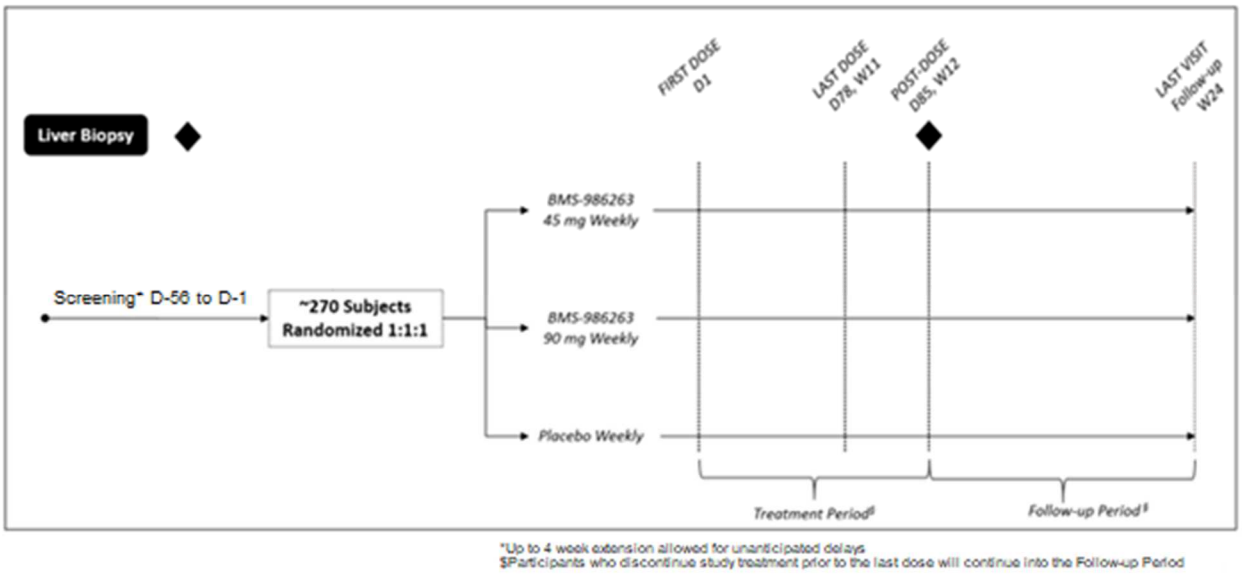
Categorical endpoints will be summarized using counts and percentages and when appropriate, may be analyzed using categorical analysis methods.

The stratified log-rank test and Kaplan-Meier estimate may be used to analyze time-to-event endpoints and will be specified in the SAP.

Subgroup analyses may be performed as specified in the SAP.

Approved v5.0 930147586 4.0

1.2 Schema



D = Day; W = Week

The total duration of the study will be up to 48 weeks, including a screening period (up to 12 weeks), a 12-week treatment period, and a 24-week follow-up period. Participants will be randomized to receive 1 of the following 3 treatments by IV infusion during the treatment period: 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW for 12 weeks. No reductions or modifications of the assigned dose are allowed. If the infusion is interrupted for any reason, the infusion may be restarted at the discretion of the investigator. If an incomplete dose is administered at any visit, the participant will resume the assigned dose/administration schedule at the next visit. Rules for discontinuation from study treatment and from the study are provided in Section 8.1 and Section 8.2, respectively. The study will utilize an external Data Monitoring Committee for the duration of the study.

Approved v5.0 930147586 4.0

2 SCHEDULE OF ACTIVITIES

Visit details are provided for the Screening Procedural Outline in Table 1. Visit details are provided for the treatment and follow-up periods in Table 2 and Table 3, respectively.

Pharmacokinetic (PK) samples must be collected on time per the collection table [redacted] All study procedures [redacted] for [redacted] assessments must be performed prior to infusion on the infusion days (with the exception of PK samples taken during and after the infusion). All electronic patient-reported outcome evaluations must be completed before any other study procedures are started.

Approved v5.0 930147586 4.0

Table 1: Screening Procedural Outline

Procedure	Screening[a] Day -56 to -1	Notes
Screening and History Assessments		
Informed consent	X	
Inclusion/exclusion criteria	X	Assess study eligibility criteria prior to Randomization.
Medical history	X	
Prior medications	X	Prior medications are medications taken within 4 weeks prior to screening.
Lifestyle restrictions	X	See Section 6.4.
Dietary and lifestyle counseling	X	See Section 6.5 for additional information.
Screening via IRT to register participant	X	See Section 7.2 for additional information.
Clinical Safety Assessments		
Full physical examination	X	If the screening physical examination is performed within 24 hours prior to dosing on Day 1 (Randomization), then a single exam may count as both the screening and Day 1 (Randomization) abbreviated physical examination. Screening examination will be a full physical examination, including general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, and extremities. (See Section 9.4.3).
Physical measurements	X	Includes body weight, height, and BMI (height and BMI calculation at screening only).
Vital signs	X	Includes body temperature, respiratory rate, blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.

Approved v5.0 930147586 4.0

Table 1: Screening Procedural Outline

Procedure	Screening[a] Day -56 to -1	Notes
Multiphasic liver CT/MRI	X	A historical liver CT/MRI conducted within 3 months prior to screening may replace the screening CT/MRI, provided that the images and report are available. An MRI scan is preferred to a CT scan, and it is preferred that the MRI be conducted at the time of the screening [redacted], if an [redacted] is conducted. See Section 6.2 for liver-related exclusion criteria.
12-lead ECG	X	ECG should be performed after the participant has been supine for at least 5 minutes.
DXA scan	X	Adequacy of DXA scan must be determined by the imaging vendor prior to Randomization. See Section 9.4.5. Urine pregnancy test should be performed in WOCBP prior to DXA scan.
Serious adverse events	X	All SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time (last visit for participation). See Section 9.2.
Clinical Efficacy Assessments		
Liver biopsy	X	See Section 9.1.2. It is recommended that key eligibility criteria should be evaluated prior to biopsy. Refer to Section 6.1 for eligibility criteria.
[redacted]		

Approved v5.0 930147586 4.0

Table 1: Screening Procedural Outline

Procedure	Screening[a] Day -56 to -1	Notes
[redacted]		
Laboratory Assessments		
Pregnancy test	X	For WOCBP only. Serum or urine pregnancy test must be completed to confirm participant is not pregnant at screening. See Section 9.2.5. Urine pregnancy test should be performed in WOCBP prior to DXA scan.
FSH	X	In women < 55 years to confirm menopause. See Section 9.4.1 and APPENDIX 4.
Hematology	X	See Section 9.4.1 and Table 8.
Chemistry	X	See Section 9.4.1 and Table 8.
Serum vitamin A (retinol)	X	Collected after fasting ≥ 10 hours. Note: Once collected, the sample must be protected from light. [redacted]
Urinalysis	X	See Section 9.4.1 and Table 8.
Serology/viral load	X	Refer to APPENDIX 7.
HIV test (only where mandated locally)	X	Refer to APPENDIX 8.
Serum AFP	X	See Section 6.2 and Section 9.4.1.
HbA1c	X	See Section 9.4.1 and Table 8.
[redacted]		

AFP = alpha-fetoprotein; BMI = body mass index; CT = computed tomography; DXA = dual-energy X-ray absorptiometry; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; IRT = interactive response technology; [redacted] MRI = magnetic resonance imaging; SAE = serious adverse event; WOCBP = women of childbearing potential

Approved v5.0 930147586 4.0

[a] The screening period may be extended up to an additional 4 weeks to accommodate unanticipated delays in obtaining required screening results.

Approved v5.0 930147586 4.0

Table 2: Treatment Period Procedural Outline

Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 1**	**D 4**	**D 8**	**D 15**	**D 22**	**D 29**	**D 36**	**D 43**	**D 46[a]**	**D 50**	**D 57**	**D 64**	**D 71**	**D 78**	**D 85**	**ETT**	**Notes**
	R		**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**		**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**		
Inclusion/Exclusion and History Assessments																	
Inclusion/exclusion criteria	X																Recheck prior to Day 1 dosing.
Medical history	X																
Prior medications	X																Prior medications are medications taken within 4 weeks prior to screening. Check prior to Day 1 dosing.
Lifestyle restrictions	X		X	X	X	X	X	X		X	X	X	X	X	X		See Section 6.4.
Clinical Safety Assessments																	
Concomitant medication use	X		X	X	X	X	X	X		X	X	X	X	X	X	X	Concomitant medications are medications taken any time after the first dose of study medication until the last study visit.
Full physical examination															X	X	A full examination will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, and extremities (See Section 9.4.3).
Abbreviated physical assessment	X			X		X					X						Abbreviated examinations will include an abdominal exam, assessments of ascites and hepatic encephalopathy, and symptom-focused assessments (See Section 9.4.3).

Approved v5.0 930147586 4.0

Table 2: Treatment Period Procedural Outline

Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 1**	**D 4**	**D 8**	**D 15**	**D 22**	**D 29**	**D 36**	**D 43**	**D 46[a]**	**D 50**	**D 57**	**D 64**	**D 71**	**D 78**	**D 85**	**ETT**	**Notes**
	R		**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**		**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**		
[redacted]																	
Physical measurements	X		X	X	X	X	X	X		X	X	X	X	X	X	X	Includes body weight only.
Vital signs	X		X	X	X	X	X	X		X	X	X	X	X	X	X	Includes body temperature, respiratory rate, blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
12-lead ECG															X	X	ECG should be performed after the participant has been supine for at least 5 minutes.
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Nonserious AEs must be collected from the time of the first dose of the study treatment through the date of the follow-up or last visit. Monitoring for AEs

Approved v5.0 930147586 4.0

Table 2: Treatment Period Procedural Outline

Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 1**	**D 4**	**D 8**	**D 15**	**D 22**	**D 29**	**D 36**	**D 43**	**D 46[a]**	**D 50**	**D 57**	**D 64**	**D 71**	**D 78**	**D 85**	**ETT**	**Notes**
	R		**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**		**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**		
																	will occur at every study visit. (See Section 9.2).
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	All SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time (last visit for participation). See Section 9.2.
Clinical Efficacy Assessments																	
[redacted]																	
Liver biopsy															X	X	Liver biopsy should be performed within ± 3 days of visit window. Four additional days are allowed under extenuating circumstances with Medical Monitor approval. In case of early termination of treatment, to be obtained at ETT visit only if the participant has completed at least the Week 6 visit. See Section 9.1.2.

Approved v5.0 930147586 4.0

Table 2: Treatment Period Procedural Outline

Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 1**	**D 4**	**D 8**	**D 15**	**D 22**	**D 29**	**D 36**	**D 43**	**D 46[a]**	**D 50**	**D 57**	**D 64**	**D 71**	**D 78**	**D 85**	**ETT**	**Notes**
	R		**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**		**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**		
[redacted]																	

Approved v5.0 930147586 4.0

Table 2: Treatment Period Procedural Outline

Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 1**	**D 4**	**D 8**	**D 15**	**D 22**	**D 29**	**D 36**	**D 43**	**D 46[a]**	**D 50**	**D 57**	**D 64**	**D 71**	**D 78**	**D 85**	**ETT**	**Notes**
	R		**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**		**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**		
[redacted]																	
Laboratory Assessments																	
Pregnancy test[c]	X		X	X	X	X	X	X		X	X	X	X	X	X	X	For WOCBP only. Serum or urine pregnancy test must be completed within 24 hours prior to each infusion to confirm the participant is not pregnant. See Section 9.2.5.
Hematology	X			X		X		X			X		X		X	X	Preinfusion when on a dosing day. See Section 9.4.1 and Table 8.
Chemistry	X			X		X		X			X		X		X	X	Preinfusion when on a dosing day. See Section 9.4.1 and Table 8.
Serum vitamin A (retinol)								X							X	X	Collected after fasting ≥ 10 hours. Note: Once collected, the sample must be protected

Approved v5.0 930147586 4.0

Table 2: Treatment Period Procedural Outline

Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 1**	**D 4**	**D 8**	**D 15**	**D 22**	**D 29**	**D 36**	**D 43**	**D 46[a]**	**D 50**	**D 57**	**D 64**	**D 71**	**D 78**	**D 85**	**ETT**	**Notes**
	R		**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**		**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**		
																	from light. See [redacted] Section 9.4.3.
Metabolic panel	X														X	X	Collected after fasting ≥ 10 hours. See Section 9.4.1 and Table 8.
HbA1c	X														X	X	See Section 9.4.1 and Table 8.
Insulin	X														X	X	Collected after fasting ≥ 10 hours and prior to infusion when on a dosing day. See Section 9.4.1 and Table 8.
Urinalysis	X			X		X		X			X		X		X	X	See Section 9.4.1 and Table 8.
Serum AFP						X					X				X	X	See Section 6.2 and Section 9.4.1.
PK [redacted] Sampling																	
Blood PK sampling	See Notes																Refer to [redacted] for sampling schedule
[redacted]																	

Approved v5.0 930147586 4.0

Table 2: Treatment Period Procedural Outline

Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 1**	**D 4**	**D 8**	**D 15**	**D 22**	**D 29**	**D 36**	**D 43**	**D 46[a]**	**D 50**	**D 57**	**D 64**	**D 71**	**D 78**	**D 85**	**ETT**	**Notes**
	R		**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**		**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**		
Randomization and Study Drug/Placebo Administration																	
Randomization via IRT	X																Study eligibility should be confirmed before contacting IRT to randomize. Eligible participants will be centrally randomized using IRT. Randomization to a treatment group will be assigned prior to dosing (Section 7.2).
Study Drug or Placebo	X		X	X	X	X	X	X		X	X	X	X	X			See Section 7.1 and Section 7.5.

AE = adverse event; AFP = alpha-fetoprotein; [redacted] D = Day; ECG = electrocardiogram; [redacted] ETT = Early Treatment Termination; HbA1c = hemoglobin A1c; IRT = interactive response technology; [redacted] PK = pharmacokinetics; [redacted] R = Randomization; SAE = serious adverse event; [redacted] W = Week; WOCBP = women of childbearing potential

[a] Day 46 is an optional visit.

[redacted]

[c] Serum or urine pregnancy test should be performed in WOCBP prior to [redacted] to confirm that participant is not pregnant.

Approved v5.0 930147586 4.0

Table 3: Follow-up Period Procedural Outline

Procedure/Visit Day (visit window)	**Follow-up Visit 1 (Week 4) (±3 days)**	**Follow-up Visit 2 (Week 12) (±7 days)**	**Follow-up Visit 3 (Week 24/EOS) (±7 days)**	**EST**	**Notes**
Clinical Safety Assessments					
Concomitant medication use	X	X	X	X	Concomitant medications are medications taken any time after the first dose of study medication until the last study visit.
Full physical examination			X	X	A full examination will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, and extremities. (See Section 9.4.3).
Abbreviated physical assessment	X	X			Abbreviated examinations will include an abdominal exam, assessments of ascites and hepatic encephalopathy, and symptom-focused assessments. (See Section 9.4.3).
Physical measurements	X	X	X	X	Includes body weight only.
Vital signs	X	X	X	X	Includes body temperature, respiratory rate, blood pressure, heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
[redacted]					
DXA scan			X	X	The EST DXA scan assessment should be performed only if the participant has received at least 1 dose of study drug. The EST DXA scan should be performed within 7 days of the EST visit. Urine pregnancy test should be performed in WOCBP prior to DXA scan.
Adverse events	X	X	X	X	Nonserious AEs must be collected from the time of the first dose of the study drug through the date of the follow-up or last visit.

Approved v5.0 930147586 4.0

Table 3: Follow-up Period Procedural Outline

Procedure/Visit Day (visit window)	**Follow-up Visit 1 (Week 4) (±3 days)**	**Follow-up Visit 2 (Week 12) (±7 days)**	**Follow-up Visit 3 (Week 24/EOS) (±7 days)**	**EST**	**Notes**
					Monitoring for AEs will occur at every study visit. See Section 9.2.
Serious adverse events	X	X	X	X	All SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time (last visit for participation). See Section 9.2.
Clinical Efficacy Assessments					
[redacted]					

Approved v5.0 930147586 4.0

Table 3: Follow-up Period Procedural Outline

Procedure/Visit Day (visit window)	**Follow-up Visit 1 (Week 4) (±3 days)**	**Follow-up Visit 2 (Week 12) (±7 days)**	**Follow-up Visit 3 (Week 24/EOS) (±7 days)**	**EST**	**Notes**
[redacted]					
Laboratory Assessments					
Hematology	X	X	X	X	See Section 9.4.1 and Table 8.
Chemistry	X	X	X	X	See Section 9.4.1 and Table 8.
Metabolic panel			X	X	Collected after fasting ≥ 10 hours. See Section 9.4.1 and Table 8.
HbA1c			X	X	See Section 9.4.1 and Table 8.
Urinalysis	X	X	X	X	See Section 9.4.1 and Table 8.
Serum AFP	X	X	X	X	See Section 6.2 and Section 9.4.1.
Pregnancy test	X		X[a]	X[a,b]	For WOCBP only. See Section 9.2.5. Urine pregnancy test should be performed in WOCBP prior to DXA scan.
PK [redacted] Sampling					
Blood PK sampling	See Notes				Refer to [redacted] for sampling schedule
[redacted]					

AE = adverse event; AFP = alpha-fetoprotein; [redacted] DXA = dual-energy X-ray absorptiometry; EOS = end of study; [redacted] EST = Early Study Termination; HbA1c = hemoglobin A1c; [redacted] PK = pharmacokinetic; [redacted] SAE = serious adverse event; WOCBP = women of childbearing potential

Approved v5.0 930147586 4.0

[a] Serum or urine pregnancy test should be performed in WOCBP prior to [redacted] to confirm that participant is not pregnant.

[b] If site is not participating in the [redacted], pregnancy testing is required only if Follow-up Visit 1 (Week 4) pregnancy testing is not completed.

Approved v5.0 930147586 4.0

3 INTRODUCTION

BMS-986263 is a lipid nanoparticle (LNP) formulation that incorporates 6 lipid components and a [redacted]-conjugated targeting agent (di-retinamide-PEG-di-retinamide [DPD]). The DPD moiety is present on the external surface of the nanoparticle and enables targeting and uptake by hepatic stellate cells (HSCs, the cells responsible for hepatic collagen synthesis) via receptors for retinol binding protein.

The LNPs contain a small interfering ribonucleic acid (siRNA) active ingredient which is a nuclease-resistant, synthetic, double-stranded ribonucleic acid (RNA) designed to temporarily inhibit the expression of heat shock protein 47 (HSP47) via RNA interference. Briefly, RNA interference (RNAi) involves a process of degrading target messenger ribonucleic acid (mRNA) transcripts, which prevents the translation of target protein. In this case, the siRNA component of BMS-986263, which is a nuclease-resistant, synthetic double-stranded siRNA, pairs with the mRNA of HSP47, thereby blocking the translation process and preventing the formation of HSP47 protein. The resultant decreased intracellular level of HSP47 leads to a decrease in the formation of stable collagen, and it is hypothesized to result in decreased liver fibrosis.

3.1 Study Rationale

This study aims to demonstrate the antifibrotic efficacy of BMS-986263, using a liver fibrosis histological endpoint, and the safety and tolerability of BMS-986263, as assessed by adverse events (AEs), serious adverse events (SAEs), laboratory results (including assessment of potential drug-induced liver injury [DILI]), vital signs, physical examinations, electrocardiograms (ECGs), [redacted] infusion-related reaction (IRR) monitoring, and bone mineral density (BMD) monitoring, in participants with nonalcoholic steatohepatitis (NASH) and compensated cirrhosis.

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in the world today. NASH, which is the more advanced form of NAFLD, is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning), with or without fibrosis.[1] NASH is associated with increased mortality rates due to cardiovascular-, liver-, and cancer-related deaths. Currently, there are no approved drugs for the treatment of NASH. With the increasing prevalence of obesity and obesity-related diseases, NASH could soon become the leading indication for liver transplantation and the leading cause of hepatocellular carcinoma (HCC) globally.[2]

NASH patients with cirrhosis have a particularly high unmet medical need for effective therapies. Among NASH patients, the stage of fibrosis is the strongest predictor of disease-specific mortality, and patients with cirrhosis are at the greatest risk for disease-related morbidity and mortality.[3,4,5,6] Patients with cirrhosis are particularly at increased risk for poor clinical outcomes, including hepatic decompensation events and the need for liver transplant.

It is reasonable to assume that an improvement in fibrosis would be predictive of clinical benefit, and a reduction of fibrosis in patients with compensated cirrhosis, if substantial, could lead to improvements in liver function and long-term clinical outcomes.

Approved v5.0 930147586 4.0

3.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986263 is provided in the Investigator's Brochure (IB).[7]

Liver Fibrosis

Deposition of collagen is a tightly regulated process that is vital to normal organ structure and function. Cytokines associated with acute or chronic inflammation induce the production of collagen to provide a fibrotic band for healing. Regulation of fibrosis mechanisms ensures both production of sufficient quantities of specific collagen types at the appropriate time and in the appropriate location, and removal and remodeling to prevent accumulation of unneeded collagen that could impair organ and tissue function.

In some circumstances, such as when inflammatory processes and/or collagen deposition are prolonged, collagen removal and remodeling can become dysregulated, causing excessive amounts of collagen to accumulate. Hepatic fibrosis may result from a wide range of causes, including NASH, chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection, and alcoholic hepatitis. All of these chronic diseases have a necroinflammatory component and frequently result in excessive collagen deposition and scarring of the liver parenchyma. This damage often leads to progression to cirrhosis, necrosis of hepatocytes, and end-stage liver disease.

Role of HSP47 in Liver Fibrosis

The principal cell type responsible for collagen deposition in the liver is the HSC, a resident perisinusoidal cell. When stimulated by reactive oxygen intermediates or inflammatory mediators (eg, transforming growth factor-β, tumor necrosis factor-α, and platelet-derived growth factor), HSCs become activated. Upon activation, HSCs are transformed into proliferative, fibrogenic, and contractile myofibroblasts that synthesize and secrete procollagen.[8] Procollagen is enzymatically cleaved to form insoluble collagen that accumulates in tissue, resulting in fibrosis.

HSP47 is a necessary component of the collagen deposition mechanism in myofibroblasts. By acting as an intracellular chaperone of early collagen precursors for Type I to Type V collagens, HSP47 facilitates collagen formation, prevents collagen degradation, and ensures proper triple-helix formation of procollagen in the endoplasmic reticulum.[9,10] While HSP47 is not the initiating factor in the pathologic accumulation of extracellular collagen matrix, a number of experimental models have shown that HSP47 is required to produce high quality collagen.[11,12,13,14] Intracellular HSP47 levels increase with increased demand for collagen synthesis.[10] The demonstration that liver fibrosis in animals[15] and humans[16] can regress when collagen synthesis is inhibited suggests that fibrosis can be reversed. This reversal most likely involves the activity of tissue enzymes such as matrix metalloproteinases (MMPs). Various therapeutic approaches, either to inhibit collagen synthesis or to activate collagen removal mechanisms, have been investigated in animal models.[17,18] However, none have yet been applied clinically, often because of side effects resulting from an inability to specifically target particular molecules and/or cells.

Approved v5.0 930147586 4.0

3.2.1 Nonclinical Studies

Initial bioinformatic analysis predicted that BMS-986263 would be a highly selective siRNA with low probability of off-target activity. In vitro cellular studies performed with BMS-986263 confirmed specificity of the RNAi activity. Additional in vitro cellular studies demonstrated potent RNAi activity elicited by BMS-986263 against both human and rat versions of HSP47. BMS-986263 elicited knockdown of HSP47 mRNA in rat primary HSCs. The presence of DPD in the formulation was shown to be essential for achieving RNAi activity, validating the targeting strategy of this formulation for effective delivery to the HSCs.

In vivo, BMS-986263 resulted in effective knockdown of HSP47 mRNA levels in rat liver after a single dose in the dimethylnitrosamine (DMN) quick model. Significant efficacy was also observed in the rat DMN chronic model of liver fibrosis as demonstrated by reduced collagen deposition (based on hydroxyproline level); improved histopathology, fibrosis scores with trichrome stain; and improved overall health based on increased total body and relative liver weights; compared with the Vehicle group. Refer to the BMS-986263 IB[7] for further details.

The most salient toxicology findings were bone changes resulting in fractures in rats, increases in complement levels in monkeys, and fetal malformations in rabbits.

Gross and histological evidence of fractures were observed at doses ≥ 10 mg/kg/dose twice per week (BIW) in the 5-week and 8 mg/kg/dose BIW in the 13-week studies in rats.[19,20] In the 26-week rat study, there was no BMS-986263-related bone findings at any dose (no-observed-adverse-effect level [NOAEL] = 8 mg/kg/week, the highest dose administered, with steady state area under the curve (AUC) exposures of approximately 6× higher than the observed human exposure at a clinical dose of [redacted] In monkeys, there were no adverse bone effects noted at any dose after repeated dosing for up to 39 weeks.[22] The NOAEL in this study was 15 mg/kg/week (AUC multiple: 82×). Although drug product-related changes in bone size, mineral content, and mineral density were observed in female monkeys at all doses (≥ 2.5 mg/kg/week) and male monkeys at the high dose of 15 mg/kg/week, these changes were considered nonadverse based on their small magnitude, and had no associated negative impacts on bone strength.

The underlying mechanism of the fractures in the rat is an increase in osteoclast activity in the subperiosteal regions of the diaphysis of long bones, a decrease in osteoclast numbers, and reduced osteoid in the trabecular regions of the bones, which translates into reduced bone formation. The literature suggests that rats are sensitive to bone fractures related to hypervitaminosis A.[23,24] However, the majority of the protein in bone is collagen, and there is literature suggesting that HSP47 is involved in bone formation.[25,26] Given the observation of fractures in animals that received empty-LNP formulation (ie, without siRNA inhibition of HSP47) it is hypothesized that LNP played a role in the observed findings.

In the 39-week repeat-dose study in monkeys, modest and transient elevations of complement components were reported; onset of these occurred as soon as 10 minutes postinfusion and were resolved by 24 hours.[27] BMS-986263-related findings were limited to nonadverse changes in the

Approved v5.0 930147586 4.0

skin and vaginal epithelium at all doses, likely related to the [redacted] component of the formulation, and minimal decreases in red cell mass parameters at the high dose.

In a 13-day expanded range-finding study in pregnant rabbits (1 and 3 mg/kg intravenous [IV] every other day), malformations of the thoracic or lumbar vertebrae and/or ribs was observed at 3 mg/kg but not at 1 mg/kg (weekly AUC = 0.2× human AUC [redacted] These included hemivertebrae, small or enlarged vertebral arches and centra, and misaligned vertebrae, fused ribs, and fused costal cartilages (rib precursors). The observed teratogenicity is not unexpected given the LNP formulation contains a [redacted] Because these malformations occurred in the absence of any detectable maternal toxicity, ND-L02-s0201/BMS-986263 is considered to be a selective developmental toxicant in rabbits.

Additional details on the nonclinical program and the potential risks associated with the use of BMS-986263 are available in the IB.[7]

3.2.2 Clinical Studies

The clinical development program of BMS-986263 consists of 7 completed studies: 3 studies in healthy participants (ND-L02-s0201-001, ND-L02-s0201-004, and IM025001),[29,30,31] 3 studies in participants with liver fibrosis (ND-L02-s0201-002, ND-L02-s0201-003, and IM025006),[32,33,34] and 1 study in participants with hepatic impairment (HI) (Study IM025015). For further details on the completed studies, refer to the BMS-986263 IB.[7]

Clinical Efficacy

The efficacy of BMS-986263 has been investigated in 3 clinical studies:

- **Study ND-L02-s0201-002**[32] (N = 25) was a Phase 1b/2, open-label, randomized, multicenter, repeat-dose, dose-escalation study at doses of 0.2, 0.4, and 0.6 mg/kg/week administered once every week (QW) or BIW for 5 weeks in participants with moderate to extensive progressive hepatic fibrosis (METAVIR F3 to F4) due to either NASH or chronic HCV. In this study, evidence indicative of biological activity was observed with improvements noted in METAVIR, Ishak, and Knodell fibrosis scores, as well as decreased stiffness was observed with Fibroscan® at Week 5, all of which are measures of hepatic fibrosis.
- **Study ND-L02-s0201-003**[33] (N = 10) was a Phase 1b/2, open-label, randomized, multicenter, repeat-dose, dose-escalation study at doses of 0.2, 0.4, and 0.6 mg/kg/week QW for 5 weeks in participants with moderate to extensive progressive hepatic fibrosis (METAVIR F3 to F4) due to NASH, chronic HCV, or alcoholic liver disease. In this study, evidence indicative of biological activity was observed with improvements noted in METAVIR, Ishak, and Knodell fibrosis scores, as well as decreased stiffness was observed with Fibroscan® at Week 5, all of which are measures of hepatic fibrosis.
- **Study IM025006**[34] was a Phase 2, randomized, double-blind, placebo-controlled study of 45 mg BMS-986263 versus 90 mg BMS-986263 versus placebo (randomized 1:2:1) dosed weekly for 12 weeks in 61 participants with advanced fibrosis due to chronic HCV who had achieved sustained virologic response (SVR) at least 1 year prior to screening. The primary endpoint was the proportion of participants that achieved ≥ 1 stage improvement in liver fibrosis (METAVIR) on liver biopsy after 12 weeks of treatment. One patient who received

Approved v5.0 930147586 4.0

90 mg BMS-986263 had a nonevaluable biopsy at the end of study; for the primary endpoint, a missing biopsy was considered not to be improvement (failure). All results should be interpreted with caution given the small sample size.

- All participants were required to have HCV-SVR for at least 52 weeks and METAVIR Fibrosis Stage 3 or Stage 4 to be eligible to participate. The participants were enrolled on the basis of results of liver biopsy as read by the local pathologist. [redacted] baseline liver stiffness assessed by magnetic resonance elastography (MRE) [redacted] were comparable across treatment groups.
- A ≥ 1 stage improvement in METAVIR score was observed for 6 of 28 (21%), 3 of 18 (17%), and 2 of 15 (13%) participants in the 90 mg BMS-986263, 45 mg BMS-986263, and placebo groups, respectively.
  - In participants with a baseline METAVIR score of 4 (equivalent to cirrhosis), a ≥ 1 stage improvement in METAVIR score was observed for 3 of 6 (50%), 1 of 2 (50%), and 0 of 2 participants in the 90 mg BMS-986263, 45 mg BMS-986263, and placebo groups, respectively.
- The secondary endpoints included improvements in Ishak score. A ≥ 2 stage improvement in Ishak score was observed in 5 of 28 (18%), 0 of 18 (0%), and 0 of 15 participants in the 90 mg BMS-986263, 45 mg BMS-986263, and placebo groups, respectively.

Clinical Safety in Participants with Advanced Liver Fibrosis

In the 3 clinical studies in participants with advanced liver fibrosis, BMS-986263 was generally well tolerated and demonstrated an acceptable safety profile.

- In studies **ND-L02-s0201-002** and **ND-L02-s0201-003**, the most frequent AEs experienced by participants were temporally related to the infusion of the drug product and were mainly associated with IRRs. These reactions were mild to moderate in severity. The signs and symptoms of IRRs included, but were not limited to, back pain, fever, chills, hot or warm sensation, flushing, throat constriction, shortness of breath, chest tightness, tachypnea, tachycardia, hypotension, urticaria, pruritus, erythema, and/or edema. In general, back pain was the most common symptom reported for these IRRs. Refer to the BMS-986263 IB for more details on these studies.
- In **Study IM025006**, IRRs were the most frequently experienced AEs. All infusion-related AEs were mild or moderate in intensity. The AEs associated with IRRs included back pain (most commonly reported), hypertension, hives/urticaria, flushing, shortness of breath, dry mouth, and hypoxia. In the 45 mg BMS-986263 group, of the 6 participants who had IRRs, 3 participants had at least 1 infusion interrupted due to an AE. In the 90 mg BMS-986263 group, of the 15 participants who had IRRs, 13 participants had at least 1 infusion interrupted due to an AE. All subjects who had IRRs completed the treatment period.

  In this study, BMS-986263 was not associated with evidence of [redacted] based on monitoring of signs and symptoms of vitamin A toxicity and liver biopsy. None of the

Approved v5.0 930147586 4.0

participants had serum or plasma vitamin A (retinol) levels above the upper limit of normal (ULN) (defined as 3.42 µmol/L) during the course of treatment.

Clinical Safety and Pharmacokinetic (PK) in Participants with HI

- **Study IM025015** - This was a Phase 1, open-label, single-dose study to evaluate the PK, safety, and tolerability of BMS-986263 90 mg IV in participants with varying degrees of HI. Study IM025015 consisted of 2 parts. A total of 52 participants were screened, and 40 participants were enrolled in the study: 24 of these were enrolled in Part 1 (8 participants in normal matched Group D, 8 participants in mild HI [Group A], and 8 participants in moderate HI [Group B]) and 16 participants were enrolled in Part 2 (8 participants in normal matched Group E and 8 participants in severe HI [Group C]). Overall, 39 participants completed the study, and 1 participant in the moderate HI group withdrew consent during the study.

  In this study, single doses of BMS-986263 were generally safe and well tolerated in participants with normal hepatic function and several degrees of HI. Most of treatment emergent AEs (TEAEs) were mild or moderate in severity. The most frequent two TEAEs were flu-like illness and IRRs. There were no TEAEs that led to death or treatment discontinuation. One treatment emergent SAE of hematemesis was reported in a participant with moderate HI and was considered not related to BMS-986263.

  Compared to the respective matching normal group, exposure estimates of BMS-986263 siRNA exposures [geometric mean AUC(0-T) and AUC(INF)] were similar in the HI mild group, and 1.34- and 1.33-fold higher, respectively, in the moderate HI group and 2.63-fold higher for both in the severe HI group. For DPD, exposure estimates were modestly lower in both the mild HI and moderate HI groups, compared with the matching normal groups, whereas AUC(0-T), and AUC(INF) were 1.31, and 1.33 higher for the severe HI, respectively. For S104, higher exposure trends related to HI severity were noted in Cmax, AUC(0-T), and AUC(INF), with the highest exposure observed in HI severe group with a geometric mean AUC(0-T) 5.5-fold higher than the matching normal group. S104 is a component with a short half-life (~36 hours) and, based on modeling studies, it does not accumulate with weekly dosing. Additionally, S104 is an excipient with no known biological activity.

  Based on the PK of siRNA, DPD, and S104 components of BMS-986263 and safety observations from this study, no dose adjustment is recommended for BMS-986263 in patients with mild or moderate HI. Results from this and other studies will guide the dose selection for patients with severe HI.

Based on the clinical studies to date, there were no safety trends observed in the laboratory assessments, physical examinations, vital signs, and ECG assessments. There were no changes in BMD as assessed by dual-energy X-ray absorptiometry (DXA) scan and there were no cases of potential DILI in the clinical studies.

3.3 Benefit/Risk Assessment

3.3.1 Overall Benefit/Risk Assessment

In the completed clinical studies BMS-986263 has been generally well tolerated, with an acceptable safety profile in patients with mild or moderate HI. More detailed information about

Approved v5.0 930147586 4.0

the known and expected benefits and risks and reasonably anticipated AEs of BMS-986263 may be found in the IB.[7]

In Phase 1b and Phase 2 studies involving participants with advanced liver fibrosis, including compensated cirrhosis, a proportion of participants administered BMS-986263 have had an improvement of fibrosis. As previously mentioned, there is no approved therapy for patients with advanced liver fibrosis. A reduction in fibrosis in NASH patients with compensated cirrhosis may lead to a reduced risk liver decompensation, need for liver transplant, HCC, and mortality.

In nonclinical and Phase 1 and 2 clinical studies to date, potential risks associated with BMS-986263 have been identified. One is the risk of IRRs observed in the Phase 1 and 2 studies. In all cases, infusion reactions were mild to moderate in severity and self-limited. There was no evidence of anaphylaxis, and participants were not discontinued from the studies due to these reactions. In an attempt to reduce the risk of these IRRs, the total dose is administered in step-wise fashion as described in the Pharmacy Manual (see Section 7.1.1). If clinical signs and/or symptoms indicate an IRR, the infusion may be interrupted. In addition, to potentially decrease the frequency or severity of infusion reactions, premedication (antihistamines and/or corticosteroids) may be used, at the discretion of the investigator. The premedication may be administered (at the discretion of the investigator) to ensure safety of the participants, as mentioned in Section 7.1.2.

Other identified risks include the impact of exposure to DPD [redacted] associated with administration of BMS-986263. These include possible impact on bone, liver, and fetal development.

Bone Risk

Although HSP47 and generation of collagen are important for bone formation, it is hypothesized that the DPD component of BMS-986263 is responsible for bone abnormalities identified in the nonclinical rat studies. However, no significant bone abnormalities were observed in cynomolgus monkeys. In this study, participants will be assessed for changes in BMD by DXA scan; [redacted].

Reproductive Risk

In nonclinical studies, BMS-986263 had effects on fetal development, including fetal teratogenicity and skeletal malformations in nonclinical rabbit studies. In this study, women of childbearing potential (WOCBP) and male participants who are sexually active with WOCBP must agree to follow instructions for method(s) of highly effective contraception, as defined in APPENDIX 4.

Other DPD-Risks, Including Liver Risk

The theoretical risk of DPD-related liver toxicity is mitigated by the short treatment duration of this study (12 weeks). In the previous Phase 2 study in HCV-SVR participants, no participants had a constellation of clinical signs and symptoms that was suggestive of [redacted]. Furthermore, there was no laboratory evidence of potential DILI or new histologic changes suggestive of [redacted] to HSCs. In this study, all participants will be monitored closely for signs and/or symptoms of [redacted]. Moreover, liver safety will be monitored by

Approved v5.0 930147586 4.0

serial history, abdominal physical exams, and laboratory assessments. [redacted]

In this study, participants will be queried for symptoms suggestive of [redacted] including but not limited to dry skin, vaginal dryness, cheilosis, gingivitis, muscle and joint pains, fatigue, mental dullness, and depression. Physical examinations during [redacted] evaluation will be performed that include signs of [redacted] including skin and oral mucosa changes and hepatomegaly.

Additional safety monitoring will include laboratory assessments to rule out development of anemia, leucopenia, thrombocytopenia, liver enzyme (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) and total bilirubin elevations. Use of over-the-counter (OTC) herbal supplements and multivitamins containing vitamin A (including Cod liver oil), or other medications that may contain vitamin A, are prohibited while participating in the study (Section 7.7.1). Prior to starting study treatment and throughout the study, participants will be educated about vitamin A-containing foods, medications, and herbal supplements, as well as the signs and symptoms of vitamin A toxicity. In addition, liver biopsy specimens will also be assessed for histologic evidence suggestive of [redacted] (Section 9.4.6).

In order to minimize the overall risk to participants, this protocol has eligibility criteria appropriate to the population and proposed treatments, exclusionary screening tests, and specific follow-up safety assessments. In addition, the AEs and SAEs will be reviewed on an ongoing basis by the Medical Monitors and the pharmacovigilance group to look for trends and any emergent or unexpected safety issues. An independent Data Monitoring Committee (DMC) will also review safety data on a regular basis.

3.3.2 Coronavirus Disease 2019-Related

The ongoing global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to trial participants in general and it may particularly affect individuals with underlying chronic diseases. The individual benefit-risk considerations regarding COVID-19 infection remains the responsibility of the investigator. Vaccination as well as testing to exclude infection prior to enrollment and to inform decisions about participant care during the study should follow local standard practice and requirements. Non-live COVID-19 vaccination is allowed during the study, will be documented as a concomitant medication, and should follow local standard practices during administration. The efficacy and safety of COVID-19 vaccines in subjects receiving BMS-986263 are unknown. BMS-986263 is not immunomodulatory. It is not known whether taking BMS-986263 changes the risk of SARS-CoV-2 infection, or the duration or severity of COVID-19 disease. [redacted]

Approved v5.0 930147586 4.0

4 OBJECTIVES AND ENDPOINTS

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of BMS-986263 compared with placebo to improve liver fibrosis in participants with compensated cirrhosis due to NASH	• Proportion of participants who achieve ≥ 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score), as determined by liver biopsy after 12 weeks of treatment
• **Secondary**	
• To further assess the efficacy of BMS-986263 compared with placebo to improve liver fibrosis, as determined by liver biopsy, in participants with compensated cirrhosis due to NASH	• Proportion of participants with ≥ 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score), with no worsening of NASH after 12 weeks of treatment (worsening defined as an increase of the NAS by ≥ 1 point) • Proportion of participants with ≥ 2 stage improvement in liver fibrosis (NASH CRN Fibrosis Score) after 12 weeks of treatment • Proportion of participants with ≥ 1 stage improvement in liver fibrosis (modified Ishak score) after 12 weeks of treatment • Proportion of participants with ≥ 2 stage improvement in liver fibrosis (modified Ishak score) after 12 weeks of treatment • Change from baseline in CPA after 12 weeks of treatment
• To assess the safety and tolerability of BMS-986263 in participants with compensated cirrhosis due to NASH	• Incidences of SAEs, AEs, clinical laboratory values, vital signs, physical examination findings, and ECGs • Change from baseline in BMD, as measured by DXA scan, at Follow-up Week 24
• To assess the PK of BMS-986263 in participants with compensated cirrhosis due to NASH	• Plasma concentrations of siRNA, DPD, HEDC, and S104 (components of BMS-986263 for injection)

Approved v5.0 930147586 4.0

Table 4: Objectives and Endpoints

Objectives	Endpoints
• **Exploratory**	
[redacted]	
• **Exploratory**	
[redacted]	

Approved v5.0 930147586 4.0

Table 4: Objectives and Endpoints

Objectives	Endpoints
[redacted]	
• **Exploratory**	
[redacted]	

Approved v5.0 930147586 4.0

Table 4: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]

[redacted]
AE = adverse event; ALT = alanine aminotransferase;
AST = aspartate aminotransferase; BMD = bone mineral density;
CPA = collagen proportionate area; CRN = Clinical Research Network;
DPD = di-retinamide-PEG-di-retinamide; ; DXA = dual-energy X-ray absorptiometry;
ECG = electrocardiogram;
HEDC = (Bis[2-(tetradecanoyloxy)ethyl] carbamoylmethyl)-(2-hydroxyethyl)dimethylazanium bromide;
INR = international normalized ratio;
NASH = nonalcoholic steatohepatitis;
PK = pharmacokinetics;
SAE = serious adverse event;
SiRNA = small interfering ribonucleic acid;

Approved v5.0 930147586 4.0

5 STUDY DESIGN

5.1 Overall Design

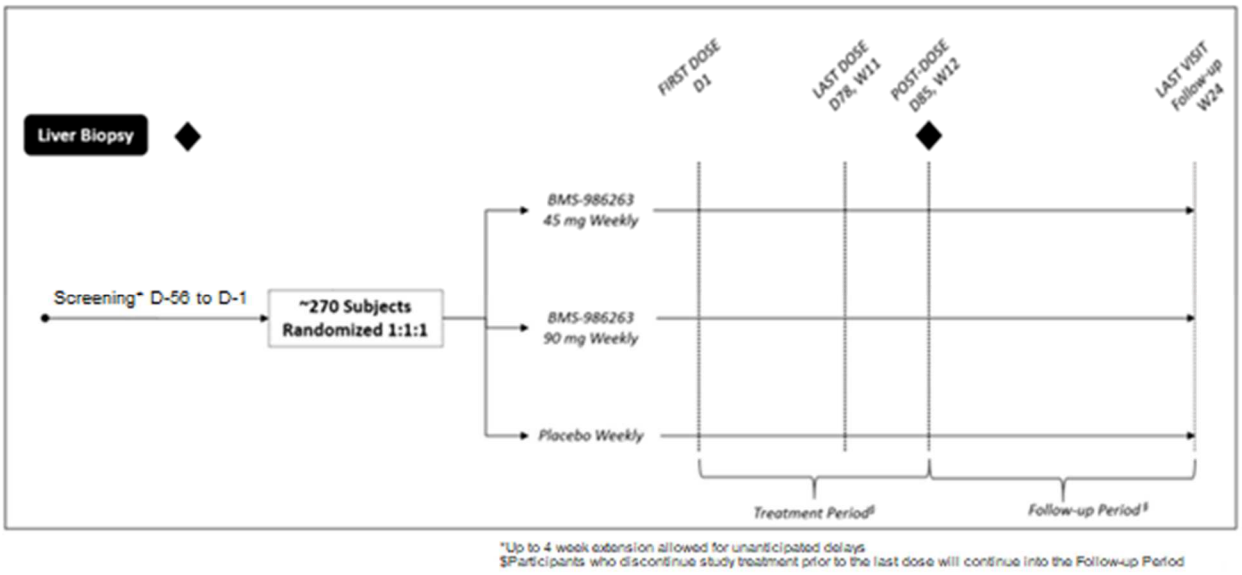
This is a randomized, double-blind, placebo-controlled, parallel-group, multiple-dose Phase 2 study to evaluate the efficacy, safety, and tolerability of BMS-986263 in adults with compensated cirrhosis due to NASH. The primary study endpoint is the proportion of participants who achieve ≥ 1 stage improvement in liver fibrosis (NASH [Clinical Research Network (CRN)] Fibrosis Score) on biopsy after 12 weeks of treatment.

The study includes:

- A screening period
- A 12-week, double-blind treatment period, during which participants will receive 1 of the following 3 treatments by IV infusion: 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW
- A follow-up period of 24 weeks during which participants will not receive investigational treatment

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



D = Day; W = Week

5.1.1 Screening Period

Eligibility will be based on specified inclusion and exclusion criteria (Section 6.1 and Section 6.2, respectively), including medical history, disease activity, and safety assessments. Eligibility criteria for this study have been carefully considered to ensure the safety of the participants and that the results of the study can be analyzed properly. It is imperative that participants fully meet all eligibility criteria. Participants will have a diagnosis of NASH with compensated cirrhosis

Approved v5.0 930147586 4.0

(requirements in Section 6.1); ≥ 80% of subjects will be required to have definite steatohepatitis on the biopsy used to confirm eligibility. In addition to the main study, additional eligibility criteria for participation [redacted] are provided in [redacted]. Participation in the [redacted] is required if available at the site, unless it is contraindicated for a participant to have an [redacted].

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Certain procedures conducted as part of the participant's routine clinical management and obtained before signing of informed consent may be utilized for screening purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (SOA) (Section 2).

Randomization should occur within 56 days (8 weeks) of signing the informed consent. The screening period may be extended (up to an additional 4 weeks) to accommodate unanticipated delays in obtaining required screening results.

Visit details are provided in the Screening Procedural Outline in the SOA (Section 2).

5.1.2 Treatment Period and Follow-up

Participants meeting eligibility criteria during the screening period will enter the treatment period. Approximately 270 participants will be randomized via interactive response technology (IRT) in a 1:1:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW by IV infusion in a double-blind manner.

Participants will be stratified at Randomization by the presence of definite steatohepatitis on biopsy (yes versus no). At least 80% of participants will be required to have definite steatohepatitis on the biopsy used to confirm eligibility. Participants will receive study treatment via IV infusion for a total of 12 weeks. Liver biopsy will be performed at Week 12.

After 12 weeks (Day 85) of treatment or after early treatment discontinuation, participants will enter the 24-week follow-up period, during which participants will not receive investigational treatment. After all participants complete the Follow-up Week 4 visit, the study will be unblinded and analyses of the available Week 12 data will be conducted (Section 10.4.4). Participants who discontinue study treatment before the Week 11 Visit will have an Early Treatment Termination (ETT) visit and will continue into the 24-week follow-up period.

See the SOA in Table 2 and Table 3 (Section 2).

5.1.3 DMC and Other External Committees

This study will utilize an external DMC for the duration of the study. Data summaries and listings will be provided to the DMC to facilitate their assessments at the regularly scheduled times and on an ad hoc basis if needed. The safety review includes SAEs and events of special interest (eg, bone fractures, IRRs, and anaphylaxis), focusing on early signal detection. This study will also utilize an Independent Pathology Review Committee (IPRC) to perform central pathology assessments of the liver biopsy samples to support study eligibility and histological efficacy endpoints analyses.

Approved v5.0 930147586 4.0

The DMC and IPRC responsibilities, authorities, and procedures will be documented and followed according to their respective charters.

5.2 Number of Participants

Approximately 270 participants are planned to be randomized in a 1:1:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW by IV infusion for 12 weeks.

5.3 End of Study Definition

The start of the study is defined as the first visit for first participant screened. End of study (EOS) is defined as the last visit or scheduled procedure shown in the SOA (Section 2) for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same. The end of the study for analysis of [redacted] samples is included in [redacted].

5.4 Scientific Rationale for Study Design

Phase 1b and Phase 2 studies of BMS-986263 enrolled participants with advanced liver fibrosis caused by NASH or HCV. Review of safety data from these studies demonstrated that BMS-986263 was generally safe and well tolerated. Based on efficacy data from the small number of participants in these studies who had advanced liver fibrosis, Study IM025017 will investigate the effects of BMS-986263 in a larger population of participants with compensated cirrhosis due to NASH.

The focus of this placebo-controlled, Phase 2 study is to demonstrate the efficacy, safety, tolerability, PK, [redacted] effects of BMS-986263 in participants with compensated cirrhosis due to NASH. The study schematic is provided in Figure 1.

The study will seek to confirm the findings of prior clinical studies demonstrating improvement in fibrosis in participants with advanced liver fibrosis. In this study, BMS-986263 at doses of 45 mg or 90 mg QW for 12 weeks, compared with placebo, will be utilized to assess proof-of-concept of the efficacy (as measured by the improvement of liver fibrosis), safety, and tolerability of BMS-986263 in the study population. The 45 mg and 90 mg doses were chosen because these doses were studied in the prior Phase 2 study of HCV-SVR patients; these doses appeared to be efficacious and were generally safe and well tolerated. A treatment duration of 12 weeks was chosen because an antifibrotic effect was observed after 12 weeks of therapy in that study. The follow-up period will allow assessment (utilizing noninvasive assessments of fibrosis) of the off-treatment durability of efficacy through Follow-up Week 24 (or up to 36 weeks total duration).

Efficacy, safety, PK, [redacted] effects will be compared with results from placebo-treated participants and across treatment arms to identify the optimal doses and dosing regimen for future development.

Complete details of the study design are provided in Section 5.

5.5 Justification for Dose

In a Phase 1 single-ascending dose study (ND-L02-s0201-001) in healthy, normal, male participants, dosing was weight-based [redacted] BMS-986263 was generally safe and

Approved v5.0 930147586 4.0

well tolerated at all dose levels. After IV infusion administration at the dose ranges given above, plasma concentrations of the siRNA component, NDT-05-0038, were consistent over time with an open, [redacted] IV infusion model.

The model-predicted values for the primary PK parameters total plasma clearance (CL) and volume of the central compartment were consistent among participants and among doses and a log-log plot of the model-predicted area under the concentration vs time curve extrapolated to infinity vs dose was linear [redacted]. The mean elimination half-life across [redacted] with no apparent dose-related trends. [redacted]

In the present study, the doses of 45 mg QW and 90 mg QW BMS-986263 will be investigated in participants with compensated cirrhosis due to NASH. Selection of the doses is based on nonclinical safety data and the clinical studies conducted to date. [redacted]

6 STUDY POPULATION

6.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1) **Signed written informed consent**
   a) Not applicable per Revised Global Protocol v01.
   b) Willing and able to complete all study-specific procedures and visits.
   c) Willing to participate in the study and sign the informed consent form (ICF) by participants (or legally acceptable representative).
2) **Type of Participant and Target Disease Characteristics**
   a) Not applicable per Revised Global Protocol v01.
   b) **Not applicable per Protocol Amendment 03** - Participants taking sodium glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, anti-obesity agents, or approved NASH treatment must have been on stable doses for at least 3 months prior to the liver biopsy used to confirm eligibility.
   c) Participants taking vitamin E at doses ≥ 800 IU/day must have been on stable doses for at least 6 months prior to the screening visit. If used, vitamin E must have been initiated prior to the liver biopsy used to determine eligibility.
   d) **Not applicable per Protocol Amendment 03** - Adequate DXA scan performed during screening confirmed by the central imaging facility prior to Randomization (see Section 6.2).
   e) **Not applicable per Protocol Amendment 03** - Liver biopsy performed within 6 months prior to the screening visit or performed during the screening period. A liver biopsy performed prior to ICF, if utilized for eligibility, must be available for central pathology reading prior to Randomization.

Approved v5.0 930147586 4.0

i) Liver biopsy consistent with NASH CRN Fibrosis Score Stage 4, as assessed by central pathology reading.

ii) Liver biopsy must either be consistent with steatohepatitis, as assessed by central pathology reading, OR, for liver biopsies without definite steatohepatitis, there should be some evidence of steatosis and/or ballooning and the following definition of NASH cirrhosis must be fulfilled:

(1) Absence of other causes of liver disease AND either of the following:

(a) At least 2 of the 3 following criteria:

(i) History of body mass index (BMI) ≥ 30 kg/m^2

(ii) History of type 2 diabetes mellitus

(iii) History of hypertension AND/OR history of dyslipidemia

OR

(b) Previous histologic readings of steatohepatitis (for biopsies > 6 months prior to screening visit) AND either history of BMI ≥ 30 kg/m^2 OR history of type 2 diabetes mellitus.

NOTE: At least 80% of participants will be required to have definite steatohepatitis on the biopsy used to confirm eligibility.

f) Adequate DXA scan performed during screening and determined by the central imaging vendor prior to Randomization (see Section 6.2).

g) Liver biopsy performed within 12 months prior to the screening visit or performed during the screening period. A liver biopsy performed prior to ICF, if utilized for eligibility, must be available for central pathology reading prior to Randomization.

i) Liver biopsy consistent with NASH CRN Fibrosis Score Stage 4, as assessed by central pathology reading.

ii) Liver biopsy must either be consistent with steatohepatitis, as assessed by central pathology reading, OR, for liver biopsies without definite steatohepatitis, there should be some evidence of steatosis and/or ballooning and the following definition of NASH cirrhosis must be fulfilled:

(1) Absence of other causes of liver disease AND either of the following:

(a) At least 2 of the 3 following criteria:

(i) History of body mass index (BMI) ≥ 30 kg/m^2

(ii) History of type 2 diabetes mellitus

(iii) History of hypertension AND/OR history of dyslipidemia

OR

(b) Previous histologic readings of steatohepatitis (in a past biopsy prior to the one utilized for eligibility) AND either history of BMI ≥ 30 kg/m^2 OR history of type 2 diabetes mellitus.

NOTE: At least 80% of participants will be required to have definite steatohepatitis on the biopsy used to confirm eligibility.

h) Participants taking sodium glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, anti-obesity agents, or approved NASH treatment must have been on stable doses for at least 3 months prior to screening.

Approved v5.0 930147586 4.0

3) Age and reproductive status

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants

i) Female participants ages ≥ 21 years to ≤ 75 years of age, inclusive, at the time of screening.

ii) Not applicable per Revised Global Protocol v01.

iii) WOCBP must have a negative highly sensitive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the following: start of study treatment and each dose of study treatment.

(1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

(2) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, SOA.

(3) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

iv) Not applicable per Revised Global Protocol v01.

v) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

(1) Is not a WOCBP (female participants must have documented proof that they are not of childbearing potential)

OR

(2) Is a WOCBP and is using a contraceptive method that is highly effective (with a failure rate of < 1% per year), as described in APPENDIX 4, during the intervention period and for at least 20 days after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

vi) WOCBP must agree to follow instructions for highly effective method(s) of contraception, as defined in APPENDIX 4 and as described below and included in the ICF.

(1) WOCBP are permitted to use hormonal contraception methods (as described in APPENDIX 4)

Approved v5.0 930147586 4.0

(2) Women who are not of childbearing potential are exempt from contraceptive requirements

b) Male Participants

i) Male participants ages ≥ 21 years to ≤ 75 years of age, inclusive, at the time of screening.

ii) Male participants who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception, as defined in APPENDIX 4 and as described below.

iii) Not applicable per Revised Global Protocol v01.

iv) Not applicable per Revised Global Protocol v01.

v) Not applicable per Revised Global Protocol v01.

vi) Not applicable per Revised Global Protocol v01.

vii) Not applicable per Revised Global Protocol v01.

viii) Breastfeeding partners should be advised to consult their healthcare providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

ix) Azoospermic male participants are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

x) Male participants must be willing to and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Male participants should continue to use a condom during the intervention period and for at least 20 days after the last dose of study intervention.

xi) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral) even if the participants have undergone a successful vasectomy, during the intervention period and for at least 20 days after the last dose of study intervention.

xii) Male participants must refrain from donating sperm during the intervention period and for at least 20 days after the last dose of study intervention.

xiii) Female partners of male participants participating in the study should be advised to use highly effective methods of contraception during the intervention period and for at least 20 days after the last dose of study intervention in the male participant.

6.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

Approved v5.0 930147586 4.0

1) Target disease exclusions

a) Other active causes of liver disease (eg, alcoholic liver disease, HBV infection [see APPENDIX 7)], chronic HCV infection [see APPENDIX 7], autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, drug-induced hepatotoxicity, Wilson disease, homozygous α-1-antitrypsin deficiency, iron overload [with blood iron saturation > 50%], or hemochromatosis).

b) Past or current evidence of hepatic decompensation (eg, ascites, variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis).

c) **Not applicable per Protocol Amendment 03** - Liver transplantation (past or planned).

d) Not applicable per Revised Global Protocol v01.

e) **Not applicable per Revised Global Protocol v02** - Model for End-stage Liver Disease (MELD) Score > 14 at screening (APPENDIX 6). Participants who have a MELD Score > 14 due to an isolated elevated INR and who are taking an anticoagulant known to prolong INR or who have Gilbert Syndrome and direct bilirubin ≤ ULN may be included after discussion with the Medical Monitor.

f) **Not applicable per Revised Global Protocol v02** - Evidence of HCC at screening based on serum alpha-fetoprotein (AFP) levels, as indicated below, or any imaging technique (eg, magnetic resonance imaging [MRI], computed tomography [CT], or ultrasound; based on local assessment):

   i) AFP > 20 ng/mL (> 16.5 IU/mL) OR

   ii) LI-RADS[35] 3, 4, or 5 noted on the last historical CT or MRI, regardless of the AFP at screening. If screening ultrasound has a hepatic lesion ≥ 10 mm in size, the participant must have the last historical CT or MRI performed within 3 months prior to screening or a new CT or MRI can be performed.

g) **Not applicable per Revised Global Protocol v02** - Child-Pugh Score > 5 at screening (APPENDIX 5). Participants who have a Child-Pugh Score > 5 due to an isolated elevated INR and who are taking an anticoagulant known to prolong INR, or who have Gilbert Syndrome and direct bilirubin ≤ the ULN, may be included after discussion with the Medical Monitor.

h) **Not applicable per Protocol Amendment 03** - MELD Score > 14 at screening (APPENDIX 6). Participants with a MELD Score > 14 with elevated total bilirubin and who have Gilbert Syndrome and direct bilirubin ≤ ULN may be included after discussion with the Medical Monitor.

i) **Not applicable per Protocol Amendment 03** - Evidence of HCC at screening based on (i) serum alpha-fetoprotein (AFP) > 20 ng/mL (> 16.5 IU/mL) or (ii) Liver Reporting & Data System[35] 3, 4, or 5 as determined by historical CT/ MRI within 3 months prior to screening or from multiphasic CT/MRI of liver during screening.

j) **Not applicable per Protocol Amendment 03** - Child-Pugh Score > 6 at screening (APPENDIX 5). Participants with a Child-Pugh Score > 6 with elevated total bilirubin and who have Gilbert Syndrome and direct bilirubin ≤ the ULN, may be included after discussion with the Medical Monitor.

k) Liver transplantation (past or planned during the study).

Approved v5.0 930147586 4.0

l) MELD Score > 14 at screening (APPENDIX 6). Exception: Participants with Gilbert Syndrome who have a MELD Score > 14 with elevated total bilirubin, and direct bilirubin ≤ ULN may be included provided that total bilirubin is < 4.0 mg/dL.

m) Evidence of HCC at screening based on (i) serum alpha-fetoprotein (AFP) > 20 ng/mL (> 16.5 IU/mL) or (ii) Liver Reporting & Data System[35] 3, 4, or 5 as determined by historical computed tomography (CT)/magnetic resonance imaging (MRI)within 3 months prior to screening or from multiphasic CT/MRI of liver during screening. Both AFP and CT/MRI assessments will be required from all participants to determine eligibility.

n) Child-Pugh Score > 6 at screening (APPENDIX 5). Exception: Participants with Gilbert Syndrome who have a Child-Pugh Score > 6 with elevated total bilirubin, and direct bilirubin ≤ the ULN may be included, provided that total bilirubin is < 4.0 mg/dL.

2) Medical conditions

a) Evidence of worsening liver disease or hepatic decompensation, in the opinion of the investigator or Medical Monitor, during the screening period.

b) Medical history of gastroesophageal varices, except if esophagogastroduodenoscopy performed within 12 months prior to the screening period has shown ≤ Grade 1 varices and without red wale signs, as assessed by the investigator.[36]

c) **Not applicable per Revised Global Protocol v02** - History of alcohol consumption ≥ 21 units/week (male participants) or ≥ 14 units/week (female participants) within the 2 years prior to the biopsy used to determine eligibility. One drink "unit" or one standard drink is equivalent to 12 ounces of beer, 4 ounces of wine, or 1 ounce of hard liquor. Note: Participants should limit alcohol during their participation in the study (Section 6.4).

d) History of bariatric surgery or intestinal bypass surgery within the 5 years prior to informed consent or planned during the conduct of the study.

e) History of hepatocellular carcinoma.

f) Participants who have: 1) current malignancy or 2) a previous malignancy up to 5 years prior to screening are excluded except for those with a documented history of cured nonmetastatic squamous cell skin carcinoma, basal cell skin carcinoma, or cervical carcinoma in situ. Participants who have a liver biopsy that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory, or other diagnostic evaluations, are also excluded.

g) History of bone disease, including osteoporosis and osteomalacia, Paget's disease of bone, or a history of unexplained fractures or fractures after minimal trauma as assessed by the investigator.

h) Any disease or condition which, in the opinion of the investigator, might compromise participant safety (eg, hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, skeletal, central nervous system, or complement-mediated disease).

i) Any acute or chronic cardiovascular condition (eg, ischemic heart disease, congestive heart failure) considered clinically significant by the investigator.

j) Uncontrolled hypertension, as defined by systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg at screening, unless discussed with Medical Monitor. Blood pressure may be rechecked as clinically indicated.

Approved v5.0 930147586 4.0

k) Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for human immunodeficiency virus (HIV) or have acquired immunodeficiency syndrome-related illness, as reported by the participant and/or documentation. NOTE: Testing for HIV must be performed at sites where mandated locally (see APPENDIX 8).

l) History, within the last 2 years, of alcohol or drug abuse (in the opinion of the investigator), significant mental illness, or physical dependence on any opioid as per clinical discretion of the investigator.

m) **Not applicable per Revised Global Protocol v02** - History of illegal IV drug use within the 3 years prior to screening.

n) History of major surgery within 3 months of screening; this includes but is not limited to surgery that involves a risk to the life of the participant, specifically, within the cranium, chest, abdomen, or pelvic cavity.

o) **Not applicable per Revised Global Protocol v02** - History of weight gain/loss ≥ 10% of body weight in the 6 months prior to the eligibility liver biopsy.

p) Inability to tolerate IV medication or other study procedures, eg, lack of venous access.

q) Inability to safely undergo a liver biopsy, in the opinion of the investigator.

r) **Not applicable per Protocol Amendment 03** - History of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (either suspected or confirmed) within 4 weeks prior to signing consent. Additionally, in the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and, based on investigator assessment in consultation with the Sponsor's Medical Monitor, there are no sequelae that would place the participant at a higher risk when receiving investigational treatment.

   NOTE: COVID reverse transcription - polymerase chain reaction (RT-PCR) viral testing may be required prior to Randomization based on specific country/local guidelines, and the results of this testing may impact study participation. Testing results should be discussed with the Medical Monitor to confirm eligibility.

s) History of alcohol consumption ≥ 21 units/week (male participants) or ≥ 14 units/week (female participants) within the 2 years prior to the biopsy used to determine eligibility. One drink "unit" or one standard drink is equivalent to 12 ounces (360 mL) of beer, 4 ounces (120 mL) of wine, or 1 ounce (30 mL) of hard liquor. Note: Participants should limit alcohol during their participation in the study (Section 6.4).

t) History of illegal IV drug use within the 2 years prior to screening.

u) **Not applicable per Protocol Amendment 03** - History of weight gain/loss ≥ 10% of body weight in the 3 months prior to the eligibility liver biopsy and any significant weight changes (± 10% of body weight) during screening.

v) History of severe COVID-19 infection (either suspected or confirmed) within 4 weeks prior to signing consent or a previous mild or moderate COVID-19 infection within 10 days prior screening. Additionally, for any COVID-19 infection prior to enrollment, symptoms must have completely resolved and, based on investigator assessment in consultation with the Sponsor's Medical Monitor, there are no sequelae that would place the participant at a higher risk when receiving investigational treatment.

   NOTE: COVID reverse transcription - polymerase chain reaction (RT-PCR) viral testing may be required prior to Randomization based on specific country/local guidelines, and the

results of this testing may impact study participation. Testing results should be discussed with the Medical Monitor to confirm eligibility.

w) Any significant weight changes (± 10% of body weight) in the 3 months prior and during screening.

3) Prior and concomitant therapy

a) Participants taking any OTC vitamin A-containing supplements or multivitamins, or vitamin A-containing medications after signing the ICF.

b) Participants unable to comply with restrictions and prohibited treatments.

c) **Not applicable per Revised Global Protocol v02** - Participants who have taken other investigational agents within 3 months prior to the liver biopsy used to confirm eligibility or within 12 weeks or 5 half-lives prior to the first dose of study treatment, whichever is longer.

d) Prior exposure to BMS-986263.

e) The participant has received recent treatment with alternative therapies, which, in the opinion of the investigator, could potentially confound clinical or laboratory assessments (eg, herbal supplements).

f) Concomitant use of nintedanib is prohibited. Prior use of nintedanib is permitted but must be discontinued at least 3 days before the first dose of study treatment.

g) **Not applicable per Protocol Amendment 03** - Participants who have received live attenuated vaccine or investigational SARS-CoV-2 vaccine within 3 months prior to the first dose of study treatment. Participants who have received a vaccine approved for Emergency Use Authorization by the United States (US) Food and Drug Administration (FDA) may be considered for inclusion, after discussion with the Medical Monitor.

h) Participants who have taken other investigational agents except for investigational SARS-CoV-2 vaccine within 3 months prior to the liver biopsy used to confirm eligibility or within 12 weeks or 5 half-lives prior to the first dose of study treatment, whichever is longer.

i) Participants taking any anticoagulants after signing the ICF.

j) Participants who have received live attenuated vaccine or investigational SARS-CoV-2 vaccine within 3 months prior to the first dose of study treatment. Participants who have received a vaccine approved for Emergency Use Authorization by the United States (US) Food and Drug Administration (FDA) or other applicable country-specific regulatory agencies may be considered for inclusion.

4) Physical and laboratory test findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population.

b) The participant's baseline laboratory test results include abnormal values considered to be clinically significant by the investigator.

c) **Not applicable per Revised Global Protocol v02** - The participant's laboratory test results at screening include any of the following:

- Albumin < 3.5 g/dL

Approved v5.0 930147586 4.0

- INR > 1.4 (participants who have an INR > 1.4 and who are taking an anticoagulant known to prolong INR may be included after discussion with the Medical Monitor)
- ALT value ≥ 5× the ULN
- AST value ≥ 5× the ULN
- Total bilirubin > 1.5 mg/dL, unless participant has a diagnosis of Gilbert Syndrome and direct bilirubin ≤ ULN
- Platelet count < 140,000/µL
- Hemoglobin A1c ≥ 9.0%
- Serum vitamin A (retinol) > ULN

d) Glomerular filtration rate < 30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease equation at screening.

e) Centrally-read DXA scan BMD T-Score of -2.5 or less at the femoral neck, total hip, or lumbar spine during screening (in participants 40 years of age or older).

f) **Not applicable per Protocol Amendment 03** - The participant's laboratory test results at screening include any of the following:

- Albumin < 2.8 g/dL
- INR > 2.2
- ALT value ≥ 5× the ULN
- AST value ≥ 5× the ULN
- Total bilirubin > 3.0 mg/dL, unless participant has a diagnosis of Gilbert Syndrome and direct bilirubin ≤ ULN
- Platelet count < 85,000/µL
- Hemoglobin A1c ≥ 9.0%
- Serum vitamin A (retinol) > ULN

g) The participant's laboratory test results at screening include any of the following:

- Albumin < 2.8 g/dL
- International normalized ratio (INR) > 2.2
- ALT value ≥ 5× the ULN
- AST value ≥ 5× the ULN
- Total bilirubin > 3.0 mg/dL, unless participant has a documented diagnosis of Gilbert Syndrome, provided that total bilirubin is < 4.0 mg/dL and direct bilirubin is ≤ ULN
- Platelet count < 85,000/µL
- Hemoglobin A1c ≥ 9.5%
- Serum vitamin A (retinol) > ULN

5) Allergies and adverse drug reaction

a) Not applicable per Revised Global Protocol v01.

b) History of allergies to soybeans or eggs.

Approved v5.0 930147586 4.0

c) History of allergy [redacted]

6) Other exclusion criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

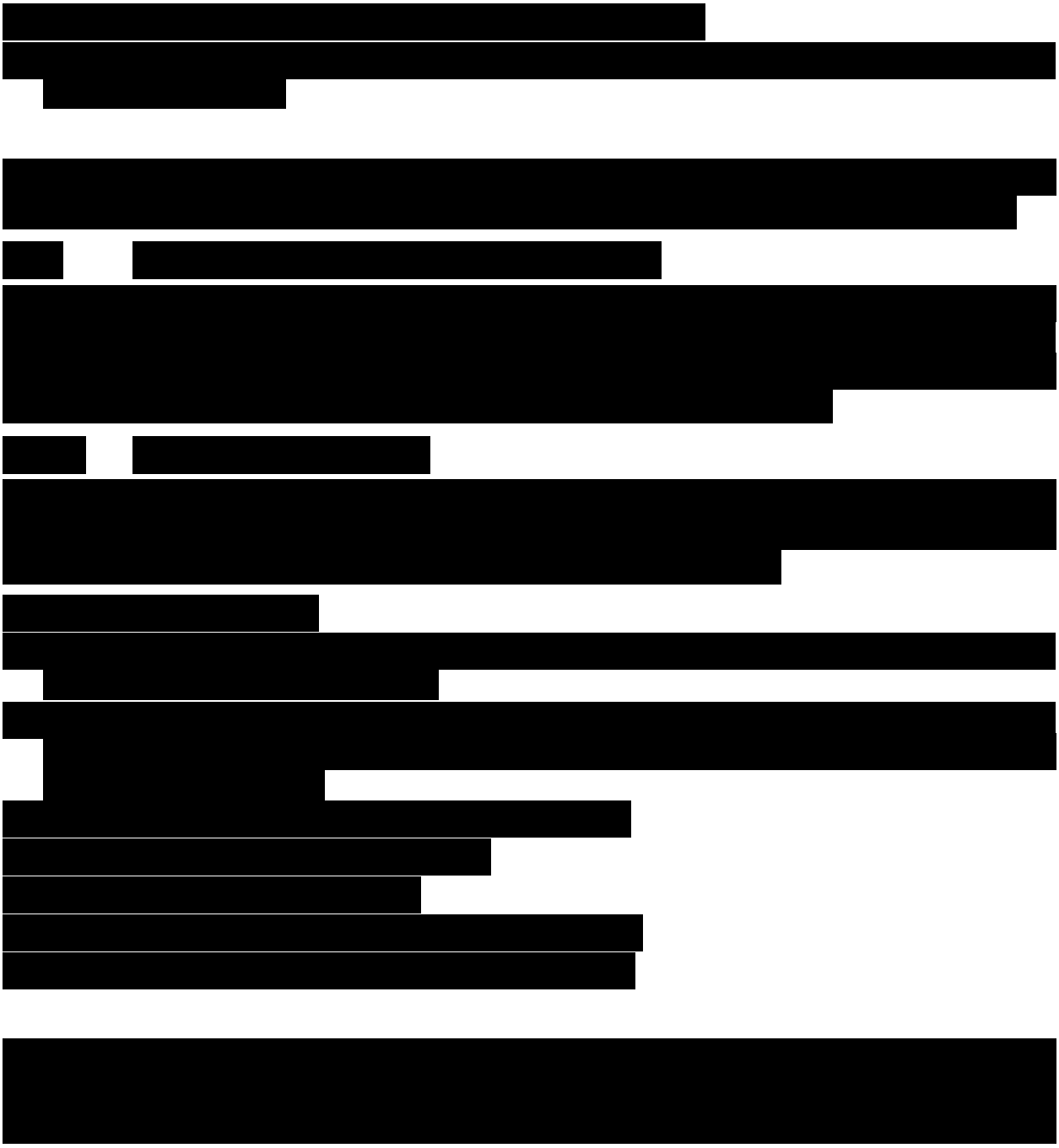
b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

c) Any factor, which in the opinion of the investigator would jeopardize the evaluation or safety or be associated with poor adherence to the protocol.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

[redacted]

Approved v5.0 930147586 4.0



6.4 Lifestyle Restrictions

Participants should not consume ≥ 7 units/week of alcohol during the study. One drink "unit" or 1 standard drink is equivalent to 12 ounces (360 mL) of beer, 4 ounces (120 mL) of wine, or 1 ounce (30 mL) of hard liquor.

During the study, OTC herbal supplements or multivitamins containing vitamin A (including Cod liver oil), or other medications that may contain vitamin A are prohibited (Section 7.7.1). Prior to starting study treatment and throughout the study, the investigator will educate participants about vitamin A-containing foods, medications, and herbal supplements

Approved v5.0 930147586 4.0

(https://ods.od.nih.gov/factsheets/VitaminA-Consumer, or equivalent country-specific national dietary recommendations), as well as the signs and symptoms of [redacted]. Consultation with a nutritionist should be considered if necessary.

6.5 Dietary and Lifestyle Counseling

At the screening visit, after receiving the signed ICF, sites will provide all participants with the following dietary and lifestyle counseling:

- Reduce body weight (if obese or overweight) through diet and exercise
- Follow a balanced diet
- Increase physical activity
- Avoid alcohol as much as possible

6.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study (ie, enroll) but are not subsequently randomized into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs. [redacted]

6.6.1 Retesting During Screening Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pretreatment failure (ie, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented.

Retesting of laboratory parameters and/or other assessments within any single screening or lead-in period will be permitted (in addition to any parameters that require a confirmatory value). The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state. Laboratory parameters and/or assessments that are included in Table 1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Participants who are screen failures may be rescreened only once; additional rescreening may be allowed after consultation with the Medical Monitor. An additional rescreening is permitted for study participants who have failed screening due to SARS-CoV-2 infection. All participants who are re-enrolled will be assigned a new participant identification. For participants who are rescreened, [redacted] DXA scan assessments can be reused without repeating if performed 3 months prior to rescreening visit (Section 2).

Approved v5.0 930147586 4.0

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both investigational [medicinal] product (IP/IMP) and non-investigational [medicinal] product (nonIP/nonIMP) as shown in Table 5.

An IP, also known as IMP in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as nonIP.

Table 5: Study Treatments

Product Description/Class and Dosage Form	Potency	IP/ NonIP	Blinded or Open-Label	Packaging/ Appearance	Storage Conditions (Per Label)
BMS-986263 for injection	10 mg per vial; 3 mg/mL after reconstitution	IP	Blinded[a]	[redacted]	[redacted]
Placebo[b] for BMS-986263 for injection/ [redacted]	NA	IP	Blinded[a]	[redacted]	[redacted]

IP = investigational product; IV = intravenous; NA = not applicable

[a] The medication is provided to the pharmacy open-label, and an unblinded pharmacist (or another appropriately delegated qualified individual) will prepare the blinded solutions for IV infusion.

[b] [redacted]

Approved v5.0 930147586 4.0

7.1 Treatments Administered

The investigator must ensure that the IP will be used only in accordance with the protocol and Pharmacy Manual. The selection and timing of dose for each participant is shown in Table 6.

Table 6: Study Treatment Doses, Dosing Frequency, and Route of Administration

Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Frequency of Administration	Route of Administration
45 mg BMS-986263	[redacted]	QW	IV infusion
90 mg BMS-986263		QW	IV infusion
Placebo		QW	IV infusion

IV = intravenous; QW = once every week

Treatment Preparation

An unblinded pharmacist (or another appropriately delegated qualified individual) will prepare matching IV infusion solutions [redacted] according to the participant's treatment assignment (Section 7.2). [redacted]

Please refer to the Pharmacy Manual for complete information on BMS-986263 and placebo storage, handling, and exact volumes, and instructions on the preparation of study treatment infusion.

Treatment Administration

The study treatment will be infused using an IV pump, as described in the Pharmacy Manual. The IV access will be kept open before and after the infusion with sufficient quantities of 0.9% saline or 5% dextrose in water to assure it remains patent. The time the infusion is initiated/adjusted/concluded, including any interruptions, will be documented in the electronic case report form (eCRF).

Study treatment infusions should be administered on the same day of each week to the extent that this is possible with a window of ± 3 days. Infusions must be separated by at least 3 days. At the study treatment infusion visits, all study procedures and assessments must be completed prior to initiation of the study treatment infusion (with the exception of PK samples collected during and postinfusion). When fasting is required for the preinfusion study procedures, participants may eat once all of the preinfusion testing and assessments are performed.

Approved v5.0 930147586 4.0

7.1.1 Study Treatment Infusion Rate

The study medication is suggested to be infused in a step-wise approach as described below, as used in the IM025006 final clinical study report (CSR)[34]. The total dose of the study medication should not be infused in less than 60 minutes. The initial rate of the administration should not be any greater than the initial rate specified below.

Recommended blinded treatment stepped titration infusion rates:

[redacted]

The infusion rates may be decreased by the investigator based on the participant's previous tolerance of the infusion, including any IRRs that may have occurred in the past. Consultation with the Medical Monitor is recommended if any other modification of these recommended infusion rates is being considered. In addition, the investigator may choose to pause the infusion depending on the participant's clinical condition and history. If clinical signs and/or symptoms indicate an IRR, the infusion may be interrupted. If the infusion is interrupted for any reason, the infusion may be restarted at the discretion of the investigator.

Additional details on IRRs, including the management of IRRs, are provided in Section 9.2.9.

7.1.2 Premedication

Based on the discretion of the investigator, the participants may be administered IV or oral premedication approximately [redacted], respectively, before the start of the study treatment infusion. The investigator may choose to administer IV antihistamines (eg, diphenhydramine hydrochloride 50 mg, famotidine 20 mg) or oral antihistamines (eg, levocetirizine 5 mg) and/or IV corticosteroids (eg, hydrocortisone 100 mg or methylprednisolone sodium succinate 125 mg).

Participants who receive antihistamine premedication should be advised that the premedication may be sedating and cautioned against driving or operating heavy machinery for at least 3 hours after administration. For sites participating in the [redacted], the pretreatment [redacted] activities must be completed prior to the start of any premedication.

7.2 Method of Treatment Assignment

At the time of the screening visit, before any study-related procedures are performed, the investigative site will access the enrollment option of the IRT system for assignment of a subject number. This number is assigned sequentially by the system and will be unique across all sites. If a potential participant is rescreened, a new identification number will be used.

Before the study is initiated, each user (at investigative sites) will receive log-in information and directions on how to access the IRT. Study treatment will be dispensed and administered at the study visits as listed in SOA (Section 2).

Approved v5.0 930147586 4.0

Eligible participants will be centrally randomized using IRT to receive BMS-986263 or placebo according to a computer-generated block randomization scheme and in accordance with stratification criteria. Randomization to a treatment group will be assigned prior to dosing.

7.3 Blinding

7.3.1 Maintaining the Blind

Blinded treatment assignments will be managed using IRT. All infusion solutions (prepared by an unblinded pharmacist (or another appropriately delegated qualified individual) at the investigative site per the Pharmacy Manual) are matching in appearance, and will be supplied as shown in Table 6. Investigative site staff, Sponsor and designee personnel, and participants and their families will remain blinded to treatment assignments.

The investigative site staff will include the following:

- An unblinded pharmacist (or another appropriately delegated qualified individual), who will be responsible for preparing the infusion solutions and providing in a blinded manner to the study team, ensuring that the infusion solutions are protected from light as described in the Pharmacy Manual. The unblinded pharmacist (or another appropriately delegated qualified individual) must not reveal potentially unblinding information to the study team.

7.3.2 Circumstances for Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary (ie, that it will alter the participant's immediate medical management). In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual TASK of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The principal investigator or appointed designee should only call in for emergency unblinding AFTER the decision to unblind the participant has been documented.

In case of an emergency, the investigator has unrestricted access to randomization information via IRT and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. After the unblinding, the investigator shall notify the Medical Monitor and/or Study Director. The method of unblinding for emergency purposes is described in the reference manual(s).

Approved v5.0 930147586 4.0

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind. Any request to unblind a participant for nonemergency purposes should be discussed with the Medical Monitor.

Designated staff of BMS Research & Development may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of PK samples [redacted]. A bioanalytical scientist in the Bioanalytical Sciences department of BMS Research & Development (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

The study will be unblinded once all participants have completed the Follow-up Week 4 visit and all data have been collected through that time point to facilitate analyses (Section 10.4.4).

7.4 Dosage Modification

No reductions or modifications of the assigned dose are allowed. If the infusion is interrupted for any reason, the infusion may be restarted at the discretion of the investigator. If an incomplete dose is administered at any visit, the participant will resume the assigned dose/administration schedule at the next visit. See Section 9.2.9 for management of IRRs.

7.5 Preparation/Handling/Storage/Accountability

The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

[redacted]

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and BMS contacted immediately.

Please refer to the Pharmacy Manual for IP preparation.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

The IP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration, and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Approved v5.0 930147586 4.0

Further guidance and information for final disposition of unused study treatment are provided in APPENDIX 2.

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

7.6 Treatment Compliance

Not applicable.

7.7 Concomitant Therapy

All medications taken from 4 weeks prior to the screening visit until the last study visit must be recorded on the eCRF. Prior medications are defined as medications taken within 4 weeks of the screening visit. Concomitant medications are defined as any medication taken after the first dose of study medication until the last study visit. Concomitant medications (prescription, OTC, or herbal) should be administered during the study only if they are prescribed for treatment of specific clinical events.

Participants taking vitamin E, SGLT2 inhibitors, GLP-1 receptor agonists, anti-obesity agents, or an approved NASH treatment at stable doses prior to screening (as specified in Section 6.1) should maintain stable dosing throughout the entire study. In certain circumstances, dose modifications of concomitant medications may be made based upon the investigator's clinical judgement, after consultation with the Medical Monitor.

SARS-CoV-2 vaccines approved for Emergency Use Authorization by local regulatory agency that are not live attenuated are allowed during the study and should be handled in the same manner as other vaccines.

7.7.1 Prohibited and/or Restricted Treatments

Restrictions and prohibitions on prior and concomitant medications and/or treatments are as follows:

1) Prior exposure to BMS-986263 is prohibited.
2) NASH therapies with only accelerated approval from the US FDA or conditional approval from the European Medicines Agency are prohibited from the time of the liver biopsy to confirm eligibility until Week 12 or early termination.
3) OTC herbal supplements or multivitamins containing vitamin A (including Cod liver oil), or other medications that may contain vitamin A are prohibited after signing the ICF and throughout the study.
4) Other investigational agents. Any other investigational agent must be discontinued at least 3 months prior to the liver biopsy used to confirm eligibility or within 12 weeks or 5 half-lives prior to the first dose of study treatment, whichever is longer.
5) Medical or surgical treatments for obesity should not be initiated while the participant is participating in the study.
6) Concomitant use of nintedanib is prohibited. Prior use of nintedanib is permitted but must be discontinued at least 3 days before the first dose of study treatment.

Approved v5.0 930147586 4.0

7) Participation in other interventional clinical trials.
8) Use of anticoagulants is prohibited after signing the ICF and throughout the study, unless needed in the opinion of the investigator for safety reasons after Randomization.

[redacted]

7.8 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS-supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that each participant receives appropriate standard of care to treat the condition under study.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns or other reasons; b) the development of BMS-986263 is terminated for any reason, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue IP (and non-IP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study and/or program by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Symptoms, physical exam findings, or laboratory abnormalities consistent with [redacted] that, at the discretion of the investigator, cannot be explained by another cause.

Approved v5.0 930147586 4.0

- For participants with normal Day 1 (Randomization) liver enzymes, total bilirubin, and INR, if there is new elevation of ALT or AST > 3 × ULN, repeat testing should be performed within 48 hours to 72 hours. If elevation persists, then DILI discontinuation criteria will be applied and study treatment will be discontinued if any of the following occur:
  - ALT or AST > 8 × ULN
  - ALT or AST > 5 × ULN for more than 2 weeks
  - ALT or AST > 3 × ULN and (total bilirubin > 2 × ULN or INR > 1.5)
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

    Note: If necessary, a local laboratory may be used for repeat testing, and results should be promptly communicated to the site. The site should also promptly communicate results to BMS. Participants meeting the criteria above may have potential DILI, see Section 9.2.7 for reporting requirements.

- For participants with elevated AST, ALT, or total bilirubin at Day 1 (Randomization), if there is a new elevation of ALT or AST > 2 × baseline, or total bilirubin > 1.5 × Day 1 total bilirubin (and to > ULN), repeat testing should be performed within 48 hours to 72 hours. If elevation persists, then study treatment will be discontinued if any of the following occur:
  - ALT or AST levels increase to > 5 × Day 1 (Randomization) measurement
  - ALT or AST levels increase > 2 × Day 1 (Randomization) measurements AND the increase is accompanied by a concomitant increase in total bilirubin to > 2 × Day 1 bilirubin or the INR concomitantly increases by > 0.3
  - Appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

    Note: If necessary, a local laboratory may be used for repeat testing, and results should be promptly communicated to the site. The site should also promptly communicate results to BMS. Participants meeting the criteria above may have potential DILI, see Section 9.2.7 for reporting requirements.

- Clinical signs of hepatic decompensation, including ascites, variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis.
- Liver transplantation or planned liver transplant during the study.
- HCC.
- Any significant protocol violation (eg, demonstrated lack of treatment compliance). The violation should be discussed with the Medical Monitor prior to discontinuing the participant. Waivers for protocol violations will not be provided by the Sponsor or the Medical Monitor.
- The participant becomes pregnant (study treatment must be discontinued immediately). In the case of pregnancy (Section 9.2.5), the investigator must notify the Medical Monitor/designee of this event within 24 hours of awareness of the pregnancy. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.
- Emergency unblinding performed by principal investigator.

Approved v5.0 930147586 4.0

See the SOA (Section 2) for details on the data to be collected at the time of treatment discontinuation and follow-up and any further evaluations that need to be completed.

Participants are not to be replaced. If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate eCRF page. As indicated, appropriate follow-up and/or alternate medical care must be arranged for the participant.

Participants who discontinue study treatment before the Week 11 visit will have an ETT visit and will continue into the 24-week follow-up period. AEs and SAEs will be followed-up in line with Section 9.2.3 and APPENDIX 3.

8.1.1 Poststudy Treatment Study Follow-up

Participants who discontinue study treatment prior to last dose will have an ETT visit and will continue into the 24-week follow-up period. All participants who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in Table 2 and Table 3 of the SOA (Section 2). The only exception to these requirements is when a participant withdraws consent for all study procedures, including posttreatment study follow-up, or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. See the SOA (Section 2, Table 2 and Table 3) for details on the data to be collected at the time of treatment discontinuation and follow-up and any further evaluations that need to be completed. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate eCRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Assessments for the end of treatment/EOS visit must be performed, provided that the participant has not withdrawn consent for these activities.
- All required eCRF pages must be completed, including the date of, and explanation for, the withdrawal.
- As indicated, appropriate follow-up and/or alternate medical care must be arranged for the participant.

Approved v5.0 930147586 4.0

[redacted]

8.3 Lost to Follow-up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the SOA (Section 2).
- Protocol waivers or exemptions are not allowed.

Approved v5.0 930147586 4.0

- All immediate safety concerns must be discussed with the Medical Monitor immediately upon occurrence or awareness, to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before Randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the SOA (Section 2).

9.1 Efficacy Assessments

Every effort must be made to ensure that the same evaluator(s) completes the assessment for each participant. If the evaluator(s) is unable to complete the evaluation, then a qualified individual with overlapping experience may perform the assessment. Documentation of who performed the assessment is to be recorded in source documents. Assessments should be performed at approximately the same time of day throughout the duration of the study. Day 1 (Randomization) assessments must be performed per protocol (standard of care assessments may not be used for baseline). Procedures not specified in the protocol that are part of standard of care may be performed if they do not interfere with study procedures; any data arising from such procedures are not to be reported in the eCRF.

[redacted]

9.1.2 Liver Biopsy Assessments

Efficacy endpoints will be assessed from liver biopsy samples. The following will be used as primary and secondary efficacy endpoint assessments:

- Histological Assessments (Section 9.1.2.1)
  - NASH CRN Fibrosis Score
  - NAFLD Activity Score (NAS)
  - Modified Ishak Score
- Morphometric Analysis of collagen proportionate area (CPA) (Section 9.1.2.2)

Approved v5.0 930147586 4.0

Liver biopsy assessments (performed by central pathology) are used to screen for study eligibility and to evaluate efficacy. A historical biopsy may be acceptable to determine eligibility, if (1) the liver biopsy was performed within 12 months prior to screening, as defined in Section 6.1, and (2) adequate sample is available for assessment by central pathology. If a historical biopsy is unavailable, a liver biopsy will be performed during screening and will be assessed by central pathology reading to determine eligibility. A percutaneous liver biopsy is preferred to a transjugular biopsy. The investigator must consult with the Medical Monitor prior to performing a transjugular biopsy. Participants must have a liver biopsy demonstrating NASH CRN Fibrosis Score Stage 4 liver fibrosis (as determined by central pathology) and meeting all other liver biopsy-related inclusion and exclusion criteria as defined in Section 6.1 and Section 6.2, respectively, to be eligible. Liver biopsy assessments at screening may be shared with the sites. Any local incidental findings of potential clinical relevance identified at screening that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment. Participants who have a prolonged INR and/or lower platelet count may receive treatments to correct coagulation abnormalities and/or low platelet counts prior to liver biopsy based on investigator's clinical judgment in order to reduce the risk of bleeding. It is the investigator's responsibility to assess any potential risks that may be associated with the use of these agents (eg, transfusion of fresh/frozen plasma or platelets).[37] Additional details on liver biopsy sample collection, preparation, and submission, as well as central pathology procedures are described in the Laboratory Manual.

Tissue from biopsies performed during the study will be collected for analysis. Histological assessments related to efficacy of BMS-986263 will be performed by central pathology reading. The on-treatment liver biopsy results will remain blinded to site personnel until at least post-database lock. If local pathology assessment is necessary, a portion of the sample should be submitted to a local pathologist following the standard procedure utilized by the study site. Any local incidental findings of potential clinical relevance identified at this post-baseline assessment that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment.

Liver tissue should be collected using a 16-gauge (or larger lumen) cutting needle (eg, Bard, Microvasive, or TruCut) whenever possible. Use of suction needles (eg, Menghini, Jamshedi, or Klatskin) should be avoided because they may cause fragmentation of fibrotic specimens and impede the evaluation of fibrosis.[38] Use of suction needles should be discussed with the Medical Monitor. At least 2 cm length of tissue should be obtained. Additional details on the acquisition, quality requirements, histological preparation, and shipping of histological samples are in the Laboratory Manual.

9.1.2.1 Histological Scoring

For associated endpoints, the NASH CRN system[39] will be used to score the histologic samples by the central pathologist and results are reported as the NASH CRN Fibrosis Score and the NAS. The NASH CRN system is based on the concept that stage of fibrosis and necroinflammatory lesions should be evaluated separately; it assesses liver biopsies for degree of fibrosis (0 to 4), steatosis (0 to 3), lobular inflammation (0 to 3), and hepatocellular ballooning (0 to 2).

Approved v5.0 930147586 4.0

NASH CRN Fibrosis

For the NASH CRN Fibrosis Score, fibrosis is staged on a 0 to 4 scale: 0 (none); 1 (perisinusoidal or periportal fibrosis); 2 (perisinusoidal and portal/periportal fibrosis); 3 (bridging fibrosis); 4 (cirrhosis).

NAS

Steatosis, lobular inflammation, and ballooning scores are added together in an unweighted fashion to determine the NAS, which ranges from 0 to 8 (Table 7).

The NAS should not be considered a replacement for the diagnosis of NASH.

Table 7: NAS Scoring System

Histology Variable	Grade	Score
Steatosis	< 5%	0
	5 – 33%	1
	> 33 – 66%	2
	> 66%	3
Lobular Inflammation[a]	None	0
	< 2	1
	2 – 4	2
	> 4	3
Ballooning	None	0
	Few	1
	Many	2

NAS = NAFLD Activity Score

[a] Foci per x 200 field

Modified Ishak Score

A modified Ishak scoring system[40] will be used as a secondary endpoint to grade fibrosis in the histologic samples. The Ishak system (0 to 6 scale) was originally developed to grade portal-based liver fibrosis associated with viral hepatitis. The modified Ishak system has been adapted to grade central-based liver fibrosis associated with NASH, and it also uses a 0 to 6 scale:

- 0: No fibrosis
- 1: perisinusoidal or periportal fibrosis
- 2: perisinusoidal and portal/periportal fibrosis
- 3: bridging fibrosis with linkage of < 50% of vascular structures (portal and centrilobular)
- 4: bridging fibrosis with linkage of > 50% of vascular structures (portal and centrilobular)
- 5: early or incomplete cirrhosis

Approved v5.0 930147586 4.0

- 6: established or advanced cirrhosis

9.1.2.2 Morphometric Analysis of CPA [redacted] in Stained Tissue

Assessment of CPA is a method by which the amount (percentage) of collagen in stained tissue sections is analyzed using morphometric image analysis. This allows for a quantitative assessment of fibrosis. [redacted] in stained tissue sections is also analyzed using morphometric image analysis.

Analysis of CPA is included as a secondary endpoint [redacted].

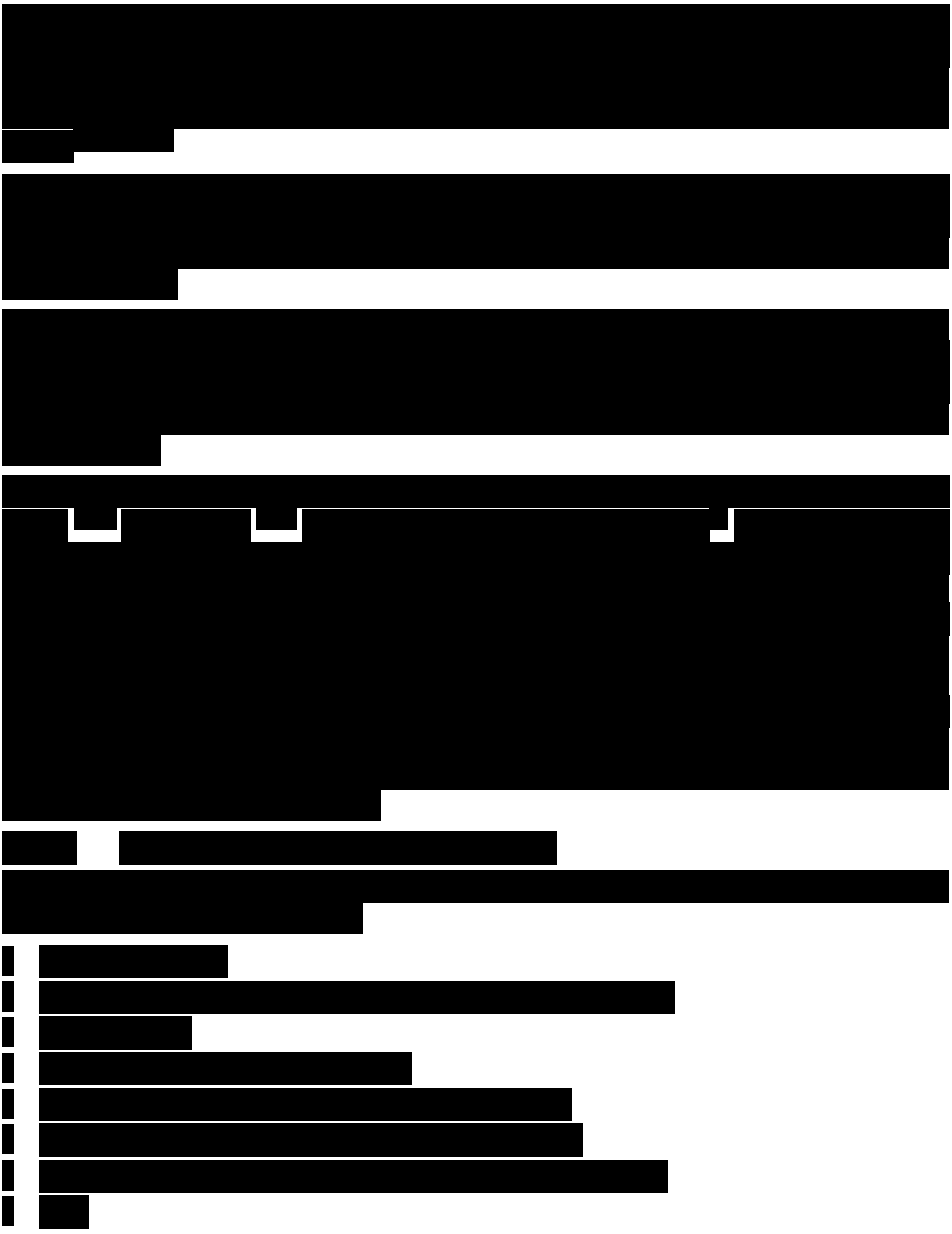
Approved v5.0 930147586 4.0

[redacted]

Approved v5.0 930147586 4.0

[redacted]

Approved v5.0 930147586 4.0



Approved v5.0 930147586 4.0

[redacted]

Approved v5.0 930147586 4.0

[redacted]

9.2 Adverse Events

The definitions of an AE or SAE can be found in APPENDIX 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Contacts for SAE reporting specified in APPENDIX 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until discharge, at the time points specified in the SOA (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants. The Reference Safety Information in Sections 5.6.1 and 5.6.2 of the IB[7] should be used to determine the expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation of dosing (or participant's participation in the study if the last scheduled visit occurs at a later time).

- The investigator must report any SAE that occurs after this time period and that is believed to be related to study treatment or protocol-specified procedure (eg, a follow-up skin biopsy).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF.
- All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in APPENDIX 3.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor or designee.

The method of evaluating intensity and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in APPENDIX 3.

Approved v5.0 930147586 4.0

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

Participants will be queried for symptoms suggestive of vitamin A toxicity including but not limited to dry skin, vaginal dryness, cheilosis, gingivitis, muscle and joint pains, fatigue, mental dullness, and depression.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution, or stabilization, or reported as SAEs if they become serious (APPENDIX 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the EOS treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the eCRF. Completion of supplemental eCRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (AESI) (defined in Section 9.2.8) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in APPENDIX 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will report AEs to regulatory authorities and IECs according to local applicable laws including European Directive 2001/20/EC and the following FDA CFRs: 21 CFR Part 312 and Part 320. A Suspected Unexpected Serious Adverse Reaction is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives (20 days) after study product administration, the study treatment must be discontinued

Approved v5.0 930147586 4.0

immediately and the investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to the Sponsor or designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in APPENDIX 3.

The investigator must also notify the Medical Monitor or designee of this event within 24 hours of awareness of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the AE eCRF page:

- Any laboratory test result that is clinically significant or meets the definition of an AE or SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

If a laboratory test result meets the definition of an AE or SAE, the laboratory test result should be reported as an AE or SAE and submitted to the Sponsor or designee, as specified in APPENDIX 3.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

9.2.7 Potential DILI

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. The definition of potential DILI, as well as study treatment discontinuation criteria, are provided in Section 8. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see APPENDIX 3 for reporting details). Participants who meet criteria for potential DILI should have relevant laboratory testing (eg, ALT, AST, total bilirubin, and INR) repeated at least weekly until abnormalities have resolved or returned to baseline. Tests should be repeated within 3 days; then within every 3 days thereafter until reversal is noted; and thereafter, every week until normalization (or return to baseline). The investigator should make every effort to determine if any other cause for the liver test abnormalities is present.

Approved v5.0 930147586 4.0

9.2.8 Adverse Events of Special Interest

All AEs and SAEs that arise in the study will be reported and investigated. However, because of the characteristics of the disease under study and BMS-986263 in particular, some AEs are considered AESI. AESI may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the BMS-986263 clinical development program, bone fractures, IRRs, and anaphylaxis have been identified as potential AESI; however, there has been no definitive assessment of the causal relationship between these events and treatment with BMS-986263.

9.2.9 Infusion-related Reactions

An IRR is defined as: Any AE that occurs after the start and within 24 hours after the start of infusion of the IP and meets at least 1 of the following criteria:

- Considered to be at least possibly related to the IP.
- Resulted in interruption of infusion.
- Resulted in change of the infusion rate.
- Was considered by the investigator to be an IRR.

Note: Local reactions related to the infusion site are not considered IRRs.

In previous clinical studies of BMS-986263, in participants who experienced IRRs, back pain was the most common symptom reported for these IRRs. Other signs and symptoms less commonly associated with IRRs included, but were not limited to the following: hot or warm sensation, flushing, throat constriction, shortness of breath, chest tightness, tachypnea, tachycardia, hypertension, urticaria, pruritus, and/or erythema. These reactions routinely had a rapid onset within [redacted] after start of the infusion and were generally short lasting with most resolving within [redacted] of their occurrence.

The details of IP administration and infusion rate for this study are provided in Section 7.1.

If a participant experiences an IRR, temporary interruption of the infusion and/or reduction of the infusion rate may lead to improvement of signs and symptoms. The infusion may be restarted, at the discretion of the investigator, after signs and symptoms of IRRs have abated.

Medications, emergency equipment, and trained personnel able to treat immediate or delayed IRRs should be available for immediate access at the clinical site(s).

9.2.10 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, x-ray filming, or any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

Approved v5.0 930147586 4.0

9.3 Overdose

For this study, any dose of BMS-986263 for injection > 10% above the assigned dose (eg, [redacted] of study drug infusion) within a 24-hour time period will be considered an overdose. See APPENDIX 3 for AE/SAE reporting requirements for overdose.

In the event of an overdose, the investigator should do the following:

1) Contact the Medical Monitor immediately.
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until BMS-986263 can no longer be detected systemically (at least 20 days).
3) Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (on a case-by-case basis).
4) Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

9.4 Safety

Planned time points for all safety assessments are listed in the SOA (Section 2). All urgent safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.

The safety and tolerability of BMS-986263 will be assessed by evaluation of the incidence of all AEs (including AESI) and SAEs, laboratory results (including assessment of potential DILI), vital signs, physical examinations, ECG monitoring, [redacted] IRR monitoring, and change in BMD.

The participants must not have documented bone abnormalities at baseline as defined in the exclusion criteria (Section 6.2). DXA scan will be used to assess BMD.

9.4.1 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report. A central laboratory will perform the analyses and will provide reference ranges for these tests, except as noted below.

Hematology, serum chemistry, and urinalysis assessments are listed in Table 8.

Table 8: Hematology, Chemistry, and Urinalysis Assessments

Hematology		
• CBC with differential • PT • PTT • INR	• RBC • WBC (absolute) • Hemoglobin • Hematocrit • MCV	• MCH concentration • Red cell distribution width • Platelet count
Blood Chemistry		
• AST • ALT • Total bilirubin	• Creatine kinase • BUN • Uric acid	• Sodium • Potassium • Chloride

Approved v5.0 930147586 4.0

Table 8: Hematology, Chemistry, and Urinalysis Assessments

• Direct bilirubin • ALP • LDH • GGT • Creatinine	• Glucose • PTH • Total protein • Albumin	• Carbon dioxide • Calcium • Phosphorus • GFRa
Urinalysis		
• pH • Specific gravity • Protein (quantitative) • Albumin (quantitative) • Glucose	• Ketones • Leukocyte esterase • Nitrite • Creatinine • Microscopic examination (only to follow-up abnormal findings)	• Urine protein, total (quantitative) for urine protein to creatinine ratio • Urinary albumin to urinary creatinine ratio
Metabolic Panel (≥ 10 hours fast)		
• Lipid panel (triglycerides, total cholesterol, LDL, HDL)		
Other Analyses		
• FSH[b] • AFP	• HbA1c • Insulin	• Pregnancy test (WOCBP only; can be performed locally) • Serology/viral load (APPENDIX 7) • HIV testing must be performed where mandated by local requirements (APPENDIX 8), and the test will be performed at a local lab

AFP = alpha-fetoprotein; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; FSH = follicle-stimulating hormone; GFR = glomerular filtration rate; GGT = gamma-glutamyl transferase; HbA1c = hemoglobina A1c; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell; WOCBP = women of childbearing potential

[a] Estimated GFR, as calculated by the Modification of Diet in Renal Disease equation [56]

[b] FSH performed only in female participants < 55 years to confirm menopause (APPENDIX 4)

9.4.2 Vital Signs

Refer to SOA in Section 2 for timing of vital signs assessments.

9.4.3 Physical Examinations

Schedules for physical examinations are provided in the SOA (Section 2). Complete and/or abbreviated physical examinations may be performed by a Doctor of Medicine (MD) or equivalent,

Approved v5.0 930147586 4.0

or someone who is authorized to perform the examinations by training and has been delegated this task by the principal investigator.

A physical exam for signs of [redacted], including skin and oral mucosa changes and hepatomegaly, will be performed at visits listed in the SOA (Section 2).

A full examination will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, and extremities. If the screening full physical examination is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and Day 1 (abbreviated) physical examination.

Abbreviated physical exams will include an abdominal exam, assessments of ascites and hepatic encephalopathy, and symptom-focused assessments. An abbreviated examination may note any changes in the participant's condition (body systems) since the last assessment and does not preclude examination of any of the other body systems as clinically indicated. Every effort should be made to ensure the same evaluator will complete the examination for each participant at all visits throughout the study. Documentation of who performed the examination is to be recorded in source notes.

9.4.4 Electrocardiograms

Refer to SOA in Section 2 for timing of ECGs.

9.4.5 Imaging Safety Assessment – DXA Scan

DXA scan (hip [including femoral neck] and lumbar spine) will be performed at the time points indicated in the SOA (Section 2).

Image acquisition guidelines and submission processes will be outlined in the site imaging manual, to be provided by the central imaging vendor. The sites will be trained and qualified in imaging procedures prior to scanning the first study participant. All images will be submitted to the central imaging vendor for assessment of the BMD.

Adequacy of DXA scan must be determined by the central imaging vendor prior to Randomization. The site will be informed of quality issues or the need to repeat scanning from the central imaging vendor. Note that at least 1 of the requested anatomic sites (hip [including femoral neck] or lumbar spine) must be evaluable for participants to be eligible for the study (See Section 6.2).

Any local incidental imaging findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment.

[redacted]

Approved v5.0 930147586 4.0

[redacted]

9.5 PK [redacted] Sampling Schedule for BMS-986263

Blood for PK samples will be drawn according to the sampling schedule shown in [redacted] Blood for PK samples drawn on dosing days is strongly recommended to be taken from the contralateral arm to the IV drug administration. Information on the collecting, processing, and submission of samples to the central laboratory are in the reference manual(s).

[redacted]

Approved v5.0 930147586 4.0

[redacted]

Approved v5.0 930147586 4.0

[redacted]

Approved v5.0 930147586 4.0

Approved v5.0 930147586 4.0

[redacted]

Approved v5.0 930147586 4.0

[redacted]

Approved v5.0 930147586 4.0

[redacted]

Approved v5.0 930147586 4.0

[redacted]

Approved v5.0 930147586 4.0

[redacted]

Approved v5.0 930147586 4.0

[redacted]

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

In this study, approximately 270 participants will be randomized via IRT in a 1:1:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW by IV infusion in a double-blind manner. The primary endpoint is the proportion of participants with ≥ 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score) as determined by liver biopsy after 12 weeks of treatment.

Assuming a Chi-Square test with an $\alpha = 0.05$ and expected response rates for BMS-986263 90 mg, BMS-986263 45 mg, and placebo of 45%, 40%, and 20%, respectively, approximately 85 evaluable participants per treatment group in this study will have at least 80% power to detect superiority over placebo versus each dose, assuming a minimum difference of 20% from placebo. Accounting for a 6% dropout rate, approximately 90 participants will be randomized per treatment group.

10.2 Populations for Analyses

The following populations are defined for analysis purposes:

Population	Description
Enrolled	All participants who sign informed consent.
Randomized	All participants who are randomized to a treatment, analyzed as per randomized treatment.
Modified intent-to-treat (mITT)	All participants who are randomized to a treatment and receive at least 1 dose of study medication analyzed as per randomized treatment. All primary efficacy analyses will be conducted using this population.
PK	All participants who receive at least 1 dose of BMS-986263 and have any available concentration-time data.
Safety (As-treated)	All randomized participants who receive at least 1 dose of study treatment, analyzed according to the treatment actually received. All safety analyses will be conducted using this population.

Approved v5.0 930147586 4.0

10.3 Endpoints

10.3.1 Primary Endpoint

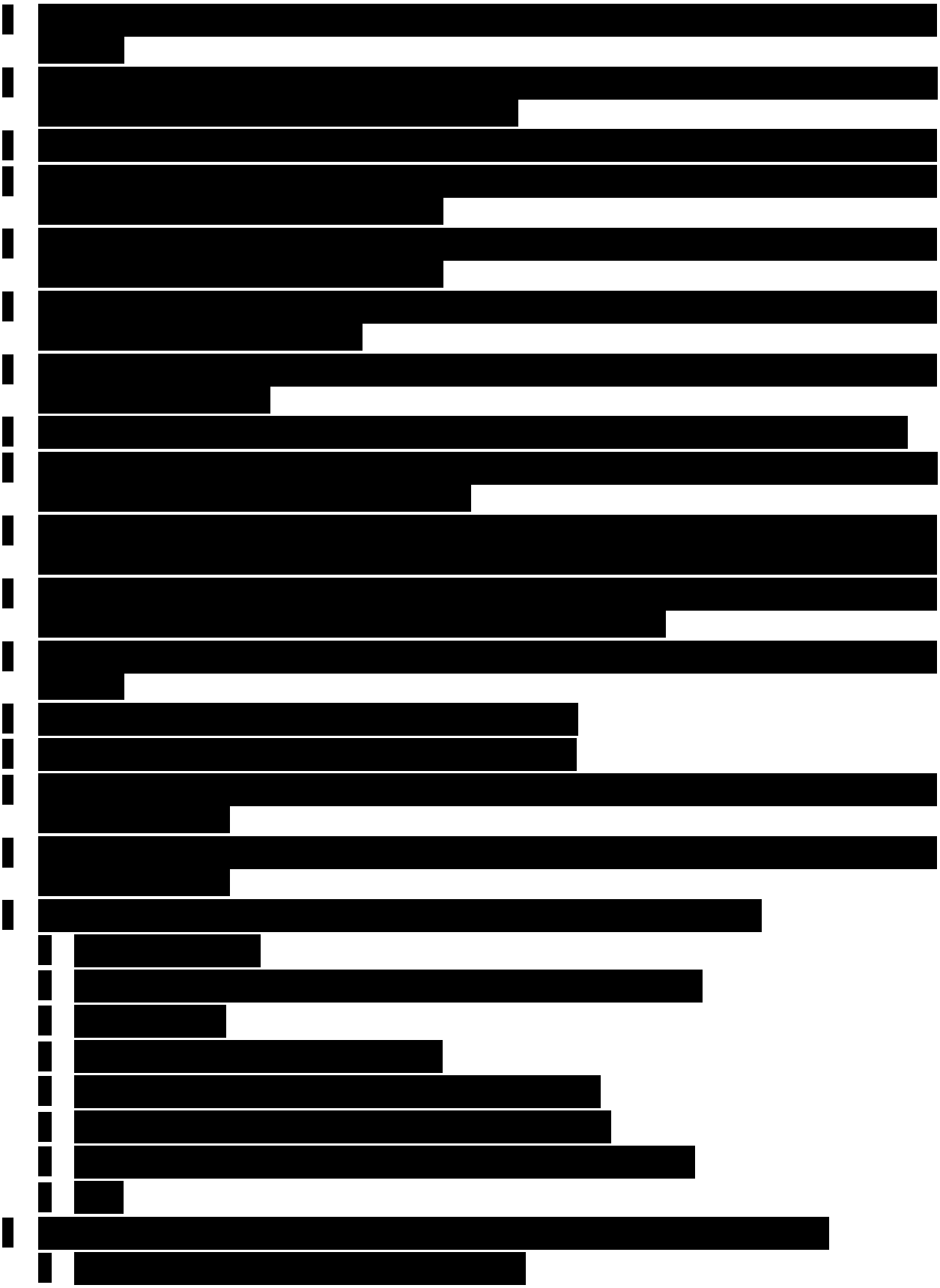
- Proportion of participants who achieve ≥ 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score), as determined by liver biopsy after 12 weeks of treatment

10.3.2 Secondary Endpoints

- Proportion of participants with ≥ 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score), with no worsening of NASH after 12 weeks of treatment (worsening of NASH is defined as an increase of the NAS by ≥ 1 point)
- Proportion of participants with ≥ 2 stage improvement in liver fibrosis (NASH CRN Fibrosis Score) after 12 weeks of treatment
- Proportion of participants with ≥ 1 stage improvement in liver fibrosis (modified Ishak score) after 12 weeks of treatment
- Proportion of participants with ≥ 2 stage improvement in liver fibrosis (modified Ishak score) after 12 weeks of treatment
- Change from baseline in CPA after 12 weeks of treatment
- Incidences of SAEs, AEs, clinical laboratory values, vital signs, physical examination findings, and ECGs
- Change from baseline in BMD, as measured by DXA scan, at Follow-up Week 24
- Plasma concentrations of siRNA, DPD, HEDC, and S104 (components of BMS-986263 for injection)

[redacted]

Approved v5.0 930147586 4.0



Approved v5.0 930147586 4.0

10.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to the first unblinding event of the study and will provide detailed specifications of the analysis of all efficacy endpoints and safety and will also describe the populations used for analyses and procedures for accounting for missing, unused, and spurious data.

This section provides a summary of planned statistical analyses.

10.4.1 Efficacy Analyses

Efficacy analyses will be performed using the mITT population. Participants who discontinue early and do not have an ETT liver biopsy or otherwise have the result from the liver biopsy missing will be considered a "nonresponder" for the evaluation of the primary endpoint and other binary endpoints based on liver biopsy.

Primary Endpoint: To evaluate the effect of BMS-986263 (90 mg QW and 45 mg QW) on NASH CRN Fibrosis Stage at Week 12, a 95.0% confidence interval (CI) of response rate for treatment versus placebo will be used to estimate the difference between the proportions of participants with ≥ 1 stage improvement in fibrosis on liver biopsy. Additionally, the odds ratio will be used to estimate improvement of treatment as compared with placebo for the proportion of participants with ≥ 1 stage improvement in fibrosis on biopsy at Week 12. A logistic regression will be performed with platelet count as continuous independent covariate and stratified by the Randomization strata with a Z-test statistic at a two-sided significance level of α◦=◦0.05 to assess the difference in distribution of response rate separately between each BMS-986263 treatment group and placebo. To control for the family-wise (two-sided) Type◦1◦error rate of α◦=◦0.05, the statistical tests will be performed in the following hierarchical order: 1) BMS-986263 90◦mg versus placebo, and 2) BMS-986263 45◦mg versus placebo. If the first comparison is not statistically significant, then the second comparison will be treated as descriptive in nature.

Secondary [redacted] Endpoints: No adjustment will be made for multiplicity for secondary [redacted] endpoints. Secondary [redacted] endpoints will be analyzed in a similar method as the primary endpoint unless otherwise specified in the SAP.

Selected continuous endpoints will be characterized using descriptive statistics and may be analyzed by analysis of covariance methods and/or by a mixed model for repeated measurements. Treatment differences at prespecified time points will be estimated using least squares means. Full details regarding this model and covariance structure will be provided in the SAP.

Categorical endpoints will be summarized using counts and percentages and when appropriate, may be analyzed using categorical analysis methods.

Approved v5.0 930147586 4.0

The stratified log-rank test and Kaplan-Meier estimate may be used to analyze time-to-event endpoints and will be specified in the SAP.

Subgroup analyses may be performed as specified in the SAP.

10.4.2 Safety Analyses

Safety analyses will be performed using the safety population. For analysis, all treatment-emergent AEs recorded that occur during the conduct of the study will be listed and summarized by system organ class, preferred term, and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. ECG readings will be evaluated by the investigator and abnormalities, if present, will be summarized and listed.

Safety assessments include incidences of AEs, SAEs, and AESI (Section 9.2), AEs leading to discontinuation, and death, as well as marked abnormalities in clinical laboratory tests, vital sign measurements, ECGs, physical examinations, and change in BMD collected by DXA scan from baseline to Follow-up Week 24. Furthermore, the occurrence of IRRs will be analyzed as a function of the infusion rates and compared between treatment groups.

[redacted]

10.4.3.1 PK [redacted]

PK [redacted] of BMS-986263 will be analyzed based on the time points indicated in [redacted] Plasma concentrations of the components of the LNP, such as DPD, S104, and HEDC will also be measured.

PK evaluation is a secondary endpoint. Plasma concentrations of siRNA, DPD, HEDC, and S104 (components of BMS-986263 for injection) will be listed and summarized descriptively by dose, day, and time.

[redacted]

Analysis of PK and exposure-response relationships of BMS-986263 will be conducted using a population approach as appropriate and reported separately from the CSR.

[redacted]

Approved v5.0 930147586 4.0

10.4.4 Week 12 Analyses

After all participants have either completed the Follow-up Week 4 visit or have discontinued the study prior to the Follow-up Week 4 visit, the study will be unblinded and the primary analysis for the study will be conducted.

10.4.5 Interim Analysis

Two interim analyses may be performed after approximately 30% and 50% of participants have either completed the Follow-up Week 4 visit or have discontinued the study prior to the Follow-up Week 4 visit.

The purpose of the 30% interim analyses will be to assess futility. The DMC will review the available data to make recommendation on the following options:

- Continue the study as planned
- Terminate the study for futility

The futility decision criteria and the review process by the DMC will be specified in the DMC Charter and the DMC SAP.

The purpose of the 50% interim analysis will be to help in early planning for accelerating further clinical development of the compound. No formal test of statistical significance is planned. Results will be descriptive and based on the estimation of effect size and associated CIs. Thus, no adjustments to overall Type I error will be made.

The interim analysis results on both occasions will be reviewed by the independent DMC; and the Sponsor's Internal Review Committee (IRC) if needed. The blinding to investigators and the study team will be maintained until the end of the study.

Within the DMC Charter, for each interim analysis, the Sponsor will specify:

- Conditions under which interim results could be shared with select individuals within BMS to help in early planning of clinical development of the compound
- Steps taken to ensure the blinding of the other BMS personnel (that are not unblinded) and investigators to interim results
- Statistical summaries that will be prepared for review

Details of the interim analyses will be described in the DMC SAP and DMC Charter, which will be revised and finalized prior to the DMC meeting.

Approved v5.0 930147586 4.0

11 REFERENCES

[1] Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67(1):328-57.

[2] Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology 2014;59(6):2188-95.

[3] Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149(2):389-97 e10.

[4] Ekstedt M, Hagstrom H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61(5):1547-54.

[5] Hagstrom H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017;67(6):1265-73.

[6] Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology 2017;65(5):1557-65.

[7] BMS-986263/ND-L02-s0201 Investigator's Brochure, Version 16. Bristol-Myers Squibb Company and Nitto Denko Corporation, 2022. Document Control No. Pending.

[8] Friedman SL. Molecular regulation of hepatic fibrosis, an integrated cellular response to tissue injury. J Biol Chem 2000;275(4):2247-50.

[9] Nagata K. Expression and function of heat shock protein 47: a collagen-specific molecular chaperone in the endoplasmic reticulum. Matrix Biol 1998;16(7):379-86.

[10] Sauk JJ, Smith T, Norris K, et al. Hsp47 and the translation-translocation machinery cooperate in the production of alpha 1(I) chains of type I procollagen. J Biol Chem 1994;269(6):3941-6.

[11] Nagai N, Hosokawa M, Itohara S, et al. Embryonic lethality of molecular chaperone hsp47 knockout mice is associated with defects in collagen biosynthesis. J Cell Biol 2000;150(6):1499-506.

[12] Hagiwara S, Iwasaka H, Matsumoto S, et al. An antisense oligonucleotide to HSP47 inhibits paraquat-induced pulmonary fibrosis in rats. Toxicology 2007;236(3):199-207.

[13] Nishino T, Miyazaki M, Abe K, et al. Antisense oligonucleotides against collagen-binding stress protein HSP47 suppress peritoneal fibrosis in rats. Kidney Int 2003;64(3):887-96.

[14] Wang ZL, Inokuchi T, Ikeda H, et al. Collagen-binding heat shock protein HSP47 expression during healing of fetal skin wounds. Int J Oral Maxillofac Surg 2002;31(2):179-84.

[15] Issa R, Zhou X, Constandinou CM, et al. Spontaneous recovery from micronodular cirrhosis: evidence for incomplete resolution associated with matrix cross-linking. Gastroenterology 2004;126(7):1795-808.

Approved v5.0 930147586 4.0

[16] Arthur MJ. Reversibility of liver fibrosis and cirrhosis following treatment for hepatitis C. Gastroenterology 2002;122(5):1525-8.

[17] Parsons CJ, Bradford BU, Pan CQ, et al. Antifibrotic effects of a tissue inhibitor of metalloproteinase-1 antibody on established liver fibrosis in rats. Hepatology 2004;40(5):1106-15.

[18] Ueki T, Kaneda Y, Tsutsui H, et al. Hepatocyte growth factor gene therapy of liver cirrhosis in rats. Nat Med 1999;5(2):226-30.

[19] A 5-week study of ND-L02-s0201 administered by intravenous bolus injection to rats with a 6-week recovery period (Study 20024764). Nitto Denko Technical Corp; 2012. Document Control No. 930121678.

[20] A 13-week intravenous (bolus injection) toxicity study of ND-L02-s0201 in the albino rat with a 6-week recovery period (Insymbiosis Study No. 2081/Test Facility Study No. 5000534) (Study 5000534). Insymbiosis; 2015. Document Control No. 930121930.

[redacted]

[22] A 39-week intravenous toxicity study of ND-L02-s0201 in cynomolgus monkeys, followed by a 6-week recovery period (Insymbiosis Study No. 2500/Test Facility Study No. 5001795) (Study 5001795). Insymbiosis; 2017. Document Control No. 930119570.

[23] Binkley N, Krueger D. Hypervitaminosis A and bone. Nutr Rev 2000;58(5):138-44.

[24] Lind T, Lind PM, Jacobson A, et al. High dietary intake of retinol leads to bone marrow hypoxia and diaphyseal endosteal mineralization in rats. Bone 2011;48(3):496-506.

[25] Masago Y, Hosoya A, Kawasaki K, et al. The molecular chaperone Hsp47 is essential for cartilage and endochondral bone formation. J Cell Sci 2012;125(Pt 5):1118-28.

[26] Marini JC, Reich A, Smith SM. Osteogenesis imperfecta due to mutations in non-collagenous genes: lessons in the biology of bone formation. Curr Opin Pediatr 2014;26(4):500-7.

[27] A 39-week (40 doses) intravenous toxicity study of ND-L02-s0201 in cynomolgus monkeys, with a 6-week recovery period (Insymbiosis Study No. 2500/Test Facility Study No. 5001795) (Study 5001795). Insymbiosis; 2018. Document Control No. 930125400.

[redacted]

[29] A phase 1, randomized, double-blind, placebo-controlled, escalating single dose study to evaluate the safety, tolerability and pharmacokinetics of ND-L02-s0201 injection, a vitamin A-coupled lipid nanoparticle containing siRNA against HSP47, in healthy normal subjects (Study ND-L02-s0201-001); Clinical Study Report. Nitto Denko Corporation; 2017. Document Control No. 930113265.

Approved v5.0 930147586 4.0

[30] Phase 1, open-label, randomized-sequence, single-crossover, bridging study to evaluate the single-dose pharmacokinetics, safety, and tolerability of two ND-L02-s0201 formulations, frozen versus lyophilized, administered by intravenous infusion to healthy male and female subjects (Study ND-L02-s0201-004); Clinical Study Report. Nitto Denko Corporation; 2017. Document Control No. 930115313.

[31] A randomized, placebo-controlled, double-blind, multiple dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of BMS-986263 in healthy participants (Study IM025001); Clinical Study Report. Bristol-Myers Squibb Company; 2018. Document Control No. 930132863.

[32] A phase 1b/2, open label, randomized, repeat-dose, dose-escalation study to evaluate the safety, tolerability, biological activity, and pharmacokinetics of ND-L02-s0201 injection, a vitamin A-coupled lipid nanoparticle containing siRNA against HSP47, in subjects with moderate to extensive hepatic fibrosis (METAVIR F3-4) (Study ND-L02-s0201-002); Clinical Study Report. Nitto Denko Corporation; 2017. Document Control No. 930113585.

[33] A phase 1, repeat dose study to evaluate the safety, tolerability, biological activity, and pharmacokinetics of ND-L02-s0201 injection in Japanese subjects with advanced hepatic fibrosis (METAVIR F3-4) (Study ND-L02-s0201-003); Clinical Study Report. Nitto Denko Corporation; 2017. Document Control No. Pending.

[34] A randomized, double-blind, placebo-controlled, 2-part, parallel group, multiple dose Phase 2 study to evaluate the efficacy and safety of BMS-986263 in adults with advanced hepatic fibrosis from hepatitis C who have achieved sustained virologic response (Study IM025006). Bristol-Myers Squibb Company; 2020. Document Control No. 930152959.

[35] American College of Radiology. CT/MRI LI-RADS® v2018 CORE. 2018. Accessed 05 September 2019.

[36] Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46(3):922-38.

[37] Laubham M, Kallwitz E. Coagulation in chronic liver disease and the use of prothrombin complex concentrate for an emergent procedure: a case report and review of literature. J Community Hosp Intern Med Perspect 2018;8(3):138-41.

[38] Bedossa P. Diagnosis of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: Why liver biopsy is essential. Liver Int 2018;38 Suppl 1:64-6.

[39] Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41(6):1313-21.

[40] Anstee QM, Neuschwander-Tetri BA, Wong VW, et al. Cenicriviroc for the treatment of liver fibrosis in adults with nonalcoholic steatohepatitis: AURORA Phase 3 study design. Contemp Clin Trials 2020;89:105922.

[redacted]

Approved v5.0 930147586 4.0

[redacted]

Approved v5.0 930147586 4.0

[redacted]

56 Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247-54.

[redacted]

Approved v5.0 930147586 4.0

12 APPENDICES

Approved v5.0 930147586 4.0

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
[redacted]	
AE	adverse event
AESI	adverse events of special interest
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APRI	AST-to-platelet ratio index
[redacted]	
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration-time curve
AUC(INF)	area under the concentration-time curves from zero to infinity
AUC(0-T)	area under the concentration-time curves from time zero to the time of the last quantifiable concentration
BIW	twice per week
BMD	bone mineral density
BMI	body mass index
BMS	Bristol-Myers Squibb
[redacted]	
BUN	blood urea nitrogen
C3M	matrix metalloproteinase-derived collagen Type III-specific neoepitope peptide
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CL	total plasma clearance
[redacted]	
Cmax	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CPA	collagen proportionate area
CRN	Clinical Research Network
CSR	clinical study report
CT	computed tomography
[redacted]	
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DMN	dimethylnitrosamine
DNA	deoxyribonucleic acid
DPD	di-retinamide-PEG-di-retinamide

Approved v5.0 930147586 4.0

DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
ELF	enhanced liver fibrosis
ePRO	electronic patient-reported outcomes
EOS	End of Study
EST	Early Study Termination
ETT	Early Treatment Termination
FDA	Food and Drug Administration
FIB-4	Fibrosis-4
FSH	follicle-stimulating hormone
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HbcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HEDC	(Bis[2-(tetradecanoyloxy)ethyl] carbamoylmethyl)-(2-hydroxyethyl)dimethylazanium bromide
HI	hepatic impairment
HIV	human immunodeficiency virus
HSC	hepatic stellate cell
HSP47	heat shock protein 47
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IPRC	Independent Pathology Review Committee
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
IV	intravenous
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
LDL	low-density lipoprotein

Approved v5.0 930147586 4.0

LNP	lipid nanoparticle
MCH	mean corpuscular hemoglobin;
MCV	mean corpuscular volume
MELD	Model for End-stage Liver Disease
mITT	modified intent-to-treat
[redacted]	
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
NOAEL	no-observed-adverse-effect level
OTC	over-the-counter
[redacted]	
PK	pharmacokinetics
[redacted]	
PRO-C3	N-terminal Type III collagen propeptide
[redacted]	
PT	prothrombin time
PTH	parathyroid hormone
PTT	partial thromboplastin time
[redacted]	
QW	once every week
RBC	red blood cell
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
[redacted]	
RT-PCR	reverse transcription - polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGLT2	sodium glucose cotransporter 2
siRNA	small interfering ribonucleic acid
SOA	Schedule of Activities
SVR	sustained virologic response
TEAE	treatment emergent adverse event
[redacted]	
ULN	upper limit of normal
[redacted]	

Approved v5.0 930147586 4.0

WBC	white blood cell
WOCBP	women of childbearing potential

Approved v5.0 930147586 4.0

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the electronic case report form (eCRF) is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP),
- As defined by the International Council for Harmonisation (ICH)
- In accordance with the ethical principles underlying European Union Directive 2001/20/EC
- US Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- Applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants. The investigator or BMS should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to subjects/participants and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

Approved v5.0 930147586 4.0

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local Health Authority) except where necessary to eliminate an immediate hazard(s) to study subjects/participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC for
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local Health Authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects/participants prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that subjects/participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects/participants, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form (ICF) which will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Approved v5.0 930147586 4.0

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the subjects/participants, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects'/participants' signed ICF and, in the US, the subjects'/participants' signed Health Insurance Portability and Accountability Act Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

The rights, safety, and well-being of the study subjects/participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records).

Approved v5.0 930147586 4.0

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by Bristol-Myers Squibb [BMS], its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If..	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • Amount received and placed in storage area • Amount currently in storage area • Label identification number or batch number • Amount dispensed to and returned by each participant, including unique participant identifiers • Amount transferred to another area/site for dispensing or storage • Nonstudy disposition (e.g., lost, wasted) • Amount destroyed at study site, if applicable • Amount returned to BMS • Retain samples for bioavailability/bioequivalence, if applicable • Dates and initials of person responsible for investigational product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include investigational product sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the standard operating procedures (SOPs)/standards of the sourcing pharmacy.

Approved v5.0 930147586 4.0

If..	Then
	These records should include: • Label identification number or batch number • Amount dispensed to and returned by each participant, including unique participant identifiers • Dates and initials of person responsible for investigational product dispensing/accountability, as per the Delegation of Authority Form.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the case report form (CRF) must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and paper Pregnancy Surveillance Form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the electronic data capture tool using the unique user account

Approved v5.0 930147586 4.0

provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain eCRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to eCRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor or sourced by the investigator) such as partially used study treatment containers, vials, and syringes may be destroyed on-site.

Approved v5.0 930147586 4.0

If..	Then
Study treatments supplied by BMS (including its vendors)	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible study monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible study monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met, the responsible study monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of nonstudy treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

Approved v5.0 930147586 4.0

For sites that will not destroy study treatment on-site, it is the investigator's or designee's responsibility to arrange for disposal of all empty study treatment containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of full or partially used study treatments supplied by BMS or its vendors will be arranged by the responsible study monitor.

CLINICAL STUDY REPORT

A signatory investigator must be selected to sign the clinical study report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the signatory investigator:

- Participant recruitment (eg, among the top quartile of enrollers)
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Scientific expertise or contribution to data interpretation and review

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing study site or investigator participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, subinvestigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights, and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Approved v5.0 930147586 4.0

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Subinvestigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

Approved v5.0 930147586 4.0

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

ADVERSE EVENTS

AE Definition

An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events <u>NOT</u> Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Approved v5.0 930147586 4.0

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

SAE Definition is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability or permanent damage
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event (see Section 9.2.7 for the definition of potential DILI).

Approved v5.0 930147586 4.0

Pregnancy and potential DILI must follow the same transmission timing and processes to BMS as used for SAEs (see Section 9.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the subject/participant, causing minimal discomfort, and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. A "reasonable possibility of a relationship" conveys that there are facts, evidences, and/or arguments to suggest a causal relationship rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Approved v5.0 930147586 4.0

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. Note: Follow-up SAE reports must include the same investigator term(s) initially reported. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

SAEs, whether related or not related to study drug, and pregnancies must be reported immediately to BMS (or designee) but no later than 24 hours of awareness of the event.

SAEs must be recorded on the SAE Report Form. For studies capturing SAEs through electronic data capture, electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on-site.

Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Fax Number: Refer to Contact Information list.

SAE Telephone Contact - For questions on SAE/pregnancy reporting: Refer to Contact Information list.

Approved v5.0 930147586 4.0

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, female participants under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Female participants treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the IMP to pass.

Approved v5.0 930147586 4.0

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of < 1% per year when used consistently and correctly.[a]

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b]
  - oral (birth control pills)
  - intravaginal (vaginal birth control suppositories, rings, creams, gels)
  - transdermal
- Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy

- Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b]
  - oral
  - injectable
- Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy

Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b]
- Intrauterine device (IUD)[c]
- Intrauterine hormone-releasing system (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b,c]
- Bilateral tubal occlusion

- Vasectomized partner

Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.

Approved v5.0 930147586 4.0

- Sexual abstinence

  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in the Schedule of Activities, Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.
- Periodic abstinence (including but not limited to calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine hormone-releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That are User Dependent

Failure rate of > 1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)

Approved v5.0 930147586 4.0

Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • LAM

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and APPENDIX 3.

Approved v5.0 930147586 4.0

APPENDIX 5 CHILD-PUGH SCORING

Parameter	Classification	Score
Bilirubin (Total)[a]	< 2 mg/dL (< 34.2 µmol/L)	+1
	2-3 mg/dL (34.2-51.3 µmol/L)	+2
	> 3 mg/dL (> 51.3 µmol/L)	+3
Albumin[a]	> 3.5 g/dL (> 35 g/L)	+1
	2.8-3.5 g/dL (28-35 g/L)	+2
	< 2.8 g/dL (< 28 g/L)	+3
International Normalized Ratio[a]	< 1.7	+1
	1.7-2.2	+2
	> 2.2	+3
Ascites	Absent	+1
	Slight	+2
	Moderate	+3
Encephalopathy	No encephalopathy	+1
	Mild to moderate (Grade 1-2)	+2
	Severe (Grade 3-4)	+3

[a] All laboratory parameters must be taken from the same blood draw.
Note: in the event of retesting of Child-Pugh Score, all laboratory parameters should be retested to allow for accurate calculations.

For the calculation of the Child-Pugh Score[1, 2] the sum of the scoring points from the 5 clinical parameters (total bilirubin, albumin, INR, ascites, and encephalopathy) corresponds to 1 of 3 categories:

Child-Pugh A = 5 to 6 points

Child-Pugh B = 7 to 9 points

Child-Pugh C = ≥ 10 points.

REFERENCES:

1. Cholongitas E, Papatheodoridis GV, Vangeli M, et al. Systematic review: The model for end-stage liver disease--should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? Aliment Pharmacol Ther 2005;22(11-12):1079-89.

2. Weissenborn K. Hepatic Encephalopathy: Definition, Clinical Grading and Diagnostic Principles. Drugs 2019;79(Suppl 1):5-9.

Approved v5.0 930147586 4.0

APPENDIX 6 FORMULAS FOR MEASUREMENTS

- Model for End-stage Liver Disease (MELD)
  Score = (9.57*ln[creatinine]) + (3.78 * ln[Bilirubin]) + (11.20* ln[INR]) + 6.43
- Enhanced liver fibrosis (ELF)[1] assessment combines hyaluronic acid, procollagen 3 amino terminal peptide, and tissue inhibitor of metalloproteinase 1. An algorithm is used to evaluate each of these markers by immunoassay to create an ELF Score
- Fibrosis-4 (FIB-4)[2] Score = (age [years] × aspartate aminotransferase [AST] level [U/L])/(platelet count [x10^9/L] × square root of alanine aminotransferase [ALT] [U/L])
- Nonalcoholic fatty liver disease (NAFLD) Fibrosis Score[3] = -1.675 + 0.037 × age (years) + 0.094 × body mass index (kg/m^2) + 1.13 × impaired fasting glucose/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet count [× 10^9/L] – 0.66 × albumin (g/dL)
- AST-to-platelet ratio index (APRI)[4] Score = ([AST divided by AST Upper Limit of Normal]/platelet count [× 10^9/L]) × 100

Note: all laboratory parameters must be taken from the same blood draw. In the event of retesting, all laboratory parameters should be retested to allow for accurate calculations.

REFERENCES:

1. Anstee QM, Lawitz EJ, Alkhouri N, et al. Noninvasive tests accurately identify advanced fibrosis due to NASH: Baseline data from the STELLAR trials. Hepatology 2019.
2. Shah AG, Lydecker A, Murray K, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7(10):1104-12.
3. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45(4):846-54.
4. Adams LA, George J, Bugianesi E, et al. Complex non-invasive fibrosis models are more accurate than simple models in non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2011;26(10):1536-43.

Approved v5.0 930147586 4.0

APPENDIX 7 CRITERIA FOR DIAGNOSIS AND EXCLUSION OF PARTICIPANTS WITH HEPATITIS B VIRUS AND CHRONIC HEPATITIS C VIRUS INFECTION

HBV Infection

HBsAg	HBsAb	HBcAb	HBV Infection	Excluded?
Positive	Negative	Positive	Yes	Yes
Negative	Negative	Positive	Maybe	See (a)
Negative	Positive	Positive	Maybe	See (a)
Positive	Positive	Negative	Maybe	See (b)
Negative	Negative	Negative	No	No
Negative	Positive	Negative	No	No

HBsAB = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBcAB = hepatitis B core antibody; HBV = hepatitis B virus

a) 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.

b) Participant must be excluded unless:
   - Participant was recently vaccinated for HBV (within 2 weeks of testing) AND repeat hepatitis B surface antigen (HBsAg) is negative (repeat HBsAg should occur 4 to 6 weeks after vaccination).

Any positive HBV DNA result is exclusionary.

HCV Infection

A participant who is hepatitis C virus (HCV) antibody positive must be excluded unless:

- The participant has a history of clearance of HCV infection for > 2 years prior to the screening biopsy **AND** the HCV ribonucleic acid is undetectable at the screening visit.

Approved v5.0 930147586 4.0

APPENDIX 8 COUNTRY-SPECIFIC REQUIREMENTS

Argentina, Germany, and Any Other Countries in Which Exclusion of HIV-Positive Participants is Locally Mandated

	Country-specific Language
Section 2 Schedule of Activities, Table 1 Screening Procedural Outline – Laboratory Assessments	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion criterion 2) k)	Replace "Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for human immunodeficiency virus (HIV) or have acquired immunodeficiency syndrome-related illness, as reported by the participant and/or documentation." with "Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who have a positive human immunodeficiency virus (HIV) test."

Approved v5.0 930147586 4.0

APPENDIX 9 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 02, 25-Nov-2020

The primary purpose of this Global Revised Protocol is to expand the patient population from Child-Pugh A5 to Child-Pugh A6, including corresponding laboratory exclusion criteria, based on preliminary results from hepatic impairment (HI) study IM025015. Key secondary revisions include the following:

- Adding results from Part 1 of HI study IM025015, which supports the changes in Child-Pugh/laboratory exclusion criteria
- Adjustment of step-wise infusion rates (decreased number of steps)
- [redacted]
- Adding guidance [redacted] related to the coronavirus disease 2019 (COVID-19) pandemic
- Changing statistical sample size calculation, study stratification factors, and statistical analysis methodology for primary endpoint
- Excluding participants from the study who are taking anticoagulants
- Replacing liver ultrasound as a screening procedure for detection of hepatocellular carcinoma (HCC) with multiphasic liver computed tomography (CT)/magnetic resonance imaging (MRI)
- Updating exclusion criterion related to history of weight gain/loss
- Updating exclusion criterion related to history of illegal intravenous (IV) drug use
- Adding option for participants who have a prolonged international normalized ratio (INR) and/or lower platelet count to potentially receive treatments for coagulation abnormalities and/or low platelet counts prior to liver biopsy

All changes applied to the body were applied to the synopsis, as necessary; synopsis changes are not included in the list below.

Only major additions and deletions are provided in this summary; all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications are not included.

The rationale(s) for changes to this Revised Protocol are provided in the summary of key changes table, as shown below:

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
2 Schedule of Activities, Table 1 6.2 Exclusion Criteria 1) Target disease exclusions	Replaced as follows: 1)f) → 1)i)	Replaced liver ultrasound at screening with multiphasic liver CT/MRI because diagnostic performance of liver ultrasound for early detection of HCC can be reduced particularly in subjects with central obesity or marked parenchymal heterogeneity due to cirrhosis, justifying the adoption of a more sensitive method for detection of HCC prior to initiation of study treatment.
2 Schedule of Activities, Table 2 3.3.2 COVID-19-Related 4 Objectives and Endpoints, Table 4 5.4 Scientific Rationale for Study Design 6.2 Exclusion Criteria, 2) Medical Conditions and 3) Prior and concomitant therapy 6.6.1 Retesting During Screening Period 7.7.1 Prohibited and/or Restricted Treatments [redacted]	Added guidance [redacted] related to COVID-19 pandemic, including addition of the following Exclusion Criteria: 2)r) and 3)g) and replacement of the following Exclusion Criterion: 3)c) → 3)h)	Added to ensure participant/investigative site staff safety and reliability of results
3.2.2 Clinical Studies 3.3.1 Overall Benefit/Risk Assessment	Added study results from Part 1 of HI study IM025015	These study results from Part 1 of Study IM025015 in participants with mild or moderate HI support the changes in Child-Pugh exclusion criteria, including corresponding laboratory exclusion criteria.

Approved v5.0 930147586 4.0

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
4 Objectives and Endpoints, Table 4 10.3.2 Secondary Endpoints 10.4.3.1 PK [redacted]	[redacted]	To include the assessment of the plasma PK of this lipid component of BMS-986263.
5.1.2 Treatment Period and Follow-up 10.4.1 Efficacy Analyses	Platelet count removed as stratification factor at Randomization and added as independent covariate in the logistic regression	Removed because too many stratification factors may result in reduced power in analyses and imbalance in randomization.
5.1.2 Treatment Period and Follow-up	Country (Non-Japan versus Japan) removed as stratification factor at Randomization	Removed because too many stratification factors may result in reduced power in analyses and imbalance in randomization.
7.2 Exclusion Criteria 1) Target disease exclusions 3) Prior and concomitant therapy 7.7.1 Prohibited and/or Restricted Treatments	Replaced as follows: 1)e) → 1)h) Added 3)i) Added 8)	[redacted] to exclude participants who are taking anticoagulants in order to mitigate bleeding risks associated with the liver biopsy.
6.2 Exclusion Criteria 1) Target disease exclusions	Replaced as follows: 1)g) → 1)j)	Updated exclusion criterion to exclude participants with a Child-Pugh Score > 6, instead of > 5 based on results from Part 1 of Study IM025015.
6.2 Exclusion Criteria 2) Medical conditions 6.4 Lifestyle Restrictions	Replaced as follows: 2)c) → 2)s)	Updated exclusion criterion to specify alcohol consumption limits in mL, as well as in ounces.

Approved v5.0 930147586 4.0

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.2 Exclusion Criteria 2) Medical conditions	Replaced as follows: 2)m) → 2)t)	Reduced the duration of exclusionary history of illegal IV drug use from 3 to 2 years since 2 years should be sufficient to ensure study compliance related to illegal IV drug use.
6.2 Exclusion Criteria 2) Medical conditions	Replaced as follows: 2)o) → 2)u)	Updated the exclusion criterion related to history of weight gain/loss before and after the eligibility liver biopsy to ensure that the biopsy used for eligibility reflects the participant's disease severity at baseline.
6.2 Exclusion Criteria 4) Physical and laboratory test findings	Replaced as follows: 4)c) → 4)f)	Updated exclusion criterion to exclude participants with albumin < 2.8 g/dL, INR > 2.2, total bilirubin > 3.0 mg/dL, and platelet count < 85,000/µL, instead of < 3.5 g/dL, > 1.4, > 1.5 mg/dL, and < 140,000/µL, respectively, allowing enrollment of subjects with a wider range of laboratory values, supported by safety results from Part 1 of Study IM025015 in subjects with mild and moderate HI.
7.1.1 Study Treatment Infusion Rate 9.5 PK [redacted] Sampling Schedule for BMS-986263, [redacted]	Adjusted step-wise infusion durations [redacted]	Adjusted to simplify the infusion process.

Approved v5.0 930147586 4.0

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.1.2 Liver Biopsy Assessments	Added the following text: Participants who have a prolonged INR and/or lower platelet count may receive treatments to correct coagulation abnormalities and/or low platelet counts prior to liver biopsy based on investigator's clinical judgment in order to reduce the risk of bleeding. It is the investigator's responsibility to assess any potential risks that may be associated with the use of these agents (eg, transfusion of fresh/frozen plasma or platelets).	Added to allow investigators to administer treatments to correct abnormal INR or platelets prior to liver biopsy, in order to reduce the risk of bleeding associated with the liver biopsy, based on investigator's assessment of the benefits-risks of these treatments.
10.1 Sample Size Determination	Participant dropout rate changed from 10% to 6% and evaluable number of participants changed from 79 to 85 participants	To adjust the estimated dropout rate and maintain 80% power with the study sample size of approximately 270 participants.
10.1 Sample Size Determination	Replaced CMH test with Chi-Square test	The CMH test is no longer applicable to justify the sample size, as the final analysis was changed from CMH to logistic regression. Treatment group comparisons using the logistic regression model are Chi-square-based test statistics.

CMH = Cochran-Mantel-Haenszel; COVID-19 = coronavirus disease 2019; CT = computed tomography; [redacted] HCC = hepatocellular carcinoma; HI = hepatic impairment; INR = international normalized ratio; IV = intravenous; MRI = magnetic resonance imaging; PK = pharmacokinetics; US = United States

Approved v5.0 930147586 4.0

Overall Rationale for the Revised Protocol 01, 27-May-2020

The primary purpose of this Global Revised Protocol is to adjust an inclusion criterion for participants without steatohepatitis (to add a biopsy-based requirement). Key secondary revisions include the following:

- Correcting an exclusion criterion-related equation for estimated glomerular filtration rate, now replaced by literature reference
- Adding nintedanib as a concomitant medication restriction
- [redacted]
- [redacted]
- Adding/clarifying statistical analysis methods for primary and secondary [redacted] efficacy endpoints
- Updating interim analyses to include a single analysis only
- Incorporating changes previously provided in country-specific amendments and an administrative letter
- Updating sections to align with current protocol template
- Updating background clinical study data
- Adding the recommended stepped infusion rates for study treatment
- Adding required urine pregnancy test prior to visits in which dual-energy X-ray absorptiometry is conducted
- Clarifying study exclusion exceptions related to Child-Pugh exclusion criterion
- Specifically referencing an Independent Pathology Review Committee and respective charter to be utilized in the study
- Adding an appendix for exclusion of human immunodeficiency virus positive participants where locally required

All changes applied to the body were applied to the synopsis, as necessary; synopsis changes are not included in the list below.

Only major additions and deletions are provided in this summary document; all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications are not included.

The rationale(s) for changes to this Revised Protocol are provided in the summary of key changes table, as shown below:

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated Medical Monitor	Updated with current contact (initially updated with Protocol Administrative Letter 01, dated 01-Feb-2020).

Approved v5.0 930147586 4.0

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Study Acknowledgment/ Disclosure	Removed	Will be included as separate stand-alone document with added placeholder for Study Director/Medical Monitor signature (to align with US-specific Revised Protocol 00a, dated 21-Feb-2020).
1.3 Schedule of Activities, Table 2 and Table 3 3 Objectives and Endpoints 4.1.1 Screening Period [redacted] 5.4 Lifestyle Restrictions 6.7.2 Concomitant Medication Restrictions for the ^{13}C MBT Assessment [redacted] Appendix 1 Abbreviations and Trademarks	Removed [redacted] information/sections	Removed to reduce operational complexity and number of visit procedures.
1.3 Schedule of Activities, Table 1 and Table 3	Added required urine pregnancy test prior to visits in which a DXA scan is conducted	Added because pregnancy testing prior to DXA scan is standard practice.
2.2.2 Clinical Studies	Updated background clinical study data	Updated to align with data from the Study IM025006 final CSR and the current Investigator's Brochure.

Approved v5.0 930147586 4.0

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
4.1.3 DMC and Other External Committees	Referenced the utilization of an IPRC and respective charter in the study	Original protocol referenced a central pathologist; this change is to reflect use of a pathology review committee.
5.1 Inclusion Criteria 2) Type of Participant and Target Disease Characteristics	Replaced as follows: 2)a) → 2)e)	Revised to clarify liver biopsy inclusion criteria for subjects without definite steatohepatitis.
5.1 Inclusion Criteria 3) Age and reproductive status	Replaced as follows: • 3)a)b → 3)a)e • 3)a)d → 3)a)f • 3)b)c → 3)b)i • 3)b)d → 3)b)j • 3)b)e → 3)b)k • 3)b)f → 3)b)l • 3)b)g → 3)b)m	Revised to align with current protocol template.
5.2 Exclusion Criteria 1) Target disease	Replaced as follows: • 1)d) → 1)g)	Revised to clarify study exclusion exceptions related to Child-Pugh exclusion criterion.
5.2 Exclusion Criteria 3) Prior and concomitant therapy 6.7.1 Prohibited and/or Restricted Treatments	Added nintedanib as a concomitant medication restriction [added as 3)f)]	Added due to a preclinical finding of enhancement of bone toxicity with nintedanib in combination with BMS-986263.

Approved v5.0 930147586 4.0

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.2 Exclusion Criteria 5) Allergies and adverse drug reaction 6 Treatment 6.1 Treatments Administered	Updated exclusion criterion (and sections with corresponding text) to parenthetically include [redacted] as follows: • 5)a) → 5)c)	[redacted]
6.1.1 Study Treatment Infusion Rate	Added recommended stepped infusion rates for study treatment and recommended course of action if infusion rate modifications are being considered	Added to provide guidance regarding the recommended rates for study treatment infusion.
[redacted]		
8.4.1 Clinical Safety Laboratory Assessments	Replaced equation for the eGFR rate with up-to-date literature reference	Replaced because previously included equation was incomplete.

Approved v5.0 930147586 4.0

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.4.1 Efficacy Analyses/ Primary Endpoint	Replaced Chi-square test with Cochran-Mantel-Haenszel test stratified by randomization strata to test the difference in distribution of response rate among 3 treatment groups, and specified test significance level prompting pairwise comparisons to placebo	The Chi-square test does not specifically allow for adjusting for randomized strata; the Cochran-Mantel-Haenszel test does allow for this adjustment.
9.4.1 Efficacy Analyses/ Secondary [redacted] Endpoints	Added mixed model for repeated measurements	Added additional statistical analysis option for continuous secondary [redacted] endpoints.
9.4.5 Interim Analysis	Removed first interim analysis (after approximately 30% of participants completed the Follow-up Week 4 visit/discontinued prior to this visit) and specified contents of the DMC Charter related to interim analysis	To reduce the number of interim analyses performed in the study, this analysis will only be conducted one time, when 50% of participants have completed Follow-up Week 4.
Appendix 8 Country-specific Requirements	Added appendix	Added to indicate changes to be made to appropriate protocol sections related to participants who are HIV positive in countries in which it is locally mandated that such patients be excluded.

Approved v5.0 930147586 4.0