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EUDRACT Number: Not applicable
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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

Test Drug: BMS-986263

Study Director **Medical Monitor**

[redacted]

24-hour Emergency Telephone Number

[redacted]

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes	Approvers
Original Protocol	01-Nov-2017	Not Applicable	[redacted]
Amendment 01	05-Jan-2018	Incorporates changes to multiple sections of the protocol in response to Health Authority interactions. Provides clarifications of interpretation of the protocol and increases consistency within the protocol.	
Revised Protocol 01 (Final Approved v2.0)	05-Jan-2018	Incorporates Amendment 01	
Amendment 02	22-Mar-2018	Incorporates changes to multiple sections of the protocol based on regulatory interactions. Addition of dose arm in Part 1 and changes to study drug administration. Increases consistency within the protocol. Incorporates minor grammatical and editorial corrections.	
Revised Protocol 02 (Final Approved v3.0)	22-Mar-2018	Incorporates Amendment 02	
Amendment 03	19-Jun-2018	Incorporates changes to various sections of the protocol based on feedback received from the Investigator and recent submission to Health Authority. Includes clarification for study treatment administration [redacted]	
Revised Protocol 03 (Final Approved v4.0)	19-Jun-2018	Incorporates Amendment 03	
Amendment 04	17-Aug-2018	[redacted] Additionally, incorporates updates in the eligibility criteria and clarifications in study treatment discontinuation criteria.	
Revised Protocol 04	17-Aug-2018	Incorporated Amendment 04	

Document	Date of Issue	Summary of Changes	Approvers
(Final Approved v5.0)			[redacted]
Amendment 05	13-Nov-2018	Appendix 2 revised to remove text that incorrectly suggested that disease-related events do not meet the AE definition and, therefore, should not be reported as AEs. All such events must be reported as AEs.	
Revised Protocol 05 (Final Approved v6.0)	13-Nov-2018	Incorporated Amendment 05	
Amendment 06	21-Feb-2019	[redacted] Additional clarifications for select endpoints/objectives related to MRE, collection of concomitant medication data, and for SAE reporting (to designee of Sponsor) included.	
Revised Protocol 06 (Final Approved v7.0)	21-Feb-2019	Incorporated Amendment 06	

1. PROTOCOL SUMMARY

1.1 Synopsis

NAME OF SPONSOR: Bristol-Myers Squibb (BMS)	**PROTOCOL No.:** IM025006
NAME OF STUDY TREATMENT: BMS-986263	
TITLE OF STUDY: 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	

[redacted]

[redacted]

STUDY CENTERS: Approximately 41 centers in the United States

STUDY PERIOD: Up to 35 days screening followed by 12 weeks or 24 weeks of treatment in Part 1 or Part 2, respectively, and 24 weeks or 12 weeks follow-up period in Part 1 or Part 2, respectively, for a total study period of approximately 10 months.

PHASE OF DEVELOPMENT: Phase 2

PLANNED STUDY DATES: January 2018 – December 2020

OBJECTIVES:

Primary Objective:

- Part 1: To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with ≥ 1 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 12 weeks of treatment
- Part 2: To assess the effect of treatment with 45 mg Q2W, 90 mg Q2W, and 90 mg Q4W BMS-986263 on the proportion of participants with ≥ 1 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 24 weeks of treatment

Secondary Objectives:

- Part 1
    - To assess the effect of treatment with 90 mg QW BMS-986263 on the change in collagen proportionate area (CPA), as compared to placebo after 12 weeks of treatment
    - To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with ≥ 1 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment
    - To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with ≥ 2 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 12 weeks of treatment
    - To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with ≥ 2 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment
    - To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with a ≥ 15% reduction in liver stiffness as measured by MRE compared to placebo at Week 12
    - To assess the effect of treatment with 90 mg QW BMS-986263 on the change in liver stiffness from baseline as measured by MRE compared to placebo at Week 12
    - To assess the safety and tolerability of 45 mg QW and 90 mg QW BMS-986263 throughout 36 weeks of treatment and follow-up
    - To assess the PK of 45 mg QW and 90 mg QW BMS-986263
    - To describe the effect of treatment with 45 mg QW BMS-986263 on liver fibrosis after 12 weeks of treatment

- Part 2
    - To assess the effect of treatment with several doses of BMS-986263 on the change in CPA, as compared to placebo after 24 weeks of treatment
    - To assess the effect of treatment with several doses of BMS-986263 on the proportion of participants with ≥ 1 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 24 weeks of treatment
    - To assess the effect of treatment with several doses of BMS-986263 on the proportion of participants with ≥ 2 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 24 weeks of treatment
    - To assess the effect of treatment with several doses of BMS-986263 on the proportion of participants with ≥ 2 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 24 weeks of treatment
    - To assess the effect of treatment with several doses of BMS-986263 on the proportion of participants with a ≥ 15% reduction in liver stiffness as measured by MRE compared to placebo at Week 24
    - To assess the effect of treatment with several doses of BMS-986263 on the change in liver stiffness from baseline as measured by MRE compared to placebo at Week 24
    - To assess the safety and tolerability of several doses BMS-986263 throughout 36 weeks of treatment and follow-up
    - To assess the PK of BMS-986263

[redacted]

STUDY DESIGN AND METHODOLOGY:

This is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of BMS-986263 in adults with advanced hepatic fibrosis due to HCV who have achieved SVR for at least 1 year. This study will enroll approximately 60 participants in Part 1, randomized in a 1:2:1 ratio to treatment with 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW for 12 weeks; and approximately 120 participants in Part 2, randomized in a 1:1:1:1 ratio to receive 45 mg BMS-986263 Q2W, 90 mg BMS-986263 Q2W, 90 mg BMS-986263 Q4W, or placebo Q2W for 24 weeks. The primary study endpoint is the proportion of participants that

achieve ≥ 1 stage improvement in liver fibrosis (METAVIR score) on biopsy after 12 weeks of treatment in Part 1 and after 24 weeks in Part 2.

[redacted]

Part 1: The primary objective of Part 1 is to assess the effect of treatment with 90 mg QW BMS-986263 on the proportion participants with ≥ 1 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 12 weeks of treatment. This part of the study includes:

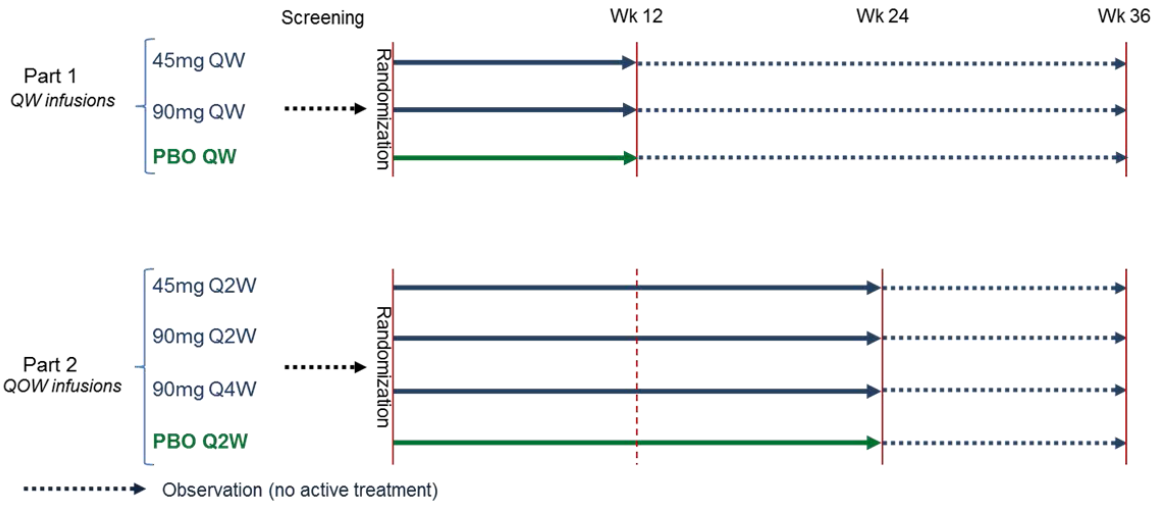
- A screening period
- A 12-week, double-blind treatment period, during which participants will receive 1 of the following 3 treatments: 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW
- A 24-week follow-up period

[redacted]

Part 2: The primary objective of Part 2 is to assess the effect of treatment with 45 mg BMS-986263 Q2W, 90 mg BMS-986263 Q2W, and 90 mg BMS-986263 Q4W on the proportion of participants with ≥ 1 stage improvement in liver fibrosis (METAVIR score) as compared to placebo after 24 weeks of treatment. This part of the study includes:

- A screening period
- A 24-week, double-blind treatment period, during which participants will receive 1 of the following 4 treatments: 45 mg BMS-986263 Q2W, 90 mg BMS-986263 Q2W, 90 mg BMS-986263 Q4W, or placebo Q2W
- A 12-week follow-up period

Study Design Schematic



PBO = placebo; QW = once weekly; QOW = every other week; Q2W = once every 2 weeks; Q4W = once every 4 weeks; Wk = Week
Note: In the 90 mg BMS-986263 Q4W arm, BMS-986263 dosing alternates with placebo every 2 weeks.

Screening for Part 1 and Part 2

Eligibility will be based on specified inclusion and exclusion criteria (Section 8.4), including medical history, disease activity and safety assessments. Randomization must occur within 35 days of signing the informed consent.

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.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. 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 (Section 1.2).

For participants who experience an acute infection or require additional time for scheduling screening procedures, the screening period may be extended beyond 35 days after consultation with the medical monitor, but not beyond a total of 56 days (8 weeks) from the signing of the informed consent.

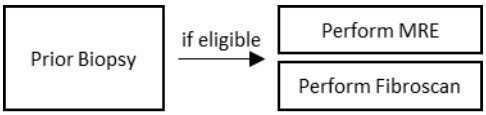
The screening visit may also be extended up to 5 additional days to accommodate unanticipated delays in obtaining required screening results. An extension beyond 5 days will require approval by the Medical Monitor.

Screening and Day 1 (Randomization) hematology and chemistry laboratory assessments must be performed at least 2 weeks apart.

Eligibility of participants requires confirmation of advanced fibrosis (METAVIR Stage 3 or Stage 4) by liver biopsy. If the participant has had a biopsy within the 8 weeks prior to enrollment in the study, this result may be used to determine eligibility only if:

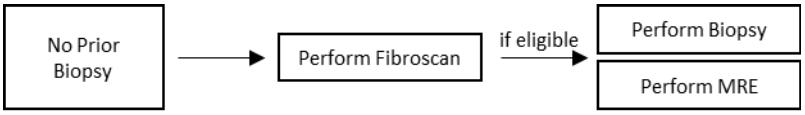
- Local pathology report is available and confirms METAVIR Stage 3 or Stage 4 fibrosis, AND
- The tissue (block or slides) is available for submission to the sponsor for analysis.

If a PRIOR BIOPSY WAS PERFORMED and meets the above criteria, MRE and FibroScan assessments must still be performed. The FibroScan must occur during the screening period unless FibroScan testing was performed within 8 weeks prior to study enrollment and results are available and collected. The MRE must occur during the screening period regardless of whether or not an MRE was performed within 8 weeks prior to study enrollment.



If a PRIOR BIOPSY WAS NOT PERFORMED within 8 weeks or the tissue is not available for submission for analysis, a biopsy must be performed during the screening period. Before performing a biopsy or MRE during the screening period, the participant must undergo an evaluation by FibroScan. If a FibroScan assessment was performed within the 8 weeks prior to enrollment, those results may be used. Only participants who demonstrate advanced liver fibrosis on FibroScan, defined as a mean result ≥ 5.0 kPa, may proceed to biopsy or MRE. In addition, eligibility of the participant based on other eligibility criteria will be assessed before acquiring a biopsy or MRE to reduce patient risk and burden. These may include, at the discretion of the investigator, confirmation of HCV SVR and a review of the participant's medical history to assess for study exclusion criteria (Section 8.4.2).

Participants with a qualifying FibroScan result will complete the screening procedures including liver biopsy and MRE assessment. The MRE must occur during the screening period regardless of whether or not an MRE was performed within 8 weeks prior to study enrollment.



Admissible prior biopsies and biopsies performed during screening will be used to determine eligibility (ie, liver fibrosis stage), and tissue from these biopsies will be used as the baseline sample for the primary endpoint analysis. The requirement that prior biopsies occur within 8 weeks prior to screening ensures that the acquired biopsy sample accurately reflects the condition of the participant at baseline to enable a valid analysis.

[redacted]

Visit details are provided in the Screening and Day 1 (Randomization) Procedural Outline for Part 1 and Part 2 in Table 1.

Part 1 Treatment Period and Follow-up

Approximately 60 participants meeting eligibility criteria during the screening period will be randomized into the Part 1 treatment period. These participants will be randomized via interactive response technology (IRT) in a 1:2:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW in a double-blind manner. The randomization of participants will be stratified by fibrosis stage (METAVIR Stage 3 or Stage 4). Participants will receive study treatment via IV administration for a total of 12 weeks.

Fibrosis stage will be assessed by liver biopsy during the screening period and on Day 85. Liver stiffness will be assessed by MRE at baseline, Day 43, Day 85 (primary efficacy endpoint), Day 169, and Day 253.

After 12 weeks (Day 85) of treatment, participants in Part 1 will enter the 24-week follow-up period. During this time, they will not receive infusions of either active drug or placebo.

[redacted]

See the Schedule of Activities for Part 1 in Table 2 and Table 3 (Section 1.2).

[redacted]

Part 2 Treatment Period and Follow-up

Participants meeting eligibility criteria during the screening period will enter the Part 2 treatment period. Approximately 120 participants will be randomized via IRT in a 1:1:1:1 ratio to receive 45 mg BMS-986263 Q2W, 90 mg BMS-986263 Q2W, 90 mg BMS-986263 Q4W, or placebo Q2W in a double-blind manner. Randomization of the participants will be stratified by fibrosis stage (METAVIR Stage 3 or Stage 4). Participants will receive study treatment via IV administration for a total of 24 weeks. Liver biopsy will be performed during the screening period and on Day 169. MRE will be collected at Day 43, Day 85, Day 169, and Day 253 in Part 2.

After 24 weeks (Day 169) of treatment, participants in Part 2 will enter the follow-up period for 12 weeks. During this time, they will not receive infusions of either active drug or placebo.

[redacted]

See the Schedule of Activities for Part 2 in Table 4 and Table 6 (Section 1.2).

STUDY POPULATION AND MAIN ELIGIBILITY CRITERIA:

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. Participants must be willing to participate in the study and sign the informed consent form (ICF).
   b. Participants must be willing and able to complete all study-specific procedures and visits.
2. Participants must provide documentation showing an SVR for at least 1 year prior to the date of screening. SVR is defined as a negative HCV RNA at least 12 weeks from the end of antiviral therapy. Thus, the minimum duration is 12 weeks of negative HCV RNA (to establish SVR) plus 1 year of sustained SVR (ie, 52 weeks + at least 12 weeks).
3. The participant must have METAVIR Stage 3 or Stage 4 fibrosis (or equivalent if using other classification; eg, Ishak) assessed by liver biopsy.
4. Participants must have a mean score of ≥ 5.0 kPa by FibroScan (Section 8.6.1.4). If a participant has not had a liver biopsy within 8 weeks of screening, the biopsy will be carried out during the screening period following determination of eligibility by FibroScan assessment (ie, has mean FibroScan score of ≥ 5.0 kPa).

5. The participant must have an adequate MRE and DXA performed during screening confirmed by the central imaging facility prior to randomization.
6. Age and reproductive status
    a. Males or females ≥ 21 and ≤ 75 years of age at the time of screening
    b. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study and prior to each dose of study treatment.
    c. To confirm menopause, females must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL.
    d. Women must not be breastfeeding
    e. WOCBP must agree to follow instructions for method(s) of highly effective contraception, as defined in Appendix 3, for the duration of treatment (BMS-986263 or placebo) plus 5 half-lives of study treatment (5 days) plus 30 days (duration of ovulatory cycle) for a total of 35 days post-treatment.
    f. Males who are sexually active with WOCBP must agree to have their female partners follow instructions for method(s) of highly effective contraception, as defined in Appendix 3, for the duration of treatment with study treatment (BMS-986263 or placebo) plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 95 days after treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.
    g. Azoospermic males are exempt from contraceptive requirements for the purposes of prevention of pregnancy (ie, male study participants with partners who are WOCBP). However, in addition to the use of highly effective methods of contraception, males in the study who are sexually active with WOCBP must use barrier methods (eg. male condom, female condom) to prevent transmission of seminal fluid that may contain traces of study drug. Barrier methods must be used for the duration of exposure with study treatment (BMS-986263 or placebo) plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 95 days after treatment completion.
    h. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male participants (and/or their caregivers, as applicable) who are sexually active with WOCBP, on the importance of using highly effective pregnancy in light of the potential for teratogenicity (Appendix 3). Investigators shall advise on the use of highly effective methods of contraception (ie, those that have a failure rate of < 1% when used consistently and correctly).

Exclusion Criteria

1. Target disease exclusions
    a. Other causes of liver disease including but not limited to alcoholic liver disease, hepatitis B virus (HBV; serologically-positive as determined using United States Centers for Disease Control and Prevention guidance for interpretation of hepatitis B serologic test results), autoimmune hepatitis, drug-induced hepatotoxicity, Wilson disease, iron overload, α-1-antitrypsin deficiency, NASH, hemochromatosis); participants having liver diseases associated with infection with any other hepatitis virus are to be excluded. It is up to the investigator to be sure the participants do not have any of the above mentioned pathologies.
    b. Detectable HCV RNA at screening
    c. Child-Pugh score > 6 at screening (Appendix 7)
    d. MELD score > 12 based on screening laboratories (Appendix 8)
    e. 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 or ultrasound; based on local assessment):
        i. AFP > 100 ng/mL (> 82.6 IU/mL) OR
        ii. AFP ≥ 50 and ≤ 100 ng/mL (≥ 41.3 IU/mL and ≤ 82.6 IU/mL) with liver imaging showing evidence of HCC
2. Medical conditions
    a. Blood transfusion in the last 6 months prior to screening due to the risk of reinfection with HCV, HBV, human immunodeficiency virus (HIV), etc

b. The participant has any disease or condition which, in the opinion of the investigator, might compromise patient safety (eg, hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, skeletal, central nervous system, or complement-mediated disease).
c. Hepatitis B surface antigen (HBsAg)-positive participants or hepatitis B core antibody (HbcAb)-positive participants with detectable hepatitis B viral DNA. Where required by local regulations or standard practice, hepatitis B surface antibody (HBsAb)-positive participants must also have HBV DNA testing performed.
d. Known immunocompromised status, including but not limited to individuals who have undergone organ transplantation or who are positive for HIV or have acquired immunodeficiency syndrome-related illness, as reported by the participant and/or documentation.
e. History of liver transplantation or planned liver transplant
f. Any history of hepatic decompensation, including ascites, variceal bleeding, hepatic encephalopathy or spontaneous bacterial peritonitis.
g. The participant has a 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. 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 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.
i. History of alcohol consumption ≥21 units/week (males) or ≥14 units/week (females) 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. Participants should limit alcohol during their participation in the study (Section 8.4.4).
j. History, within the last 2 years, of alcohol or frequent marijuana abuse (in the opinion of the Investigator), significant mental illness, or physical dependence on any opioid.
k. Positive urine test during screening for illegal drugs of abuse (with the exception of marijuana), unless these drugs are prescribed by the treating physician (prescription must be documented by the investigator or the designee in source documents).
l. History of intravenous drug use within the 3 years prior to screening.
m. History of bariatric surgery within the 5 years prior to screening or planned during the conduct of the study.
n. History of major surgery within 3 months of screening; this includes surgery that involves a risk to the life of the patient, specifically, within the cranium, chest, abdomen, or pelvic cavity.
o. History of weight gain/loss ≥ 10% of body weight in the 6 months prior to screening.
p. Inability to tolerate IV medication or other study procedures
q. Presence of pacemaker and or other metal objects in the body

3. Prior and concomitant therapy

a. Participants who take any medications that, in the opinion of the investigator, increase the risk for complications during liver biopsy (eg, chronic or high-dose nonsteroidal inflammatory drugs, anticoagulants, or fish oil supplements)
b. Participants taking anti-obesity agents (eg, ORLISTAT®) within 4 weeks of the first dose of study treatment.
c. Participants receiving interferon therapy for any disease, or received interferon therapy for any disease within 52 weeks prior to administration of study treatment.
d. The participant takes any vitamin A containing supplements or multivitamins, or vitamin A containing medications after signing the ICF.
e. Participants taking anti-diabetic or anti-dyslipidemic medication receiving stable doses for less than 30 days prior to the first dose of study medication.
f. Participants unable to comply with restrictions and prohibited treatments.
g. Participants who have not discontinued other investigational agents must be discontinued at least 12 weeks or 5 half-lives before the first dose of study treatment, whichever is longer.
h. Prior exposure to BMS-986263

i. 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).

4. Physical and laboratory test findings

   a. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory determinations beyond what is consistent with the target population
   b. Body mass index (BMI) > 34 kg/m2. Participants with a BMI of 30-34 kg/m2 must have an ALT ≤ upper limit of the normal range (ULN).
   c. The participant's baseline laboratory test results include abnormal values considered to be clinically significant by the investigator.
   d. The participant's laboratory test results at screening include any of the following:
      - albumin < 3.5 g/dL
      - INR > ULN
      - ALT value ≥ 2× the ULN
      - hemoglobin A1c ≥ 9.0%
      - total bilirubin > ULN
      - hemoglobin < lower limit of normal (LLN)
      - platelet count < 100,000/µL
      - white blood cell count ≤ 3000/µL
   e. Glomerular filtration rate < 30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease equation.
   f. The participant's vitamin A levels at screening are > ULN.
   g. Alpha-fetoprotein (AFP; see Exclusion 1e, above):
      i. AFP > 100 ng/mL (> 82.6 IU/mL) OR
      ii. AFP ≥ 50 and ≤ 100 ng/mL (≥ 41.3 IU/mL and ≤ 82.6 IU/mL) with liver ultrasound showing findings suspicious for HCC.

5. Not applicable

6. Allergies and adverse drug reaction

   a. History of allergy to BMS-986263 or related compounds

7. Other exclusion criteria

   a. Prisoners or participants who are involuntarily incarcerated. Note: Under certain specific circumstances, 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. Participants who participated in an interventional study with the last intervention occurring within 24 weeks prior to administration of study treatment.
   d. Any factor, which in the opinion of the investigator would jeopardize the evaluation or safety or be associated with poor adherence to the protocol.

MRI Contraindications

The imaging specialist at the site's imaging facility will be responsible for determining whether a participant is contraindicated from undergoing these procedures. Common conditions that may preclude the participant from scans include, but are not limited to:

   a. History of claustrophobia
   b. Physical limitations related to fitting into the bore of the magnet or weight greater than that allowable by the imaging instrument (i.e., body weight in excess of 250 pounds or 113.4 kg)
   c. Participants with a pacemaker, epicardial pacemaker wires, MRI-incompatible cardiac valve prostheses, MRI-incompatible vascular clips less than 2 months old, or MRI-incompatible aneurysm clips of any age
   d. Participants with MRI-incompatible cochlear implants

e. Participants with spinal nerve stimulators
f. Participants with an infusion pump
g. Participants with known metallic fragments in the body
h. Employment history that involves exposure to welding

The above list should not be used as a substitute for local clinical standards of care. The ultimate decision to perform any scan should rest with the site radiologist, the investigator, and the standard set by the IEC.

Lifestyle Restrictions:

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

[redacted]

NUMBER OF PARTICIPANTS:

It is planned that approximately 180 male and female participants will be evaluable for analysis. In Part 1, approximately 60 participants will be randomized in a 1:2:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW. In Part 2, approximately 120 participants will be randomized in a 1:1:1:1 ratio to 45 mg BMS-986263 Q2W, 90 mg BMS-986263 Q2W, 90 mg BMS-986263 Q4W, or placebo Q2W. If a higher than expected proportion of study participants discontinue from the study prior to the evaluation of the primary endpoint, the sponsor may choose to enroll additional participants to ensure an adequate number of participants are available for evaluation of the primary endpoint.

STUDY TREATMENT(S):

Test Product and Reference Therapy, Dose and Mode of Administration:

BMS-986263 (45 mg or 90 mg) or placebo will be administered as an IV infusion according to the treatment schedule outlined in the Schedule of Activities (Section 1.2).

[redacted]

BMS-986263 has the potential to treat liver fibrosis as it combines an HSP47 siRNA with a formulation designed to target the HSP47 siRNA to HSCs.

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

[redacted]

Study Treatment Infusion Rate

[redacted]

[redacted]

The study medication should not be infused at a duration lesser than 60 minutes. The infusion rate may be modified by the investigator based on clinical discretion and/or the participant's previous tolerance of the infusion, including any infusion reactions that may have occurred in the past. In addition, the investigator may choose to pause the infusion depending on the participant's clinical condition and history.

Of note, while the rate of infusion can be modified as described above; no reductions or modifications of the total dose to be administered are allowed.

If a participant experiences an infusion-related reaction, temporary interruption of the infusion and/or reduction of the infusion rate (for example, but not limited to, modification of infusion rate and/or a pause in the infusion) may lead to improvement of signs and symptoms. Medications, emergency equipment, and trained personnel able to treat immediate or delayed infusion-related reactions should be available for immediate access at the clinical site(s).

Premedication

To reduce the potential for possible infusion reactions, based on the discretion of the investigator, the 20 participants in Part 1 may be pretreated 15 to 30 minutes before the start of the study treatment infusion. The investigator may choose to administer any or all of the following premedications: 50 mg diphenhydramine hydrochloride IV, 20 mg famotidine IV, and/or hydrocortisone 100 mg IV. Hydrocortisone IV may be replaced with methylprednisolone sodium succinate 125 mg IV based on the discretion of the investigator. Additionally, the investigator may choose not to administer any premedication. If IV diphenhydramine is not available, an oral dose of 5 mg levocetirizine dihydrochloride or an oral dose of 50 mg diphenhydramine hydrochloride may be substituted and administered 2 hours ± 15 minutes before the start of study treatment infusion.

Participants who receive antihistamine premedication should be advised that these medications may be sedating and cautioned against driving or operating heavy machinery for at least 3 hours after administration, although a longer observation period may be necessary for an individual participant. The decision to observe a study participant beyond the required 3 hours will be at the discretion of the attending investigator.

DURATION OF TREATMENT: In Part 1, each participant will undergo 12 weeks of treatment. In Part 2, each participant will undergo 24 weeks of treatment. All treatment groups will be followed for a total of 36 weeks, consisting of 24 weeks follow-up for Part 1, and 12 weeks follow-up for Part 2 (see schematic, above).

STUDY EVALUATIONS:

Primary Efficacy Endpoint:

The primary efficacy endpoint is the proportion of participants who achieve ≥ 1 stage improvement in liver fibrosis (METAVIR score) as determined by liver biopsy after 12 weeks of treatment in Part 1 and after 24 weeks in Part 2.

Secondary Efficacy Endpoints:

- Change in CPA, as compared to placebo after 12 weeks of treatment in Part 1 and after 24 weeks of treatment in Part 2
- Proportion of participants with ≥ 1 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment in Part 1 and after 24 weeks of treatment in Part 2
- Proportion of participants with ≥ 2 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 12 weeks of treatment in Part 1 and after 24 weeks of treatment in Part 2
- Proportion of participants with ≥ 2 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment in Part 1 and after 24 weeks of treatment in Part 2
- Proportion of participants with ≥ 15% decrease from baseline in liver stiffness as measured by MRE at Day 85 in Part 1 and Day 169 in Part 2
- Change from baseline in liver stiffness as measured by MRE Day 85 in Part 1 and Day 169 in Part 2

[redacted]

Other analyses:

- Safety endpoints include incidence of adverse events (AEs), serious adverse events (SAEs), [redacted] AEs leading to discontinuation, and death, as well as marked abnormalities in clinical laboratory tests, vital sign measurements, ECGs, physical examinations [redacted]
- Pharmacokinetics, PD, [redacted] of BMS-986263 will be analyzed based on the time points indicated in the Schedule of Activities (Section 1.2).

STATISTICAL METHODS:

Primary Endpoint Part 1:

To evaluate the effect of BMS-986263 (90 mg QW) on METAVIR fibrosis Stage at Week 12, a 95.0% confidence interval (CI) of response rate for treatment vs placebo will be used to estimate the difference between the proportion

of participants with ≥ 1 stage improvement in fibrosis as determined by liver biopsy. Additionally, the odds ratio will be used to estimate improvement of treatment as compared to placebo for the proportion of participants with ≥ 1 stage improvement in fibrosis on liver biopsy at Week 12.

Primary Endpoint Part 2:

To evaluate the effect of BMS-986263 (45 mg Q2W, 90 mg Q2W, and 90 mg Q4W), on METAVIR Fibrosis Stage vs placebo, a stratified Cochran Armitage Trend Test controlling for hepatic fibrosis stage (Stage 3 or Stage 4) will be used to analyze the proportion of participants with ≥ 1 stage improvement in fibrosis on liver biopsy at Week 24. After the assessment of trend, comparisons of each treatment group with placebo will be performed utilizing a stratified (fibrosis stage) Cochran Mantel-Haenszel test (CMH). All of these analyses will be performed at 1-sided 0.05 level of significance. In addition, 95% CIs for the response rates and odds-ratios will be calculated. A sensitivity analysis using an extended CMH correlation test will be used to assess the trend among the proportions for treatment groups with an adjustment to strata (fibrosis stage). Two- sided 0.1 level of significance will be used.

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.

Continuous endpoints may be analyzed by analysis of covariance methods.

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

Subgroup analyses will be performed including hepatic fibrosis stage.

Safety Analysis:

Safety assessments 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.

[redacted]

DATE AND VERSION: 21-Feb-2019, Final Approved v7.0

1.2 Schedule of Activities

Visit details are provided for the Screening and Day 1 (Randomization) Procedural Outline for Part 1 and Part 2 in Table 1. Visit details are provided for Part 1 treatment and follow-up periods in Table 2 and Table 3, respectively, Part 2 treatment Period in Table 4 and Table 5, and Part 2 follow-up period in Table 6.

In the event that multiple procedures are required at a single timepoint, the electrocardiogram (ECG) may be obtained up to 15 minutes earlier; vital signs may be obtained up to 10 minutes earlier; and, clinical laboratory sample may be obtained up to 5 minutes earlier than the nominal time point, ensuring the pharmacokinetic (PK) samples can be collected on time. These study procedures must be performed prior to infusion.

Table 1 Screening and Day 1 (Randomization) Procedural Outline IM025006: Part 1 and Part 2

Procedure	Screening[a] Day -35 to -1	Day 1 (Randomization)	Notes
Eligibility Assessments			
Informed consent	X		The approved informed consent form (ICF) must be signed before completing any protocol-specific procedures. A participant will be considered enrolled only when the informed consent is signed.
[redacted]			
Inclusion/exclusion criteria	X		
Medical history	X	X	
Prior medications	X	X	Prior medications are medications taken within 4 weeks before the first dose of study medication and discontinued before the first dose of study medication.
Call via IRT to register participant	X		See Section 8.5.2 for additional information.
Safety Assessments			
Concomitant medication use	X	X	
Monitor for AEs		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 will occur at every study visit.
Monitor for SAEs	X	X	All SAEs must be collected from the date of participant's written consent until 30 days after the final dose of the study treatment or the participant's participation in the study if the last scheduled visit occurs at a later time. Monitoring for SAEs will occur at every study visit.

Table 1 Screening and Day 1 (Randomization) Procedural Outline IM025006: Part 1 and Part 2

Procedure	Screening[a] Day -35 to -1	Day 1 (Randomization)	Notes
Physical and Metabolic 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) evaluation. 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, extremities, height, and body weight.
Abbreviated physical assessment		X	Abbreviated examinations will include vital signs, weight, an abdominal exam, assessments of ascites and hepatic encephalopathy, and symptom-focused assessments.
[redacted]			
Collect height and weight	X	X	
Body mass index calculation	X	X	Appendix 8
Vital Signs	X	X	Includes body temperature, respiratory rate, and seated 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 electrocardiogram	X	X*	* On Day 1 (Randomization), ECGs should be recorded prior to infusion but after the participant has been supine for at least 5 minutes.
Liver biopsy	X		Refer to Section 8.6.1.1 for eligibility criteria. Key eligibility criteria should be evaluated prior to biopsy, MRE, and DXA. For participants with prior biopsies, hepatic tissue must be made available for central analysis. For participants undergoing biopsy, eligibility must be confirmed as described in Section 8.1.1.

Table 1 Screening and Day 1 (Randomization) Procedural Outline IM025006: Part 1 and Part 2

Procedure	Screening[a] Day -35 to -1	Day 1 (Randomization)	Notes
DXA	X		DXA must be conducted at least 5 days ahead of Day 1 (Randomization) to allow adequate time for results to be provided. Adequacy of DXA should be confirmed by the imaging vendor prior to randomization. See Section 8.6.2.8. Key eligibility criteria should be evaluated prior to biopsy, MRE, and DXA.
MRE	X		MRE must be conducted at least 5 days ahead of Day 1 (Randomization) to allow adequate time for results to be provided. Participants must fast for 4 hours prior to MRE. Adequacy of MRE should be confirmed by the imaging vendor prior to randomization. See Section 8.1.1 and Section 8.6.1.2. Key eligibility criteria should be evaluated prior to biopsy, MRE, and DXA.
FibroScan®	X		Use of FibroScan to determine eligibility is described in Section 8.1.1. Participants must fast for 4 hours prior to FibroScan assessments and must have a mean score of ≥ 5.0 kPa by FibroScan at baseline. See Section 8.6.1.4.
Ultrasound	X		Ultrasound must be conducted at screening for potential evidence of HCC, as described in Section 8.4.2.
[redacted]			
Laboratory Assessments			
Hematology	X	X	Pre-infusion when on a dosing day. To assess stability of liver function, Screening and Day 1 (Randomization) hematology assessments must be performed at least 2 weeks apart (Section 8.1.1). See Section 8.6.2.7 and Table 11.
Chemistry	X	X	Pre-infusion when on a dosing day. To assess stability of liver function, Screening and Day 1 (Randomization) chemistry assessments must be

Table 1 Screening and Day 1 (Randomization) Procedural Outline IM025006: Part 1 and Part 2

Procedure	Screening[a] Day -35 to -1	Day 1 (Randomization)	Notes
			performed at least 2 weeks apart (Section 8.1.1). See Section 8.6.2.7 and Table 11.
[redacted]			
HbA1C	X		See Section 8.6.2.7 and Table 11.
Urinalysis	X	X	See Section 8.6.2.7 and Table 11.
Serology/viral load	X		HBsAg-positive participants or HbcAb-positive participants will be tested for HBV DNA. Where required by local regulations or standard practice, HBsAb-positive participants must also have HBV DNA testing performed.
HCV genotype		X	Provided by historical documentation of testing only.
Drug test	X		To test for drugs of abuse (amphetamines, barbiturates, benzodiazepines, marijuana, cocaine, opiates, and phencyclidine [PCP]).
Serum AFP	X		See Section 8.4.2.
Urine pregnancy test	X	X	For WOCBP only. Urine pregnancy test must be completed to confirm participant is not pregnant prior to each infusion. See Section 8.6.2.7.

Table 1 Screening and Day 1 (Randomization) Procedural Outline IM025006: Part 1 and Part 2

Procedure	Screening[a] Day -35 to -1	Day 1 (Randomization)	Notes
FSH	X		See Appendix 3.
Pharmacokinetic [redacted] Sampling			
Blood PK sampling		X	On Day 1 (Randomization), blood PK samples should be obtained • Pre-infusion: Time is relative to the start of infusion. Samples may be collected up to 120 minutes prior to the start of the infusion. • Mid-infusion: Time is relative to the start of infusion. Samples should be collected ± 3 minutes within specified timeframe. If infusion is administered at a modified rate, the timing of collection of this sample should correspond to the middle of the modified infusion duration of the total administered dose. • End-of-infusion: Samples should be collected 2 minutes within specified timeframe. This sample should be taken immediately prior to stopping the infusion. If the end-of-infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. • Postinfusion: Time is relative to the end-of-infusion. Samples should be collected ± 3 minutes within specified timeframe. See Table 12 and Table 13.
[redacted]			

Table 1 Screening and Day 1 (Randomization) Procedural Outline IM025006: Part 1 and Part 2

Procedure	Screening[a] Day -35 to -1	Day 1 (Randomization)	Notes
[redacted]			
Randomization and Study Treatment/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 8.5.2).
Administer study treatment		X	See Section 8.5.1 and Section 8.5.4.

AE = adverse event; AFP = alpha-fetoprotein; [redacted] DXA = dual-energy X-ray absorptiometry; [redacted] ECG = electrocardiogram; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HbcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IRT = interactive response technology; [redacted] MRE = magnetic resonance elastography; [redacted] PK = pharmacokinetics; [redacted] SAE = serious adverse event; WOCBP = women of child bearing potential

[a] Participants who experience an acute infection or require additional time for scheduling screening procedures may extend the screening period beyond 35 days after consultation with the medical monitor, but not beyond a total of 56 days (8 weeks) from the signing of the informed consent. The screening visit window may also be extended up to 5 additional days to accommodate unanticipated delays in obtaining required screening results. An extension beyond 5 days will require approval by the Medical Monitor. Also, as the hematology and chemistry laboratory screening and Day 1 (Randomization) assessments must be at least 2 weeks apart, the screening duration is Day -35 to -14 days.

Table 2 On-Treatment Procedural Outline IM025006: Part 1, Treatment Period (Day 4 through Day 85)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	12-week, Double-Blind, Treatment Period														Notes
	D 4[a]	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	
		W 1	W 2	W 3	W 4	W 5	W 6		W 7	W 8	W 9	W 10	W 11	W 12	
Safety Assessments															
Concomitant medication use		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.
Monitor for AEs		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 drug through the date of the follow-up or last visit. Monitoring for AEs will occur at every study visit.
Monitor for SAEs		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 after the final dose of the study drug or their participation in the study if the last scheduled visit occurs at a later time. Monitoring for SAEs will occur at every study visit.

Table 2 On-Treatment Procedural Outline IM025006: Part 1, Treatment Period (Day 4 through Day 85)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	12-week, Double-Blind, Treatment Period														Notes
	D 4[a]	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	
		W 1	W 2	W 3	W 4	W 5	W 6		W 7	W 8	W 9	W 10	W 11	W 12	
Physical and Metabolic Assessments															
Full physical examination														X	A full examination will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, height, and body weight.
Abbreviated physical assessment			X		X		X			X					Abbreviated examinations will include vital signs, weight, an abdominal exam, assessments of ascites and hepatic encephalopathy, and symptom-focused assessments.
[redacted]															
12-lead electrocardiogram														X	ECGs should be after the participant has been supine for at least 5 minutes.
Liver biopsy														X	See Section 8.6.1.1.
[redacted]															
MRE							X							X	MRE to be performed ± 7 days of this day to allow sites scheduling flexibility. Participants must fast for 4 hours

Table 2 On-Treatment Procedural Outline IM025006: Part 1, Treatment Period (Day 4 through Day 85)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	12-week, Double-Blind, Treatment Period														Notes
	D 4[a]	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	
		W 1	W 2	W 3	W 4	W 5	W 6		W 7	W 8	W 9	W 10	W 11	W 12	
															prior to MRE. See Section 8.6.1.2.
[redacted]															
Laboratory Assessments															
Hematology			X		X		X			X		X		X	Pre-infusion when on a dosing day See Section 8.6.2.7 and Table 11.
Chemistry		X	X	X	X	X	X		X	X	X	X	X	X	Pre-infusion when on a dosing day See Section 8.6.2.7 and Table 11.
[redacted]															

Table 2 On-Treatment Procedural Outline IM025006: Part 1, Treatment Period (Day 4 through Day 85)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	12-week, Double-Blind, Treatment Period														Notes
	D 4[a]	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	
		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]															
HbA1C														X	See Section 8.6.2.7 and Table 11.
Urinalysis			X		X		X			X				X	See Section 8.6.2.7 and Table 11.
Serum AFP														X	See Section 8.6.2.7 and Table 11.
Urine Pregnancy		X	X	X	X	X	X		X	X	X	X	X		For WOCBP only. Urine pregnancy test must be completed to confirm participant is not pregnant prior to each infusion. See Section 8.6.2.1.5.

Table 2 On-Treatment Procedural Outline IM025006: Part 1, Treatment Period (Day 4 through Day 85)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	12-week, Double-Blind, Treatment Period														Notes
	D 4[a]	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	
		W 1	W 2	W 3	W 4	W 5	W 6		W 7	W 8	W 9	W 10	W 11	W 12	
Pharmacokinetic [redacted] Sampling															
Blood PK sampling	X	X	X		X	X	X	X	X	X			X	X	See Section 8.6.3 and Table 12. *Day 4 and Day 46: Postinfusion: Sample may be collected ± 1 day at the PK visit. Day 15, Day 36, Day 50, and Day 57: Pre-infusion: Samples may be collected up to 120 minutes prior to the start of the infusion. Day 85: Collect sample 1 week after last administration. Day 8, Day 29, Day 43, and Day 78: Samples should be collected at: • Pre-infusion: Samples may be collected up to 120 minutes prior to the start of the infusion. • Mid-infusion: Samples should be collected ± 3 minutes within specified timeframe. If infusion is administered at a modified rate, the timing of collection of this sample should correspond to the middle of the modified infusion duration of the total administered dose. • End-of-infusion: Samples should be collected 2 minutes within specified timeframe. This sample should be taken immediately prior to stopping the infusion. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. • Postinfusion: Samples should be collected 1 hour ± 3 minutes postinfusion.

Table 2 On-Treatment Procedural Outline IM025006: Part 1, Treatment Period (Day 4 through Day 85)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	12-week, Double-Blind, Treatment Period														Notes
	D 4[a]	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	
		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]															

Table 2 On-Treatment Procedural Outline IM025006: Part 1, Treatment Period (Day 4 through Day 85)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	12-week, Double-Blind, Treatment Period														Notes
	D 4[a]	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	
		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]															

Table 2 On-Treatment Procedural Outline IM025006: Part 1, Treatment Period (Day 4 through Day 85)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	**12-week, Double-Blind, Treatment Period**														**Notes**
	D 4[a]	**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**	
		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]															

Table 2 On-Treatment Procedural Outline IM025006: Part 1, Treatment Period (Day 4 through Day 85)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	12-week, Double-Blind, Treatment Period														Notes
	D 4[a]	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	
		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]															
Study Treatment/Placebo Administration (X = BMS-986263; O = placebo)															
45 mg BMS-986263 QW		X	X	X	X	X	X		X	X	X	X	X		See Section 8.5.1 and Section 8.5.4.
90 mg BMS-986263 QW		X	X	X	X	X	X		X	X	X	X	X		See Section 8.5.1 and Section 8.5.4.
Placebo QW		O	O	O	O	O	O		O	O	O	O	O		See Section 8.5.1 and Section 8.5.4.

AE = adverse event; AFP = alpha-fetoprotein; [redacted] D = Day; [redacted] ECG = electrocardiogram; [redacted] MRE = magnetic resonance elastography; O = placebo; [redacted] PK = pharmacokinetics; [redacted] QW = every week; [redacted] SAE = serious adverse event; W = Week; WOCBP = women of childbearing potential

[a] Days 4 and 46: PK-only collection visits; see Table 12.

Table 3 On-Treatment Procedural Outline IM025006: Part 1, Follow-up Period (Day 99 through Day 253)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	24-week, Follow-up Period										Notes
	D 99	**D 113**	**D 127**	**D 141**	**D 155**	**D 169**	**D 197 (± 7)**	**D 225**	**D 253 (± 7) EOS**	**ET**	
	W 14	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	**W 28**	**W 32**	**W 36**		
Safety Assessments											
Concomitant medication use	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.
Monitor for AEs	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 will occur at every study visit.
Monitor for SAEs	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 after the final dose of the study treatment or participant's participation in the study if the last scheduled visit occurs at a later time. Monitoring for SAEs will occur at every study visit.
Physical and Metabolic Assessments											
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, extremities, height, and body weight.
Abbreviated physical assessment		X		X		X	X	X			Abbreviated examinations will include vital signs, weight, an abdominal exam, assessments of ascites and hepatic encephalopathy, and symptom-focused assessments.

Table 3 On-Treatment Procedural Outline IM025006: Part 1, Follow-up Period (Day 99 through Day 253)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	24-week, Follow-up Period										Notes
	D 99	**D 113**	**D 127**	**D 141**	**D 155**	**D 169**	**D 197 (± 7)**	**D 225**	**D 253 (± 7) EOS**	**ET**	
	W 14	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	**W 28**	**W 32**	**W 36**		
[redacted]											
12-lead ECG									X	X	ECGs should be after the participant has been supine for at least 5 minutes.
Liver biopsy										X	Liver biopsy must be carried out at the early termination visit only if the participant's prior liver biopsy occurred > 8 weeks prior to termination. See Section 8.6.1.1.
[redacted]											

Table 3 On-Treatment Procedural Outline IM025006: Part 1, Follow-up Period (Day 99 through Day 253)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	24-week, Follow-up Period										Notes
	D 99	**D 113**	**D 127**	**D 141**	**D 155**	**D 169**	**D 197 (± 7)**	**D 225**	**D 253 (± 7) EOS**	**ET**	
	W 14	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	**W 28**	**W 32**	**W 36**		
MRE						X			X	X*	MRE is to be performed ± 7 days of this day to allow sites scheduling flexibility. Participants must fast for 4 hours prior to MRE. * MRE must be conducted at the early termination visit only if the participant's prior MRE occurred > 4 weeks prior to termination. See Section 8.6.1.2.
[redacted]											
Laboratory Assessments											
Hematology	X		X		X			X	X	X	See Section 8.6.2.7 and Table 11.
Chemistry	X	X	X		X		X	X	X	X	See Section 8.6.2.7 and Table 11.

Table 3 On-Treatment Procedural Outline IM025006: Part 1, Follow-up Period (Day 99 through Day 253)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	24-week, Follow-up Period										Notes
	D 99	**D 113**	**D 127**	**D 141**	**D 155**	**D 169**	**D 197 (± 7)**	**D 225**	**D 253 (± 7) EOS**	**ET**	
	W 14	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	**W 28**	**W 32**	**W 36**		
[redacted]											
HbA1C									X	X	See Section 8.6.2.7 and Table 11.
Urinalysis	X		X		X			X	X		See Section 8.6.2.7 and Table 11.
Serum AFP					X			X	X		See Section 8.6.2.7 and Table 11.
Urine Pregnancy		X									For WOCBP only. See Section 8.6.2.1.5.
Pharmacokinetic [redacted] Sampling											
Blood PK sampling	X									X	Day 99: To be taken 3 weeks after last administration. See Section 8.6.3 and Table 12.
[redacted]											

Table 3 On-Treatment Procedural Outline IM025006: Part 1, Follow-up Period (Day 99 through Day 253)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	24-week, Follow-up Period										Notes
	D 99	**D 113**	**D 127**	**D 141**	**D 155**	**D 169**	**D 197 (± 7)**	**D 225**	**D 253 (± 7) EOS**	**ET**	
	W 14	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	**W 28**	**W 32**	**W 36**		
[redacted]											
Study Treatment/Placebo Administration (X = BMS-986263; O = placebo)											
45 mg BMS-986263 QW											

Table 3 On-Treatment Procedural Outline IM025006: Part 1, Follow-up Period (Day 99 through Day 253)

Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	24-week, Follow-up Period										Notes
	D 99	**D 113**	**D 127**	**D 141**	**D 155**	**D 169**	**D 197 (± 7)**	**D 225**	**D 253 (± 7) EOS**	**ET**	
	W 14	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	**W 28**	**W 32**	**W 36**		
90 mg BMS-986263 QW											
Placebo QW											

AE = adverse event; AFP = alpha-fetoprotein; [redacted] D = Day; [redacted] ECG = electrocardiogram; EOS = end of study; [redacted] ET = early termination; [redacted] MRE = magnetic resonance elastography; [redacted] PK = pharmacokinetics; [redacted] QW = every week; [redacted] SAE = serious adverse event; W = Week; WOCBP = women of childbearing potential

Table 4 On-Treatment Procedural Outline IM025006: Part 2, Treatment Period (Day 4 through Day 85)

	24-week, Double-Blind, Treatment Period														Notes
Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 4[a]**	**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**	
		W 1	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**		**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**	
Safety Assessments															
Concomitant medication use		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.
Monitor AEs		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 will occur at every study visit.
Monitor SAEs		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 after the final dose of the study treatment or participant's participation in the study if the last scheduled visit occurs at a later time. Monitoring for SAEs will occur at every study visit.
Physical and Metabolic Assessments															
Full physical examination														X	A full examination will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, height, and body weight.
Abbreviated physical assessment			X		X					X					Abbreviated examinations will include vital signs, weight, an abdominal exam, assessments of ascites and hepatic encephalopathy, and symptom-focused assessments.
[redacted]															

Table 4 On-Treatment Procedural Outline IM025006: Part 2, Treatment Period (Day 4 through Day 85)

	24-week, Double-Blind, Treatment Period														Notes
Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 4[a]**	**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**	
		W 1	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**		**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**	
12-lead ECG														X	ECGs should be recorded after the participant has been supine for at least 5 minutes.
Liver biopsy															Section 8.6.1.1.
[redacted]															
MRE							X							X	MRE is to be performed ± 7 days of this day to allow sites scheduling flexibility. Participants must fast for 4 hours prior to MRE. A Week 6 (Day 43) MRE in Part 2 will be carried out only if deemed necessary based on the Week 6 analysis in Part 1 (Section 9.3.4). See Section 8.6.1.2.
[redacted]															
Laboratory Assessments															

Table 4 On-Treatment Procedural Outline IM025006: Part 2, Treatment Period (Day 4 through Day 85)

	24-week, Double-Blind, Treatment Period														Notes
Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 4[a]**	**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**	
		W 1	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**		**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**	
Hematology			X		X		X			X				X	Pre-infusion when on a dosing day. See Section 8.6.2.7 and Table 11.
Chemistry		X	X	X	X	X	X		X	X	X	X	X	X	Pre-infusion when on a dosing day. See Section 8.6.2.7 and Table 11.
[redacted]															
HbA1C														X	See Section 8.6.2.7 and Table 11
Urinalysis			X		X		X			X		X		X	See Section 8.6.2.7 and Table 11.
Serum AFP							X							X	See Section 8.6.2.7 and Table 11.
Urine Pregnancy			X		X		X			X		X		X	For WOCBP only. Urine pregnancy test must be completed to confirm the participant is not pregnant prior to each infusion. See Section 8.6.2.1.5.

Table 4 On-Treatment Procedural Outline IM025006: Part 2, Treatment Period (Day 4 through Day 85)

	24-week, Double-Blind, Treatment Period														Notes
Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 4[a]**	**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**	
		W 1	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**		**W 7**	**W 8**	**W 9**	**W 10**	**W 11**	**W 12**	
Pharmacokinetic [redacted] Sampling															
Blood PK sampling	X		X		X		X	X		X		X		X	Days 4 and 46: Postinfusion: Sample may be collected ± 1 day at the PK visit on these days. Days 15, 57, 71, 99, 113, 127, and 155: Pre-infusion: may be collected up to 120 minutes prior to start of infusion. Days 29, 43, 85, and 141: Collect samples: • Pre-infusion: up to 120 minutes prior to infusion. • Mid-infusion: ± 3 minutes within specified timeframe. If infusion is administered at a modified rate, the timing of collection of this sample should correspond to the middle of the modified infusion duration of the total administered dose. • End-of-infusion: 2 minutes within specified timeframe; taken immediately prior to stopping the infusion. If end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. • Postinfusion: 1 hour ± 3 minutes postinfusion Day 169: Postinfusion: Samples are to be collected 14 days postinfusion. [redacted] See Section 8.6.3 and Table 12.
[redacted]															

Table 4 On-Treatment Procedural Outline IM025006: Part 2, Treatment Period (Day 4 through Day 85)

	24-week, Double-Blind, Treatment Period														Notes
Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 4[a]**	**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**	
		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]															

Table 4 On-Treatment Procedural Outline IM025006: Part 2, Treatment Period (Day 4 through Day 85)

	24-week, Double-Blind, Treatment Period														Notes
Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 4[a]**	**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**	
		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]															
Study Drug/Placebo Administration (X = BMS-986263; O = placebo)															
45 mg BMS-986263 Q2W			X		X		X			X		X		X	See Section 8.5.1 and Section 8.5.4.
90 mg BMS-986263 Q2W			X		X		X			X		X		X	See Section 8.5.1 and Section 8.5.4.
90 mg BMS-986263 Q4W			O		X		O			X		O		X	See Section 8.5.1 and Section 8.5.4.
Placebo Q2W			O		O		O			O		O		O	See Section 8.5.1 and Section 8.5.4.

AE = adverse event; AFP = alpha-fetoprotein; [redacted] D = day; [redacted]; ECG = electrocardiogram; [redacted] MRE = magnetic resonance

elastography; O = placebo; [redacted] PK = pharmacokinetics; [redacted] Q2W = once every 2 weeks; Q4W = once every 4 weeks; [redacted] SAE = serious adverse event; W = week; WOCBP = women of childbearing potential

[a] Days 4 and 46: PK-only collection visits; see Table 12.

Table 5 On-Treatment Procedural Outline IM025006: Part 2, Treatment Period (Day 99 through Day 169)

	24-week, Double-Blind, Treatment Period						Notes
Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 99**	**D 113**	**D 127**	**D 141**	**D 155**	**D 169**	
	W 14	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	
Safety Assessments							
Concomitant medication use	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.
Monitor AEs	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 will occur at every study visit.
Monitor SAEs	X	X	X	X	X	X	All SAEs must be collected from the date of participant's written consent until 30 days after the final dose of the study treatment or participant's participation in the study if the last scheduled visit occurs at a later time. Monitoring for SAEs will occur at every study visit.
Physical and Metabolic Assessments							
Full physical examination						X	A full examination will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, height, and body weight.
Abbreviated physical assessment		X		X		X	Abbreviated examinations will include vital signs, weight, an abdominal exam, assessments of ascites and hepatic encephalopathy, and symptom-focused assessments.
[redacted]							
12-lead ECG							ECG is not performed during this study period.
Liver biopsy						X	See Section 8.6.1.1.

Table 5 On-Treatment Procedural Outline IM025006: Part 2, Treatment Period (Day 99 through Day 169)

	24-week, Double-Blind, Treatment Period						Notes
Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 99**	**D 113**	**D 127**	**D 141**	**D 155**	**D 169**	
	W 14	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	
[redacted]							
MRE						X	MRE to be performed ± 7 days of this day to allow sites scheduling flexibility. Participants must fast for 4 hours prior to MRE. See Section 8.6.1.2.
[redacted]							
Laboratory Assessments							
Hematology		X		X		X	Pre-infusion when on a dosing day See Section 8.6.2.7 and Table 11.
Chemistry	X	X	X	X	X	X	Pre-infusion when on a dosing day See Section 8.6.2.7 and Table 11.
[redacted]							

Table 5 On-Treatment Procedural Outline IM025006: Part 2, Treatment Period (Day 99 through Day 169)

	24-week, Double-Blind, Treatment Period						Notes
Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 99**	**D 113**	**D 127**	**D 141**	**D 155**	**D 169**	
	W 14	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	
[redacted]							
HbA1C						X	See Section 8.6.2.7 and Table 11.
Urinalysis		X		X		X	See Section 8.6.2.7 and Table 11.
Serum AFP						X	See Section 8.6.2.7 and Table 11.
Urine Pregnancy	X	X	X	X	X	X	For WOCBP only. Urine pregnancy test must be completed to confirm participant is not pregnant prior to each infusion. See Section 8.6.2.1.5.

Table 5 On-Treatment Procedural Outline IM025006: Part 2, Treatment Period (Day 99 through Day 169)

	24-week, Double-Blind, Treatment Period						Notes
Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 99**	**D 113**	**D 127**	**D 141**	**D 155**	**D 169**	
	W 14	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	
Pharmacokinetic [redacted] Sampling							
Blood PK sampling	X	X	X	X	X	X	Days 4 and 46: Postinfusion: Sample may be collected ± 1 day at the PK visit on. Days 15, 43, 57, 71, 99, 113, 127, and 155: Pre-infusion: may be collected up to 120 minutes prior to start of infusion. Days 29, 85, and 141: Collect samples: • Pre-infusion: up to 120 minutes prior to infusion. • Mid-infusion: ± 3 minutes within specified timeframe. If infusion is administered at a modified rate, the timing of collection of this sample should correspond to the middle of the modified infusion duration of the total administered dose. • End-of-infusion: 2 minutes within specified timeframe; taken immediately prior to stopping the infusion. If end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. • Postinfusion: 1 hour ± 3 minutes postinfusion Day 169: Postinfusion: Samples are to be collected 14 days postinfusion. [redacted] See Section 8.6.3 and Table 13.
[redacted]							

Table 5 On-Treatment Procedural Outline IM025006: Part 2, Treatment Period (Day 99 through Day 169)

	24-week, Double-Blind, Treatment Period						Notes
Procedure/ Visit Day (± 3 days for all visits unless otherwise noted)	**D 99**	**D 113**	**D 127**	**D 141**	**D 155**	**D 169**	
	W 14	**W 16**	**W 18**	**W 20**	**W 22**	**W 24**	
[redacted]							
Study Treatment/Placebo Administration (X = BMS-986263; O = placebo)							
45 mg BMS986263 Q2W	X	X	X	X	X		See Section 8.5.1 and Section 8.5.4.
90 mg BMS-986263 Q2W	X	X	X	X	X		See Section 8.5.1 and Section 8.5.4.
90 mg BMS-986263 Q4W	O	X	O	X	O		See Section 8.5.1 and Section 8.5.4.
Placebo Q2W	O	O	O	O	O		See Section 8.5.1 and Section 8.5.4.

AE = adverse event; AFP = alpha-fetoprotein; [redacted] D = day; [redacted] ECG = electrocardiogram; [redacted] MRE = magnetic resonance elastography; O = placebo; [redacted] PK = pharmacokinetics; [redacted] Q2W = once every 2 weeks; Q4W = once every 4 weeks; [redacted] SAE = serious adverse event; W = week; WOCBP = women of childbearing potential

Table 6 On-Treatment Procedural Outline IM025006: Part 2, Follow-up Period (Day 197 through Day 253)

	12-week, Follow-up Period				
Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	**D 197 ±7 days**	**D 225**	**D 253 ±7 days EOS**	**ET**	**Notes**
	W 28	**W 32**	**W 36**		
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.
Monitor AEs	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 will occur at every study visit.
Monitor SAEs	X	X	X	X	All SAEs must be collected from the date of participant's written consent until 30 days after the final dose of the study treatment or participant's participation in the study if the last scheduled visit occurs at a later time. Monitoring for SAEs will occur at every study visit.
Physical and Metabolic Assessments					
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, extremities, height, and body weight.
Abbreviated physical assessment	X	X			Abbreviated examinations will include vital signs, weight, an abdominal exam, assessments of ascites and hepatic encephalopathy, and symptom-focused assessments.
[redacted]					
12-lead ECG			X	X	ECGs should be after the participant has been supine for at least 5 minutes.

Table 6 On-Treatment Procedural Outline IM025006: Part 2, Follow-up Period (Day 197 through Day 253)

	12-week, Follow-up Period				
Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	**D 197 ±7 days**	**D 225**	**D 253 ±7 days EOS**	**ET**	**Notes**
	W 28	**W 32**	**W 36**		
Liver biopsy				X	Liver biopsy must be carried out at the early termination visit only if the participant's prior liver biopsy occurred > 8weeks prior to termination. See Section 8.6.1.1.
[redacted]					
MRE			X	X	MRE is to be performed ± 7 days of this day to allow sites scheduling flexibility. Participants must fast for 4 hours prior to MRE. MRE must be conducted at the early termination visit only if the participant's prior MRE occurred > 4 weeks prior to termination. See Section 8.6.1.2.
[redacted]					
Laboratory Assessments					
Hematology	X		X	X	See Section 8.6.2.7 and Table 11.
Chemistry	X	X	X	X	See Section 8.6.2.7 and Table 11.
[redacted]					

Table 6 On-Treatment Procedural Outline IM025006: Part 2, Follow-up Period (Day 197 through Day 253)

	12-week, Follow-up Period				
Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	**D 197 ±7 days**	**D 225**	**D 253 ±7 days EOS**	**ET**	**Notes**
	W 28	**W 32**	**W 36**		
[redacted]					
HbA1C			X	X	See Section 8.6.2.7 and Table 11.
Urinalysis			X	X	See Section 8.6.2.7 and Table 11.
Serum AFP			X	X	See Section 8.6.2.7 and Table 11.
Urine Pregnancy	X				For WOCBP only. See Section 8.6.2.1.5.
Pharmacokinetic [redacted] Sampling					
Blood PK sampling	X			X	[redacted] See Section 8.6.3 and Table 12.
[redacted]					

Table 6 On-Treatment Procedural Outline IM025006: Part 2, Follow-up Period (Day 197 through Day 253)

	12-week, Follow-up Period				
Procedure/Visit Day (± 3 days for all visits unless otherwise noted)	**D 197 ±7 days**	**D 225**	**D 253 ±7 days EOS**	**ET**	**Notes**
	W 28	**W 32**	**W 36**		
[redacted]					
Study Treatment/ Placebo Administration (X = BMS-986263; O = placebo)					
45 mg BMS-986263 Q2W					
90 mg BMS-986263 Q2W					
90 mg BMS-986263 Q4W					
Placebo Q2W					

AE = adverse event; AFP = alpha-fetoprotein; [redacted] D = day; [redacted] ECG = electrocardiogram; EOS = end of study; [redacted] ET = early termination; MOA = mechanism of action; MRE = magnetic resonance elastography; [redacted] Q2W = once every 2 weeks; Q4W = once every 4 weeks; [redacted] SAE = serious adverse event; W = week; WOCBP = women of childbearing potential

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	adverse event
[redacted]	
AFP	alpha-fetoprotein
Anti-HB	hepatitis B surface antibody
Anti-HBc	hepatitis B core antibody
anti-HCV	hepatitis C virus antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
[redacted]	
AST	aspartate aminotransferase
[redacted]	
BMD	bone mineral density
BMI	body mass index
BMS	Bristol-Myers Squibb
[redacted]	
BUN	blood urea nitrogen
[redacted]	
CFR	Code of Federal Regulations
CI	confidence interval
[redacted]	
CMH	Cochran Mantel-Haenszel
CPA	Collagen Proportionate Area
Ctrough	trough observed plasma concentration
CYP	cytochrome P 450
CSR	Clinical Study Report
[redacted]	
DDI	drug-drug interaction
DILI	drug-induced liver injury
[redacted]	
DMC	data monitoring committee
[redacted]	
DNA	deoxyribonucleic acid
dsDNA	double-stranded deoxyribonucleic acid
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form

EOS	end of study
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GGT	gamma-glutamyl transferase
HbcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBV core IgM	hepatitis B virus core-specific immunoglobulin mu antibody
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSC	hepatic stellate cell
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IRT	interactive response technology
IV	intravenous
LDH	lactate dehydrogenase
LLN	lower limit of normal
MCH	mean corpuscular hemoglobin;
MELD	Model End Stage Liver Disease
mITT	modified intent-to-treat
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
NASH	nonalcoholic steatohepatitis
NOAEL	no observed adverse effect level
PCP	phencyclidine

PID	participant identification number
PK	Pharmacokinetics
PT	prothrombin time
PTT	partial thromboplastin time
QW	once every week
Q2W	once every 2 weeks
Q4W	once every 4 weeks
RBC	red blood cell
RNA	ribonucleic acid
RNASEQ	RNA sequencing
SAE	serious adverse event
SAP	statistical analysis plan
SLE	systemic lupus erythematosus
SVR	sustained virologic response
ULN	upper limit of normal
WOCBP	women of childbearing potential

4. ETHICS

4.1 Ethics Committee

This study will be conducted in compliance with institutional review board (IRB)/IEC and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and in accordance with applicable regulations regarding clinical safety data management (E2A, E2B[R3]) and scientific integrity (E4, E8, E9 and E10). In addition, this study will adhere to all local regulatory requirements and requirements for data protection.

Before initiating a study, the investigator must obtain written and dated approval from the IRB/IEC for the study protocol (and any amendments), written ICF, any consent form updates, participant recruitment procedures (eg, advertisements) and any written information to be provided to participants, and a statement from the IRB/IEC that these materials comply with GCP requirements. The approval must identify the protocol version as well as the documents reviewed.

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonised Tripartite Guideline E6 (R1); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki and all applicable regulatory requirements.

4.3 Participant Information and Consent

The investigator will explain the benefits and risks of participation in the study to each participant/legally acceptable representative in language readily understood by the participant. Written informed consent must be obtained before the participant enters the study and before any study-specific procedures are performed. If important new information becomes available requiring revisions to the ICF, the IRB/IEC-approved revised form will be used for reconsent of all participants.

5. STUDY ADMINISTRATION AND CONTACTS

Contact Type / Role	Contact
Serious adverse event (SAE) and pregnancy reporting	[redacted]
Medical Monitor (advice on protocol and study treatment)	
Study Director (overall responsibility for study conduct)	

STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Bristol-Myers Squibb Company (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 protocol.

I have read the original protocol/revised protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make a reasonable effort to complete the study within the time designated.

I will provide copies of the protocol and access to all information furnished by BMS to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I will provide protocol information to my Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s]. I understand that original protocol/revised protocols must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary Health Authorities before implementation unless to eliminate an immediate hazard to subjects.

I agree that the contents of the protocol may not be disclosed to any other person or entity or used for any other purpose without the prior written consent of BMS. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to BMS of any such disclosure.

I agree that the study data derived from this protocol may only be used and disclosed in furtherance of the protocol, for the medical treatment of a study participant or for publication of study results in accordance with the terms of the clinical trial agreement or as otherwise permitted by the terms of the clinical trial agreement.

I agree not to collect or use samples (e.g., tissue, blood, serum, urine) or collect data (other than for diagnostic or treatment purposes) from the study participants while enrolled in the study, except as expressly permitted by the protocol or the terms of the clinical trial agreement.

I understand that I may terminate or suspend enrollment of the study at any time if it becomes necessary to protect the best interests of the study participants. Unless otherwise provided in the clinical trial agreement, the study may be terminated at any time by BMS, with or without cause.

Original Protocol: ☐ Revised Protocol: ☒

Protocol Number: IM025006 Site Number:

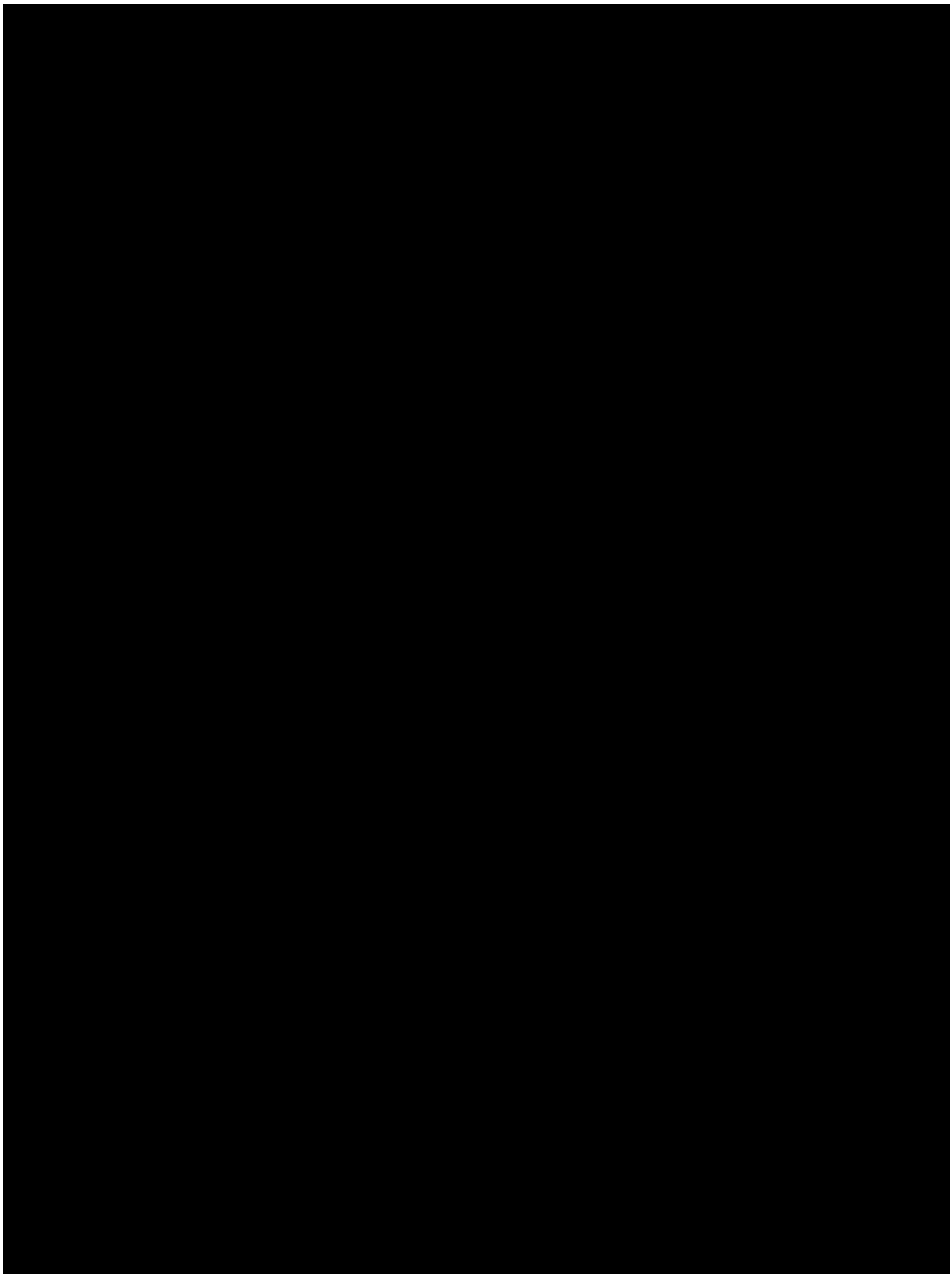
Date of Protocol or Revised Protocol:

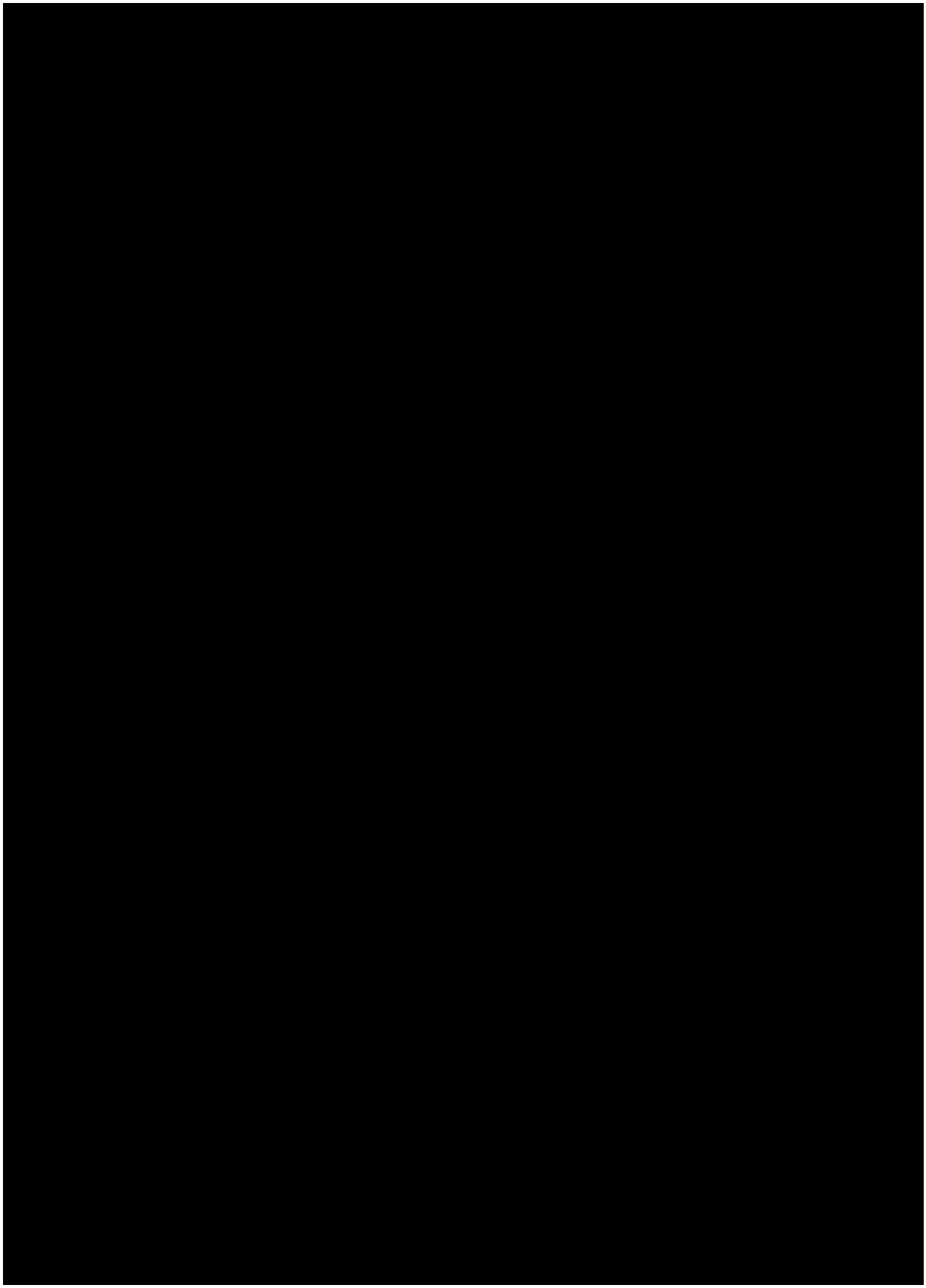
IND Number: 136,523 EUDRACT Number: Not applicable

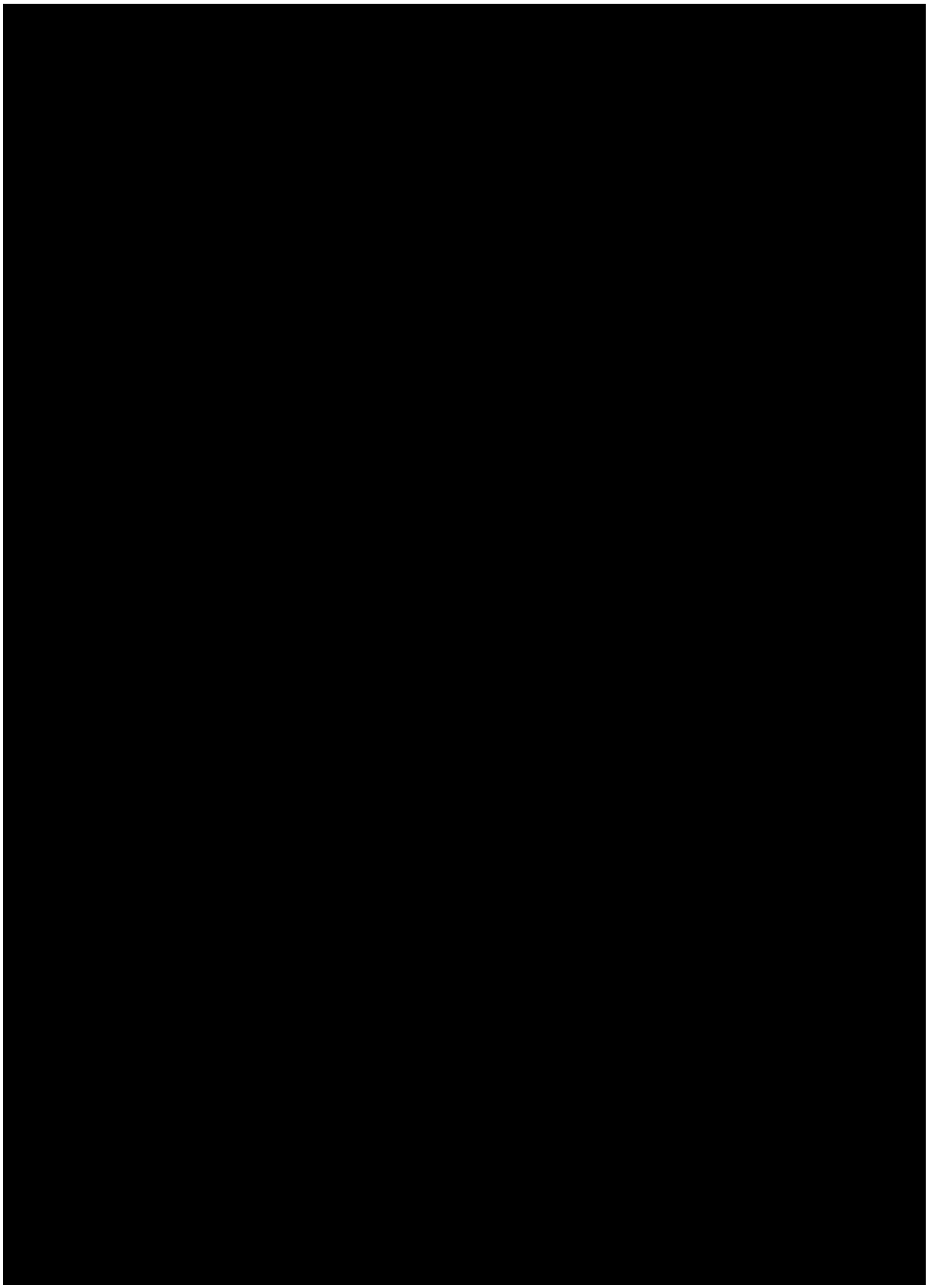
Investigator: Date:

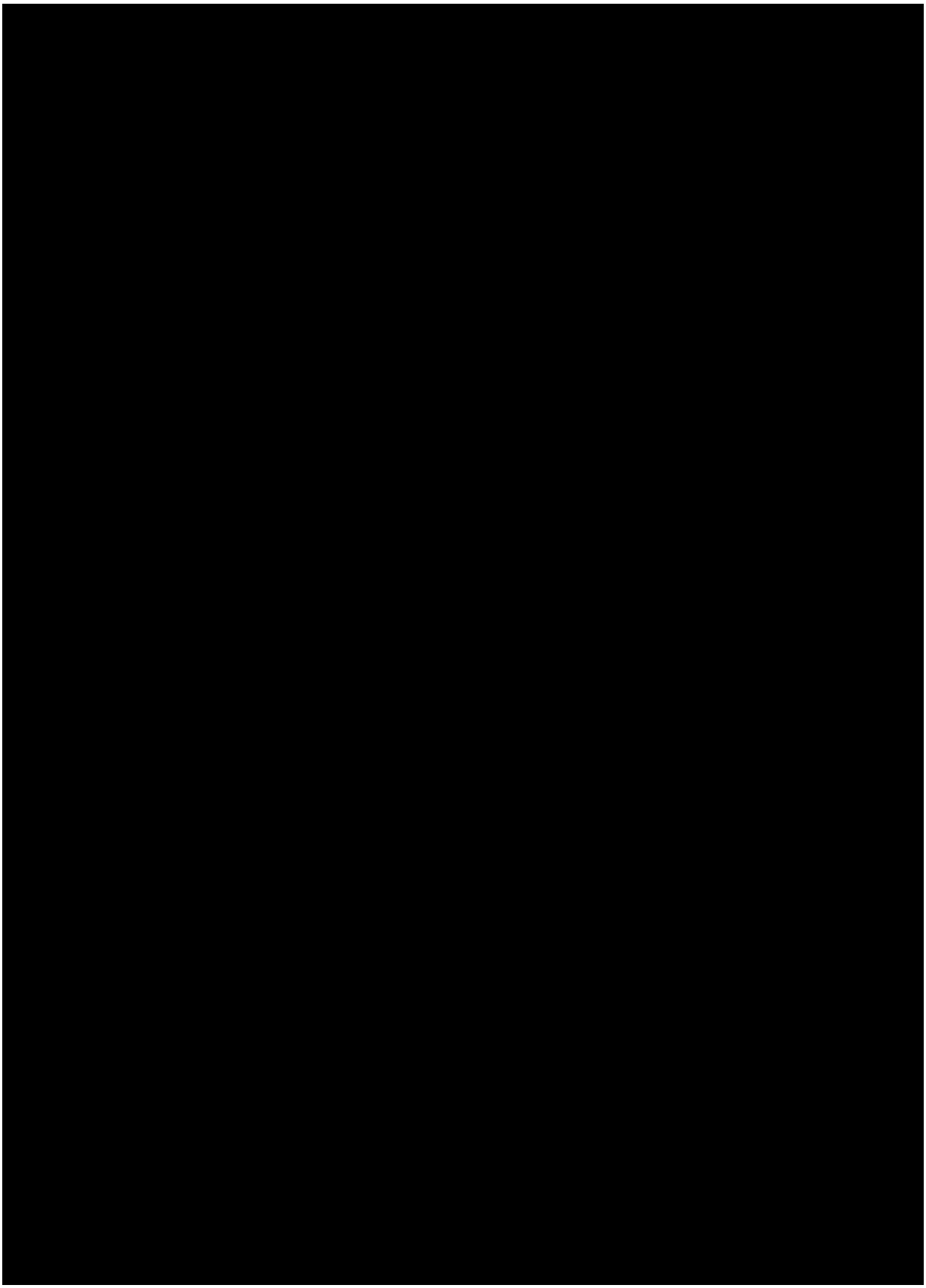
(signature)

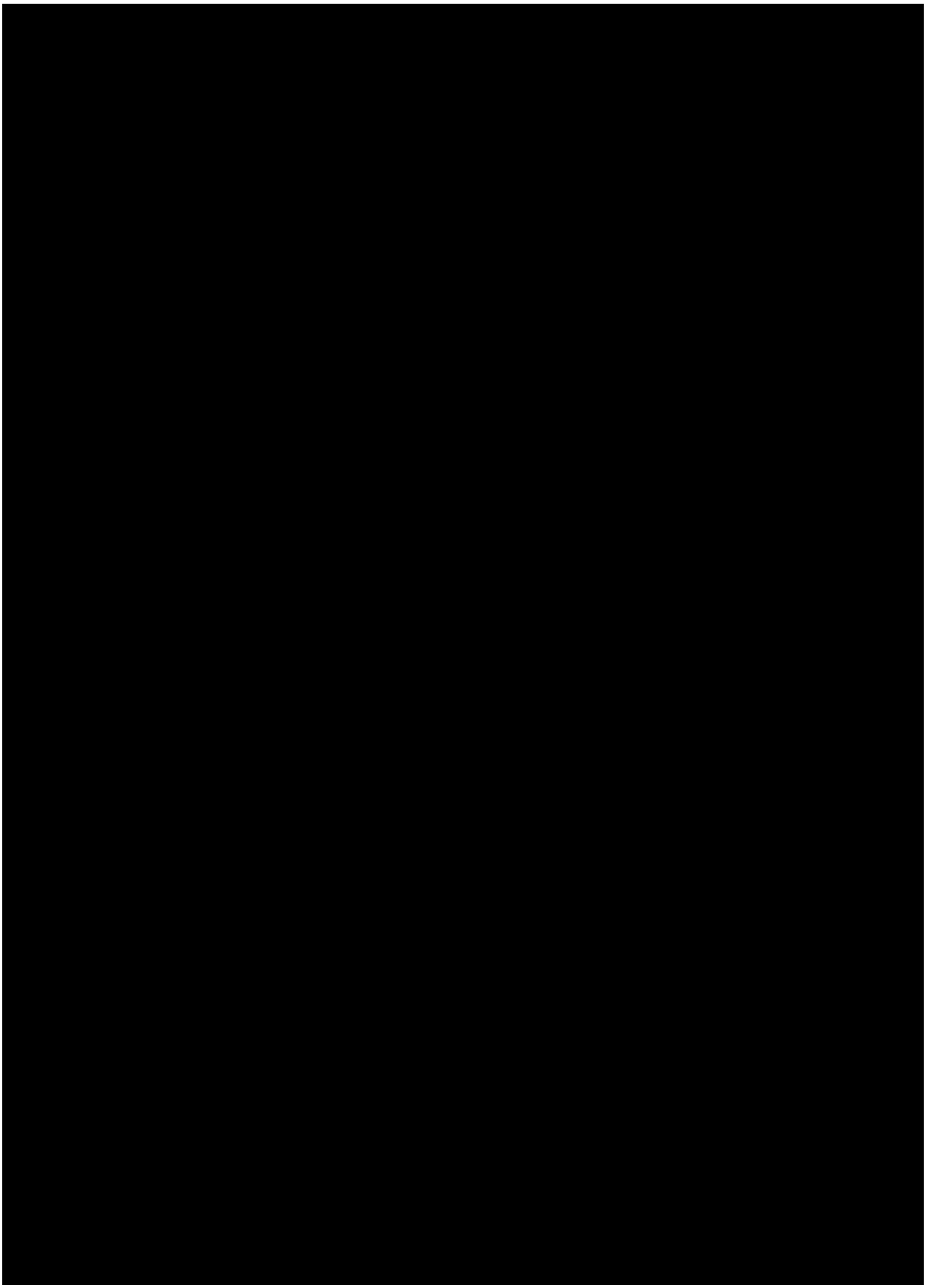
(printed name)

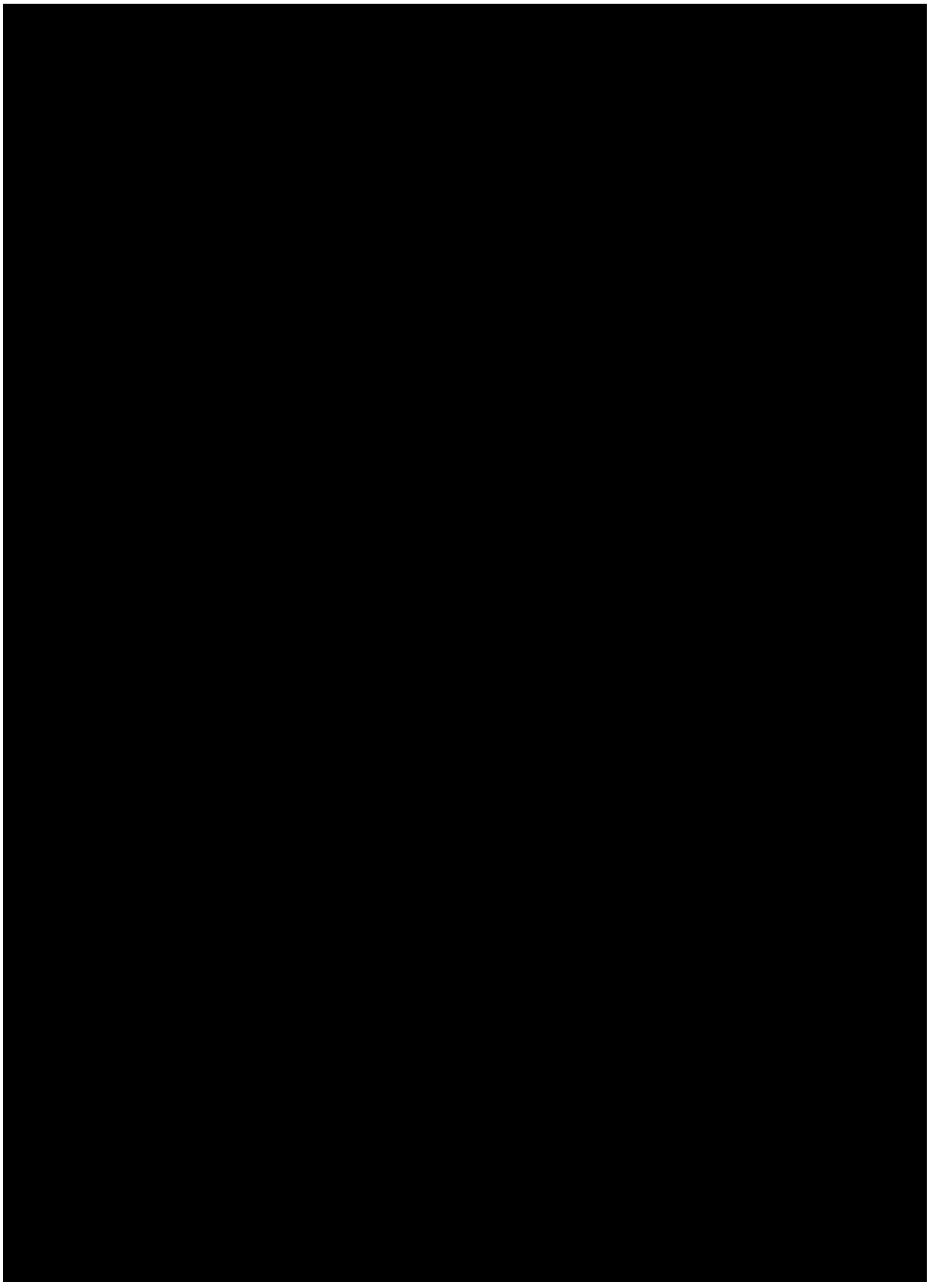


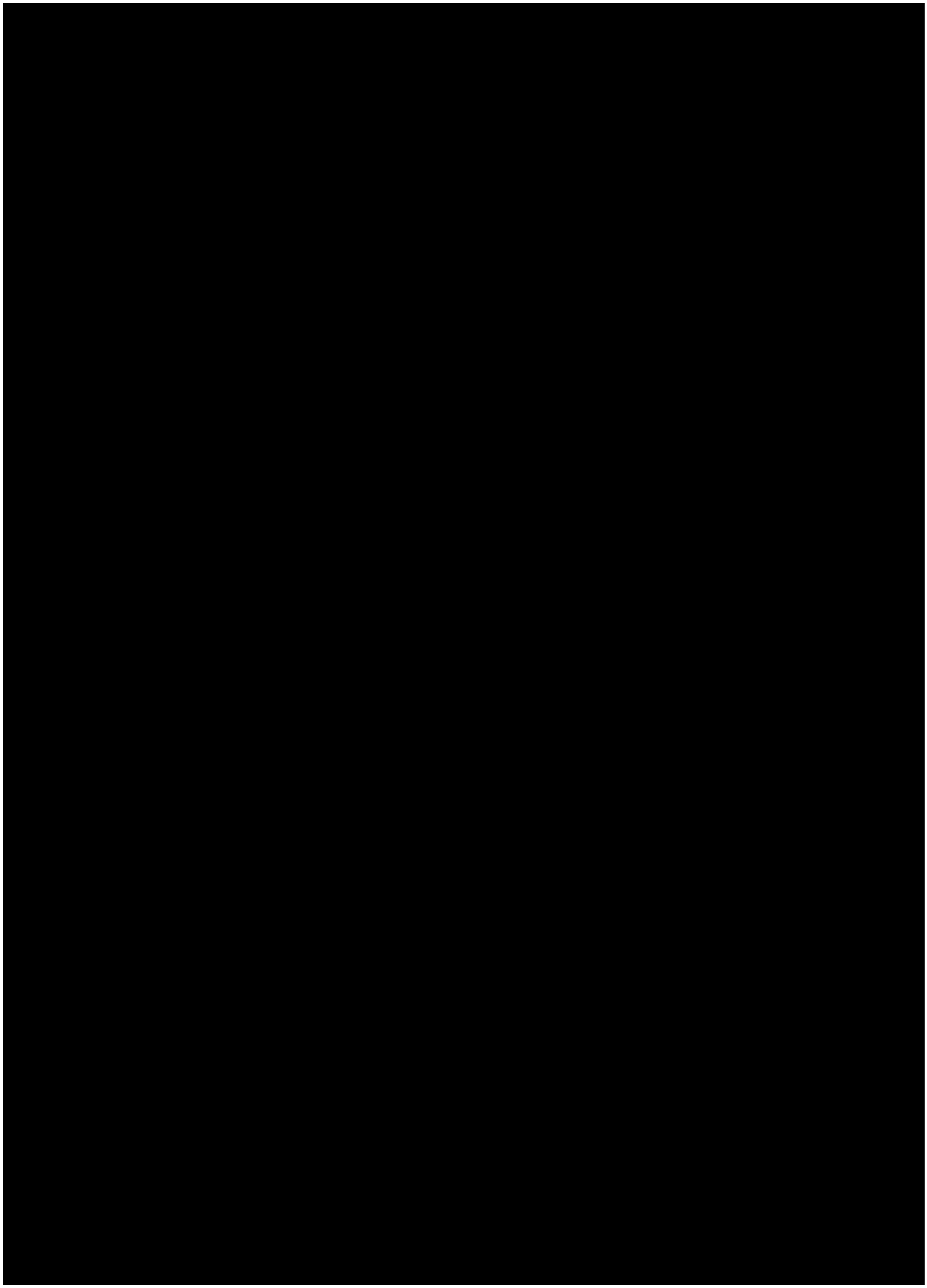


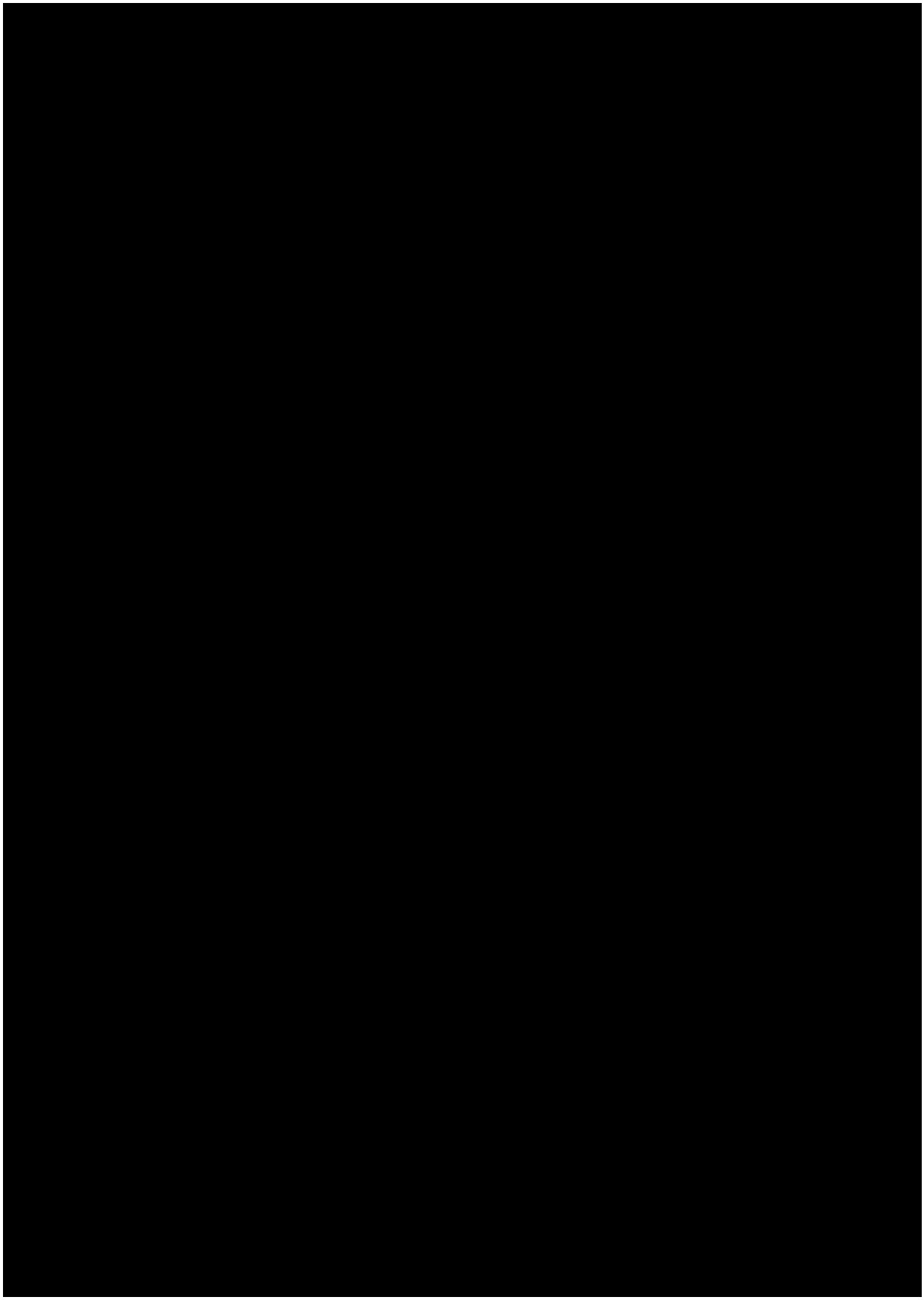


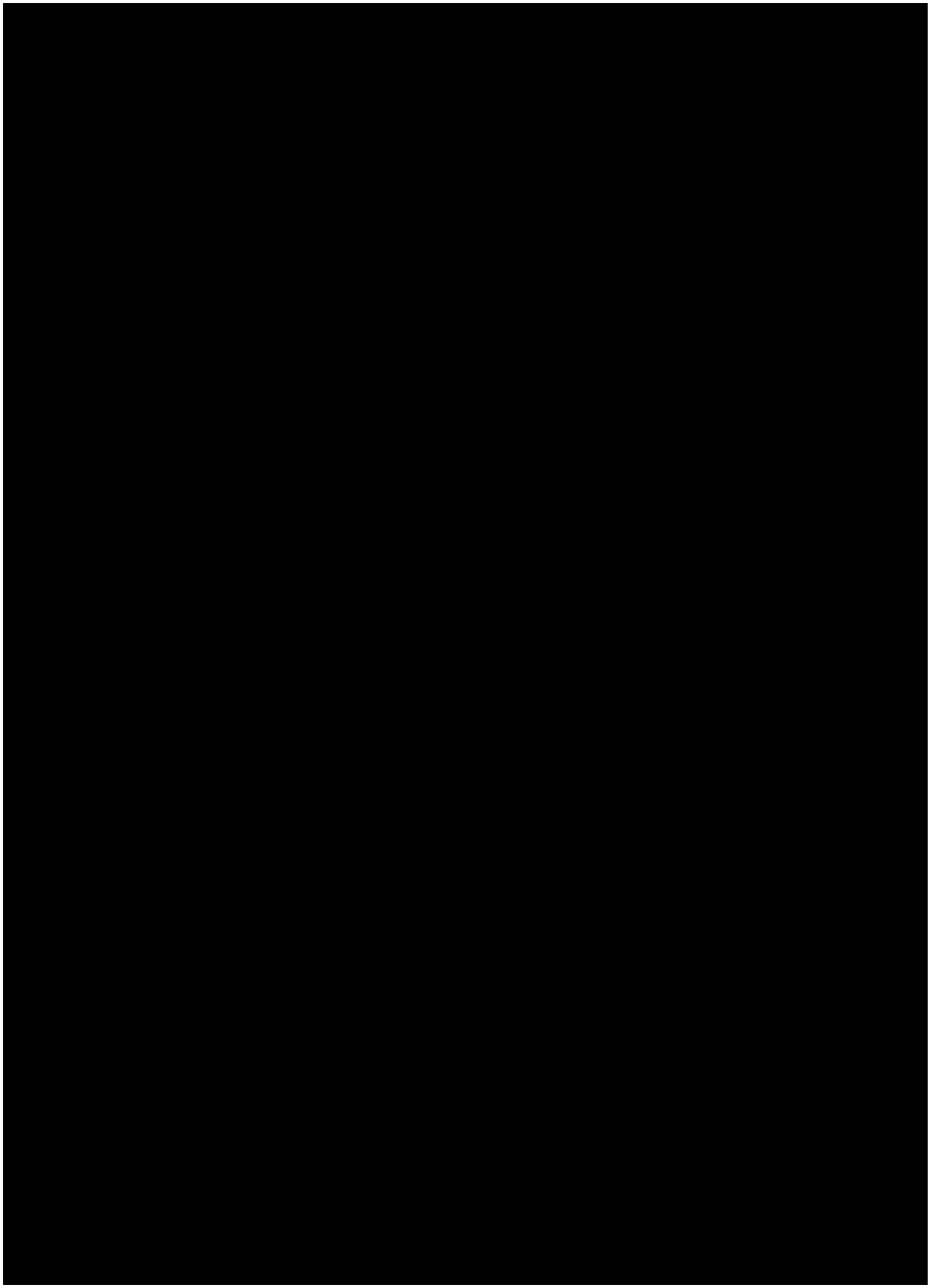


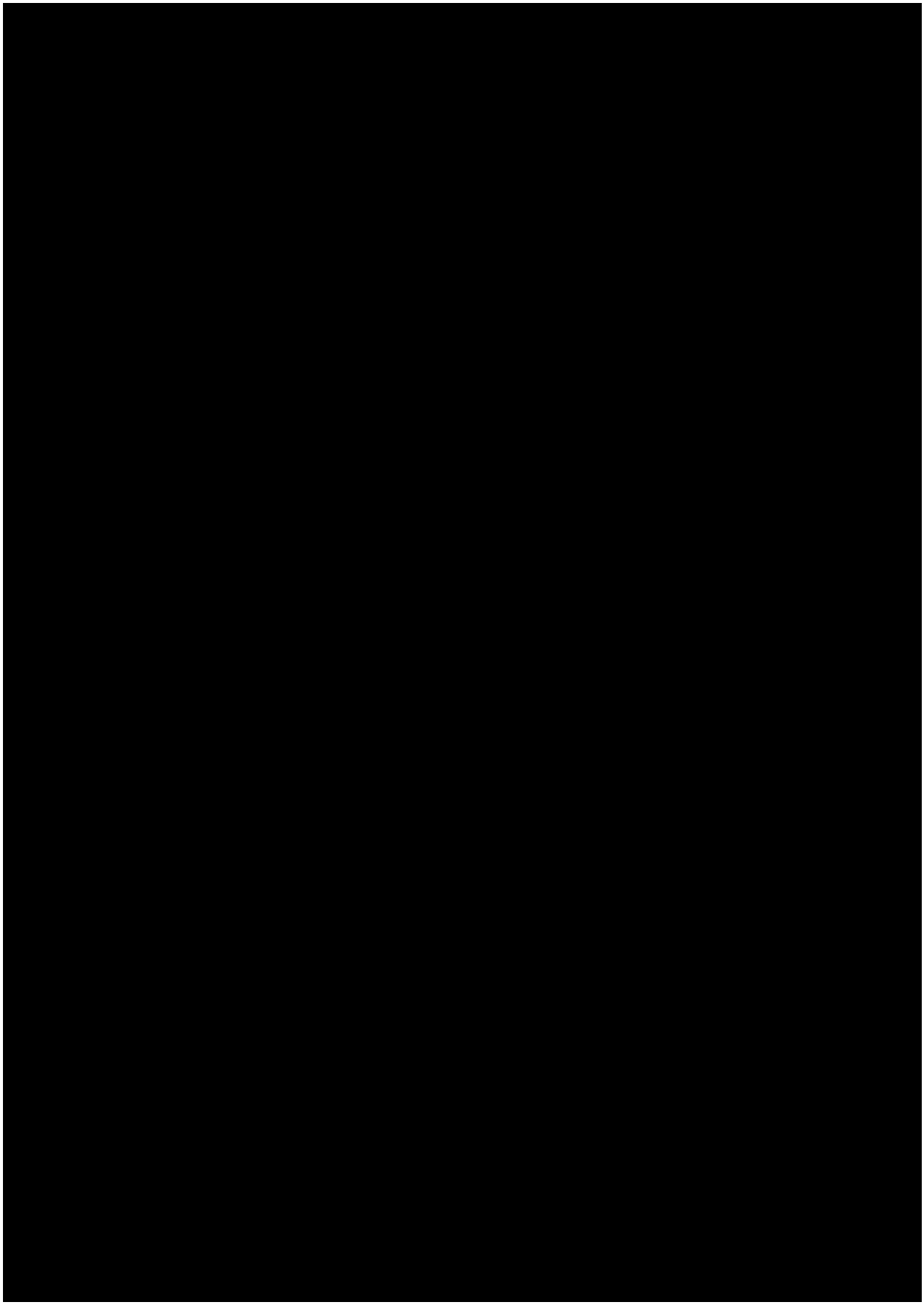












7. STUDY OBJECTIVES

Associated endpoints are described in Section 9.3. The study population is restricted to patients with advanced liver fibrosis due to HCV who have achieved SVR for a minimum of 1 year. See Section 8.4 for detailed inclusion and exclusion criteria.

7.1 Primary Study Objectives

- Part 1: To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with ≥ 1 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 12 weeks of treatment
- Part 2: To assess the effect of treatment with 45 mg Q2W, 90 mg Q2W, and 90 mg Q4W BMS-986263 on the proportion of participants with ≥ 1 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 24 weeks of treatment

7.2 Secondary Study Objectives

- Part 1
  - To assess the effect of treatment with 90 mg QW BMS-986263 on the change in collagen proportionate area (CPA), as compared to placebo after 12 weeks of treatment
  - To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with ≥ 1 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment
  - To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with ≥ 2 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 12 weeks of treatment
  - To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with ≥ 2 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment
  - To assess the effect of treatment with 90 mg QW BMS-986263 on the proportion of participants with a ≥ 15% reduction in liver stiffness as measured by MRE compared to placebo at Week 12
  - To assess the effect of treatment with 90 mg QW BMS-986263 on the change in liver stiffness from baseline as measured by MRE compared to placebo at Week 12
  - To assess the safety and tolerability of 45 mg QW and 90 mg QW BMS-986263 throughout 36 weeks of treatment and follow-up
  - To assess the PK of 45 mg QW and 90 mg QW BMS-986263
  - To describe the effect of treatment with 45 mg QW BMS-986263 on liver fibrosis after 12 weeks of treatment
- Part 2
  - To assess the effect of treatment with several doses of BMS-986263 on the change in CPA, as compared to placebo after 24 weeks of treatment
  - To assess the effect of treatment with several doses of BMS-986263 on the proportion of participants with ≥ 1 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 24 weeks of treatment

- To assess the effect of treatment with several doses of BMS-986263 on the proportion of participants with ≥ 2 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 24 weeks of treatment
- To assess the effect of treatment with several doses of BMS-986263 on the proportion of participants with ≥ 2 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 24 weeks of treatment
- To assess the effect of treatment with several doses of BMS-986263 on the proportion of participants with a ≥ 15% reduction in liver stiffness as measured by MRE compared to placebo at Week 24
- To assess the effect of treatment with several doses of BMS-986263 on the change in liver stiffness from baseline as measured by MRE compared to placebo at Week 24
- To assess the safety and tolerability of several doses of BMS-986263 throughout 36 weeks of treatment and follow-up
- To assess the PK of BMS-986263

8. INVESTIGATIONAL PLAN

8.1 Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of BMS-986263 in adults with advanced hepatic fibrosis due to HCV who have achieved SVR for at least 1 year. This study will enroll approximately 60 participants in Part 1, randomized in a 1:2:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW for 12 weeks; and approximately 120 participants in Part 2, randomized in a 1:1:1:1 ratio to receive 45 mg BMS-986263 Q2W, 90 mg BMS-986263 Q2W, 90 mg BMS-986263 Q4W, or placebo Q2W for 24 weeks. The primary study endpoint is the proportion of participants who achieve ≥ 1 stage improvement in liver fibrosis (METAVIR score) on biopsy after 12 weeks of treatment in Part 1 and after 24 weeks in Part 2.

[redacted]

Part 1: The primary objective of Part 1 is to assess the effect of treatment with 90 mg QW BMS-986263 on the proportion participants with ≥ 1 stage improvement in liver fibrosis (METAVIR score) on biopsy, as compared to placebo after 12 weeks of treatment. This part of the study includes:

- A screening period
- A 12-week, double-blind treatment period, during which participants will receive 1 of the 3 following treatments: 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW
- A 24-week follow-up period

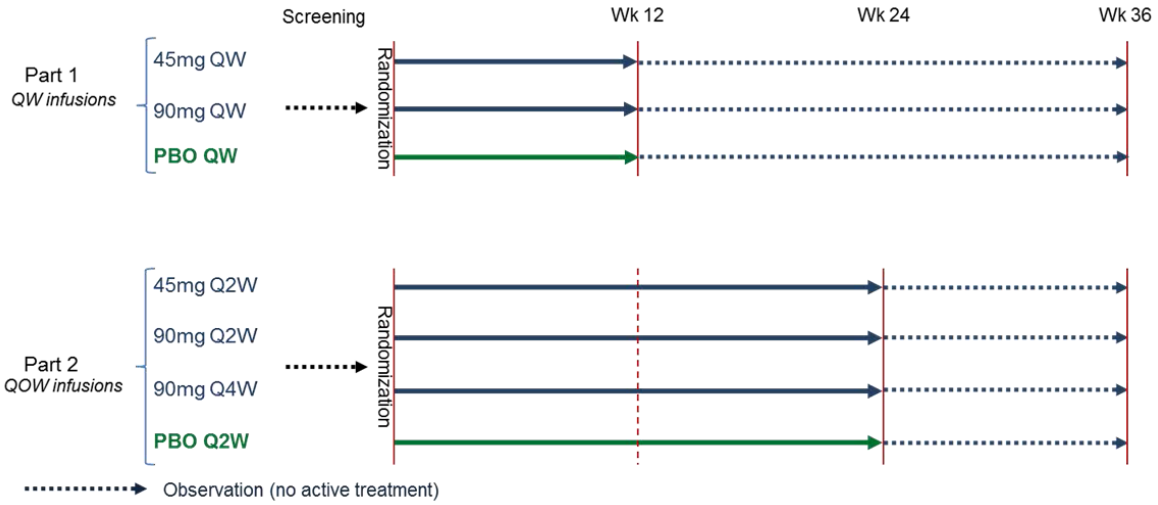
[redacted]

Part 2: The primary objective of Part 2 is to assess the effect of treatment with 45 mg BMS-986263 Q2W, 90 mg BMS-986263 Q2W, and 90 mg BMS-986263 Q4W on the proportion of participants with ≥ 1 stage improvement in liver fibrosis (METAVIR score) as compared to placebo after 24 weeks of treatment. This part of the study includes:

- A screening period
- A 24-week, double-blind treatment period, during which participants will receive 1 of the 4 following treatments: 45 mg BMS-986263 Q2W, 90 mg BMS-986263 Q2W, 90 mg BMS-986263 Q4W, or placebo Q2W
- A 12-week follow-up period

A schematic of the study design is provided in Figure 1.

Figure 1 Study Design Schematic



PBO = placebo; QW = once weekly; QOW = every other week; Q2W = once every 2 weeks; Q4W = once every 4 weeks; Wk = Week
Note: In the 90 mg BMS-986263 Q4W arm, BMS-986263 dosing alternates with placebo Q2W

8.1.1 Screening for Part 1 and Part 2

Eligibility will be based on specified inclusion and exclusion criteria (Section 8.4), including medical history, disease activity and safety assessments. Randomization must occur within 35 days of signing the informed consent. 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.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. 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 (Section 1.2).

For participants who experience an acute infection or require additional time for scheduling screening procedures, the screening period may be extended beyond 35 days after consultation with the medical monitor, but not beyond a total of 56 days (8 weeks) from the signing of the informed consent.

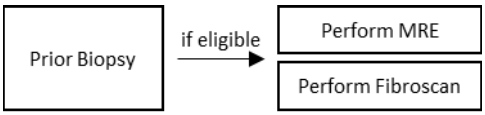
The screening visit may also be extended up to 5 additional days to accommodate unanticipated delays in obtaining required screening results. An extension beyond 5 days will require approval by the Medical Monitor.

Screening and Day 1 (Randomization) hematology and chemistry laboratory assessments must be performed at least 2 weeks apart.

Eligibility of participants requires confirmation of advanced fibrosis (METAVIR Stage 3 or Stage 4) by liver biopsy. If the participant has had a biopsy within the 8 weeks prior to enrollment in the study, this result may be used to determine eligibility only if:

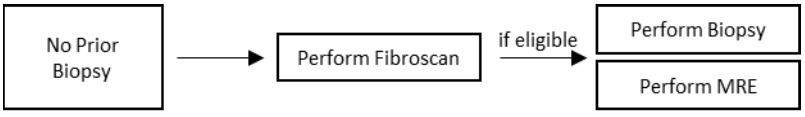
- Local pathology report is available and confirms METAVIR Stage 3 or Stage 4 fibrosis, AND
- The tissue (block or slides) is available for submission to the sponsor for analysis.

If a PRIOR BIOPSY WAS PERFORMED and meets the above criteria, MRE and FibroScan assessments must still be performed. The FibroScan must occur during the screening period unless FibroScan testing was performed within 8 weeks prior to study enrollment and results are available and collected. The MRE must occur during the screening period regardless of whether or not an MRE was performed within 8 weeks prior to study enrollment.



If a PRIOR BIOPSY WAS NOT PERFORMED within 8 weeks or the tissue is not available for submission and analysis, a biopsy must be performed during the screening period. Before performing a biopsy or MRE during the screening period, the participant must undergo an evaluation by FibroScan. If a FibroScan assessment was performed within the 8 weeks prior to enrollment, those results may be used. Only participants who demonstrate advanced liver fibrosis on FibroScan, defined as a mean result ≥ 5.0 kPa, may proceed to biopsy or MRE. In addition, eligibility of the participant based on other eligibility criteria will be assessed before acquiring a biopsy or MRE to reduce patient risk and burden. These may include, at the discretion of the investigator, confirmation of HCV SVR and a review of the participant's medical history to assess for study exclusion criteria (Section 8.4.2).

Participants with a qualifying FibroScan result will complete the screening procedures including liver biopsy and MRE assessment. The MRE must occur during the screening period regardless of whether or not an MRE was performed within 8 weeks prior to study enrollment.



Admissible prior biopsies and biopsies performed during screening will be used to determine eligibility (ie, liver fibrosis stage), and tissue from these biopsies will be used as the baseline sample for the primary endpoint analysis. The requirement that prior biopsies occur within 8 weeks prior to screening ensures that the acquired biopsy sample accurately reflects the condition of the participant at baseline to enable a valid analysis.

[redacted]

[redacted]

Visit details are provided in the Screening and Day 1 (Randomization) Procedural Outline for Part 1 and Part 2 in Table 1.

8.1.2 Part 1 Treatment Period and Follow-up

Approximately 60 participants meeting eligibility criteria during the screening period will be randomized into the Part 1 treatment period. These participants will be randomized via interactive response technology (IRT) in a 1:2:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW in a double-blind manner. The randomization of participants will be stratified by fibrosis stage (METAVIR Stage 3 or Stage 4). Participants will receive study treatment via IV administration for a total of 12 weeks.

Fibrosis stage will be assessed by liver biopsy during the screening period and on Day 85. Liver stiffness will be assessed by MRE at baseline, Day 43, Day 85 (primary efficacy endpoint), Day 169, and Day 253.

After 12 weeks (Day 85) of treatment, participants in Part 1 will enter the 24-week off- treatment follow-up period. During this time, they will not receive infusions of either active drug or placebo.

[redacted]

See the Schedule of Activities for Part 1 in Table 2 and Table 3 (Section 1.2).

[redacted]

8.1.4 Part 2 Treatment Period and Follow-up

Participants meeting eligibility criteria during the screening period will enter the Part 2 treatment period. Approximately 120 participants will be randomized via IRT in a 1:1:1:1 ratio to receive 45 mg BMS-986263 Q2W, 90 mg BMS-986263 Q2W, 90 mg BMS-986263 Q4W, or placebo Q2W in a double-blind manner. Randomization of the participants will be stratified by fibrosis stage (METAVIR Stage 3 or Stage 4). Participants will receive study treatment via IV administration for a total of 24 weeks. Liver biopsy will be performed during the screening period and on Day 169. MRE will be collected at Day 43, Day 85, Day 169, and Day 253 in Part 2.

After 24 weeks (Day 169) of treatment, participants in Part 2 will enter the follow-up period for 12 weeks. During this time, they will not receive infusions of either active drug or placebo.

[redacted]

See the Schedule of Activities for Part 2 in Table 4 and Table 6 (Section 1.2).

8.2 Data Monitoring Committee and Other Committees

An external DMC will be used in this study to perform safety monitoring throughout 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 [redacted] focusing on early signal detection. Further details on the frequency, content, and methods of data reports to the DMC will be outlined in the DMC charter along with the processes and procedures the committee will follow.

8.3 End of Study Definition

The start of the study is defined as the visit for first participant screening. The end of the study is defined as 2 years after the final Clinical Study Report (CSR) (including any addendums) is completed. A final summary report will be issued per regulations and local health authority requirements.

The last participant visit is defined as the last visit or scheduled procedure shown in the Schedule of Activities (Section 1.2) for the last participant.

The last day of the study will occur when the last participant has completed his/her Day 253 visit or discontinues early. Study completion is defined as the final date on which data for the primary endpoint in Part 2 of the study was or is expected to be collected, if this is not the same. If Part 2 is not initiated, study completion is defined as the final date on which data for the primary endpoint in Part 1 of the study was or is expected to be collected, if this is not the same.

Participants will be considered to have completed the study if they complete 253 days of evaluation, including all follow-up periods.

8.4 Study Population

8.4.1 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) Participants must be willing to participate in the study and sign the ICF.
   b) Participants must be willing and able to complete all study-specific procedures and visits.
2. Participants must provide documentation showing an SVR for at least 1 year prior to the date of screening. SVR is defined as a negative HCV RNA at least 12 weeks from the end of antiviral therapy. Thus, the minimum duration is 12 weeks of negative HCV RNA (to establish SVR) plus 1 year of sustained SVR (ie, 52 weeks + at least 12 weeks).

3. The participant must have METAVIR Stage 3 or Stage 4 fibrosis (or equivalent if using other classification; eg, Ishak) assessed by liver biopsy.
4. Participants must have a mean score of ≥ 5.0 kPa by FibroScan (Section 8.6.1.4). If a participant has not had a liver biopsy within 8 weeks of screening, the biopsy will be carried out during the screening period following determination of eligibility by FibroScan assessment (ie, has mean FibroScan score of ≥ 5.0 kPa).
5. The participant must have an adequate MRE and DXA performed during screening confirmed by the central imaging facility prior to randomization.
6. Age and reproductive status
   a) Males or females ≥ 21 and ≤ 75 years of age at the time of screening
   b) Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study and prior to each dose of study treatment.
      c) To confirm menopause, women must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL.
   d) Women must not be breastfeeding
   e) WOCBP must agree to follow instructions for method(s) of highly effective contraception, as defined in Appendix 3, for the duration of treatment (BMS-986263 or placebo) plus 5 half-lives of study treatment (5 days) plus 30 days (duration of ovulatory cycle) for a total of 35 days post-treatment.
   f) Males who are sexually active with WOCBP must agree to have their female partners follow instructions for method(s) of highly effective contraception, as defined in Appendix 3, for the duration of treatment with study treatment (BMS-986263 or placebo) plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 95 days after treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.
   g) Azoospermic males are exempt from contraceptive requirements for the purposes of prevention of pregnancy (ie, male study participants with partners who are WOCBP). However, in addition to the use of highly effective methods of contraception, males in the study who are sexually active with WOCBP must use barrier methods (eg, male condom, female condom) to prevent transmission of seminal fluid that may contain traces of study drug. Barrier methods must be used for the duration of exposure with study treatment (BMS-986263 or placebo) plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 95 days after treatment completion.
   h) WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male participants (and/or their caregivers, as applicable) who are sexually active with WOCBP, on the importance of using highly effective pregnancy prevention and the implications of an unexpected pregnancy in light of the potential for teratogenicity (Appendix 3). Investigators shall advise on the use of highly effective methods of contraception (ie, those that have a failure rate of < 1% when used consistently and correctly).

8.4.2 Exclusion Criteria

1. Target disease exclusions
   a) Other causes of liver disease, including but not limited to alcoholic liver disease, HBV (serologically-positive as determined using United States Centers for Disease Control and Prevention guidance for interpretation of hepatitis B serologic test results), autoimmune hepatitis, drug-induced hepatotoxicity, Wilson disease, iron overload, α- 1-antitrypsin deficiency, NASH, hemochromatosis); participants having liver diseases associated with infection with any other hepatitis virus are to be excluded. It is up to the investigator to be sure the participants do not have any of the above mentioned pathologies.
   b) Detectable HCV RNA at screening
   c) Child-Pugh score > 6 at screening (Appendix 7)
   d) MELD score > 12 based on screening laboratories (Appendix 8)
   e) 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 or ultrasound; based on local assessment):
      i. AFP > 100 ng/mL (> 82.6 IU/mL) OR
      ii. AFP ≥ 50 and ≤ 100 ng/mL (≥ 41.3 IU/mL and ≤ 82.6 IU/mL) with liver imaging showing evidence of HCC
2. Medical conditions
   a) Blood transfusion in the last 6 months prior to screening due to the risk of reinfection with HCV, HBV, HIV, etc.
   b) The participant has any disease or condition which, in the opinion of the investigator, might compromise patient safety (eg, hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, skeletal, central nervous system, or complement-mediated disease).
   c) Hepatitis B surface antigen (HBsAg)-positive participants or hepatitis B core antibody (HbcAb)-positive participants with detectable hepatitis B viral DNA. Where required by local regulations or standard practice, hepatitis B surface antibody (HBsAb)-positive participants must also have HBV DNA testing performed.
   d) Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for HIV or have acquired immunodeficiency syndrome (AIDS)-related illness, as reported by the participant and/or documentation.
   e) History of liver transplantation or planned liver transplant
   f) Any history of hepatic decompensation, including ascites, variceal bleeding, hepatic encephalopathy or spontaneous bacterial peritonitis.
   g) The participant has a 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) 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 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.

i) History of alcohol consumption ≥21 units/week (males) or ≥14 units/week (females) 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 8.4.4).
j) History, within the last 2 years, of alcohol or frequent marijuana abuse (in the opinion of the investigator), significant mental illness, or physical dependence on any opioid.
k) Positive urine test during screening for illegal drugs of abuse (with the exception of marijuana), unless these drugs are prescribed by the treating physician (prescription must be documented by the investigator or the designee in source documents).
l) History of intravenous drug use within the 3 years prior to screening.
m) History of bariatric surgery within the 5 years prior to screening or planned during the conduct of the study.
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 patient, specifically, within the cranium, chest, abdomen, or pelvic cavity.
o) History of weight gain/loss ≥ 10% of body weight in the 6 months prior to screening.
p) Inability to tolerate IV medication or other study procedures
q) Presence of pacemaker and or other metal objects in the body

3. Prior and concomitant therapy
   a) Participants who take any medications that, in the opinion of the investigator, increase the risk for complications during liver biopsy (eg, chronic or high-dose nonsteroidal inflammatory drugs, anticoagulants, or fish oil supplements)
   b) Participants taking anti-obesity agents (eg, ORLISTAT®) within 4 weeks of the first dose of study treatment.
   c) Participants receiving interferon therapy for any disease, or received interferon therapy for any disease within 52 weeks prior to administration of study treatment.
   d) The participant takes any vitamin A containing supplements or multivitamins, or vitamin A containing medications after signing the ICF.
   e) Participants taking anti-diabetic or anti-dyslipidemic medication receiving stable doses for less than 30 days prior to the first dose of study medication.
   f) Participants unable to comply with restrictions and prohibited treatments.
   g) Participants who have not discontinued other investigational agents must be discontinued at least 12 weeks or 5 half-lives before the first dose of study treatment, whichever is longer.
   h) Prior exposure to BMS-986263
   i) 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).
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) Body mass index (BMI) > 34 kg/m^2. Participants with a BMI of 30-34 kg/m^2 must have an ALT ≤ upper limit of the normal range (ULN).

c) The participant's baseline laboratory test results include abnormal values considered to be clinically significant by the investigator.
d) The participant's laboratory test results at screening include any of the following:
   - albumin < 3.5 g/dL
   - INR > ULN
   - ALT value ≥ 2× the ULN
   - hemoglobin A1c ≥ 9.0%
   - total bilirubin > ULN
   - hemoglobin < lower limit of normal (LLN)
   - platelet count < 100,000/μL
   - white blood cell count ≤ 3000/μL
e) Glomerular filtration rate < 30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease equation.
f) The participant's vitamin A levels at screening are > ULN
g) Alpha-fetoprotein (AFP; see Exclusion 1e, above):
   i. AFP > 100 ng/mL (> 82.6 IU/mL) OR
   ii. AFP ≥ 50 and ≤ 100 ng/mL (≥ 41.3 IU/mL and ≤ 82.6 IU/mL) with liver ultrasound showing findings suspicious for HCC.

5. Not applicable.
6. Allergies and adverse drug reaction
   a) History of allergy to BMS-986263 or related compounds
7. Other exclusion criteria
   a) Prisoners or participants who are involuntarily incarcerated. **Note:** Under certain specific circumstances, 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) Participants who participated in an interventional study with the last intervention occurring within 24 weeks prior to administration of study treatment.
   d) Any factor, which in the opinion of the investigator would jeopardize the evaluation or safety or be associated with poor adherence to the protocol.

8.4.3 MRI Contraindications

The imaging specialist at the site's imaging facility will be responsible for determining whether a participant is contraindicated from undergoing these procedures. Common conditions that may preclude the participant from scans include, but are not limited to:

a) History of claustrophobia
b) Physical limitations related to fitting into the bore of the magnet or weight greater than that allowable by the imaging instrument (i.e., body weight in excess of 250 pounds or 113.4 kg)
c) Participants with a pacemaker, epicardial pacemaker wires, MRI-incompatible cardiac valve prostheses, MRI-incompatible vascular clips less than 2 months old, or MRI--incompatible aneurysm clips of any age
d) Participants with MRI-incompatible cochlear implants

e) Participants with spinal nerve stimulators
f) Participants with an infusion pump
g) Participants with known metallic fragments in the body
h) Employment history that involves exposure to welding

The above list should not be used as a substitute for local clinical standards of care. The ultimate decision to perform any scan should rest with the site radiologist, the investigator, and the standard set by the IEC.

8.4.4 Lifestyle Restrictions

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

8.4.5 Screen Failures, Retesting, and Rescreening

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.

Study assessments and/or laboratory parameters (Table 11) may be repeated (retesting) 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. Other than exceptional circumstances, retesting is allowed only once.

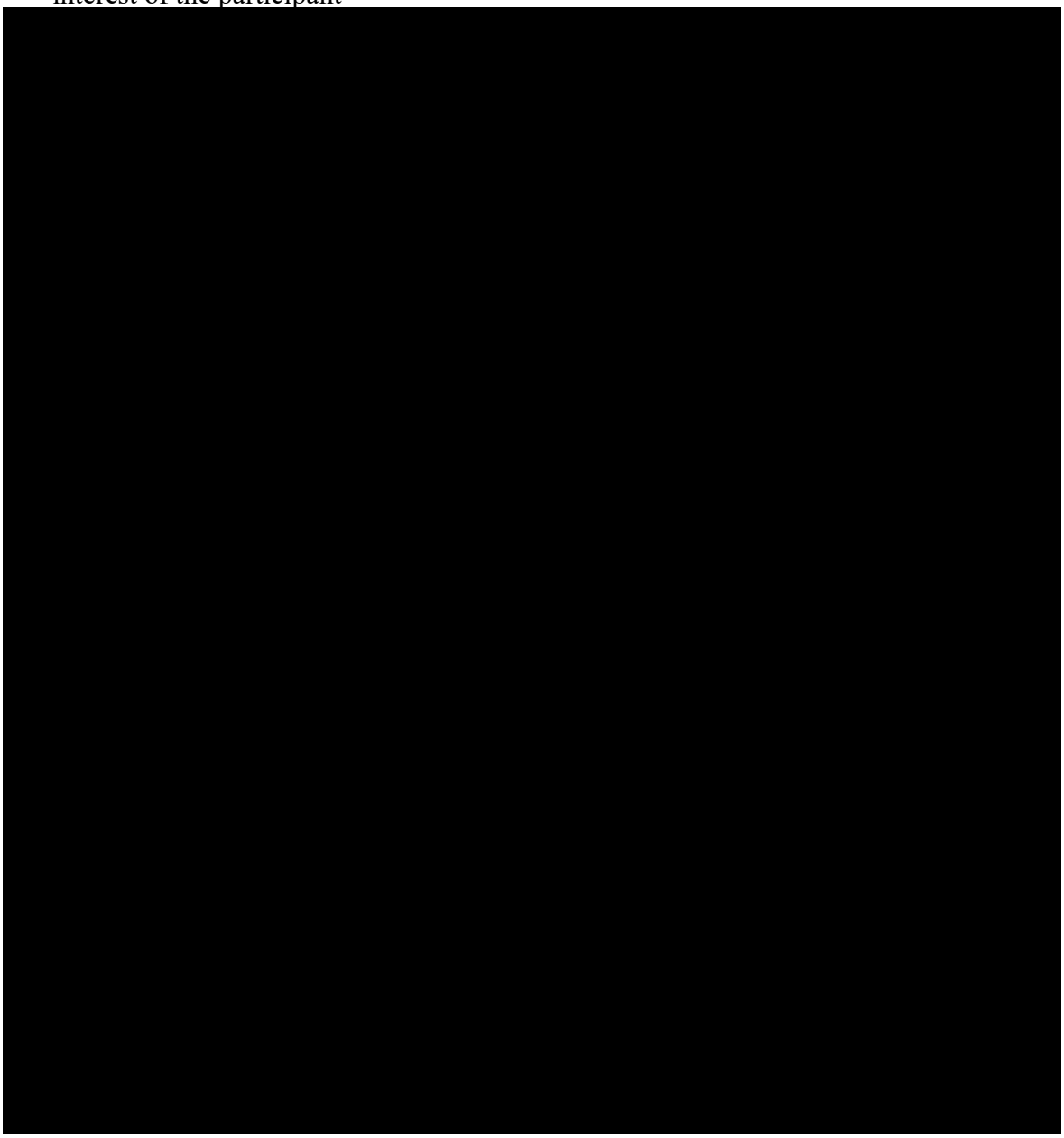
Rescreening is allowed but the participant must wait 4 weeks after the date of screen failure to re-enroll. For participants who are rescreened, biopsy, MRE and/or DXA assessments do not need to be repeated if obtained within 8 weeks of randomization. Other than exceptional circumstances, rescreening is allowed only once.

8.4.6 Withdrawal and Replacement of Participants

8.4.6.1 Discontinuation of Treatment

Participants MUST discontinue IP (and nonIP 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



[redacted]

- For participants with normal Day 1 (Randomization) liver enzymes and total bilirubin, if there is new elevation of ALT or AST > 3 × ULN, repeat testing should be performed within 48 to 72 hours. If elevation persists, then standard drug-induced liver injury (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 participant lives in a remote location, a local laboratory may be used for repeat testing, and results should be promptly communicated to the site. Participants meeting the criteria above may have potential DILI, see Section 8.6.2.1.7 for reporting requirements

- For participants with elevated AST, ALT, or total bilirubin at Day 1 (Randomization), if there is new elevation of ALT or AST > 2 × ULN or total bilirubin 1.5 × Day 1 bilirubin, repeat testing should be performed within 48 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 participant lives in a remote location, a local laboratory may be used for repeat testing, and results should be promptly communicated to the site. Participants meeting the criteria above may have potential DILI, see Section 8.6.2.1.7 for reporting requirements

- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Abnormal liver tests suggestive of liver injury, as defined in Section 8.6.2.1.7, or hepatic decompensation
- 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 investigator feels that it is no longer in the participant's best interest to continue study treatment.
- The participant becomes pregnant (study treatment must be discontinued immediately): In the case of pregnancy (Section 8.6.2.1.5), the investigator must immediately notify the medical monitor or designee of this event. In the event a female participant becomes

pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please contact the medical monitor or designee within 24 hours of awareness of the pregnancy.

See the Schedule of Activities (Section 1.2) 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.

All participants who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in Section 1.2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment 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). 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 electronic case report form (eCRF) page. As indicated, appropriate follow-up and/or alternate medical care must be arranged for the participant.

Participants who discontinue study treatment will remain in the study for continued follow-up.

8.4.6.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and will 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. Expectations are as follows:

- 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, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, 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/end of study 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.

8.4.6.3 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.

8.4.6.4 Replacement of Participants

If a higher than expected proportion of participants discontinue from the study prior to the evaluation of the primary endpoint, the sponsor may choose to enroll additional participants to ensure an adequate number of participants are available for evaluation of the primary endpoint.

Rescreening is discussed in Section 8.4.5.

8.5 Study 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 noninvestigational [medicinal] product (nonIP/nonIMP) and is described in Table 7.

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 7 Study Treatments for IM025006

Product Description / Class and Dosage Form	Potency	IP/ NonIP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986263 / siRNA / intravenous	[redacted]				
Placebo / intravenous	NA	IP	Blinded	On-site compounded solution[a]	Refer to pharmacy manual
Diphenhydramine / antihistamine / intravenous[b]	50 mg/mL; 1 mL prefilled syringe	NonIP	Open Label	Clear and colorless solution available as 50 mg/mL in a 1 mL prefilled single-use syringe	Stored at 20° to 25°C; protected from freezing and light
Famotidine / antihistamine / intravenous[b]	20 mg/50 mL; 50 mL single dose container	NonIP	Open Label	Clear and colorless solution available as 20 mg/50 mL in a 50 mL container	Stored at 20° to 25°C; protected from light
Levocetirizine dihydrochloride / diphenhydramine hydrochloride (antihistamine) / oral[b]	5 mg	NonIP	Open Label	White, oval, biconvex, film-coated functional scored tablets	Stored at 68° to 77°F, away from excess heat and moisture
Hydrocortisone Sodium Succinate / intravenous[b]	100 mg	NonIP	Open Label	White, powder for solution for injection 100 mg/2 mL	Stored at 68° to 77°F, protected from light

IP = investigational product; NA = not applicable; siRNA = small interfering ribonucleic acid
[a] The composition of the placebo solution is 100 mL D5W containing 0.3 – 0.6 mL of Intralipid® 20%.
[b] To be administered at the discretion of the investigator. Methylprednisolone sodium succinate 125 mg IV may be used instead of hydrocortisone See Section 8.5.1.2 for more details.

8.5.1 Treatments Administered

The investigator must ensure that the IP will be used only in accordance with the protocol. The selection and timing of dose for each participant is shown in Table 8.

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.

[redacted]

The study treatment will be infused using an IV pump, as described in the Pharmacy Manual. The IV will be kept open before and after the infusion with sufficient quantities of 0.9% saline

to assure it remains patent. The time the infusion is initiated/adjusted/concluded, including any interruptions, will be documented in the eCRF.

8.5.1.1 Study Treatment Infusion Rate

The study medication should not be infused at a duration lesser than 60 minutes. The infusion rate may be modified by the investigator based on clinical discretion and/or the participant's previous tolerance of the infusion, including any infusion reactions that may have occurred in the past. In addition, the investigator may choose to pause the infusion depending on the participant's clinical condition and history.

Of note, while the rate of infusion can be modified as described above; no reductions or modifications of the total dose to be administered are allowed.

If a participant experiences an infusion-related reaction, temporary interruption of the infusion and/or reduction of the infusion rate (for example, but not limited to, modification of infusion rate and/or a pause in the infusion) may lead to improvement of signs and symptoms. Medications, emergency equipment, and trained personnel able to treat immediate or delayed infusion-related reactions should be available for immediate access at the clinical site(s).

8.5.1.2 Premedication

To reduce the potential for possible infusion reactions, based on the discretion of the investigator, the participants in Part 1 may be pretreated 15 to 30 minutes before the start of the study treatment infusion. The investigator may choose to administer any or all of the following premedications: 50 mg diphenhydramine hydrochloride IV, 20 mg famotidine IV, and/or hydrocortisone 100 mg IV. Hydrocortisone IV may be replaced with methylprednisolone sodium succinate 125 mg IV based on the discretion of the investigator. Additionally, the investigator may choose not to administer any premedication. If IV diphenhydramine is not available, an oral dose of 5 mg levocetirizine dihydrochloride or an oral dose of 50 mg diphenhydramine hydrochloride may be substituted and administered 2 hours ± 15 minutes before the start of study treatment infusion.

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, although a longer observation period may be necessary for an individual participant. The decision to observe a study participant beyond the required 3 hours will be at the discretion of the attending investigator.

Table 8 Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Part 1			
BMS-986263	3 mg/mL total dose of 45 mg	QW	Intravenous
BMS-986263	3 mg/mL total dose of 90 mg	QW	Intravenous
Placebo (Part 1)	NA	QW	Intravenous
Part 2			
BMS-986263	3 mg/mL total dose of 45 mg	Q2W	Intravenous
BMS-986263	3 mg/mL total dose of 90 mg	Q2W	Intravenous
BMS-986263	3 mg/mL total dose of 90 mg	Q4W[a]	Intravenous
Placebo (Part 2)	NA	Q2W	Intravenous

NA = not applicable; QW = once every week; Q2W = once every 2 weeks; Q4W = once every 4 weeks
[a] Alternating doses of active drug (90 mg Q4W) and placebo (Q2W) will be carried out with active drug dosing on Days 29, 57, 85, 113, and 141 and placebo dosing on Days 15, 43, 71, 99, 127, and 155, as indicated in the Part 2 Schedule of Activities Table 4 and Table 6 (Section 1.2)

Restrictions related to food and fluid intake are described in Section 8.4.4.

8.5.2 Method of Treatment Assignment

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 at the study visits as listed in Schedule of Activities (Section 1.2).

At the time of the screening visit, immediately after informed consent is obtained and before any study-related procedures are performed, the investigative site will access the enrollment option using the IRT for assignment of the participant number, including participants not subsequently randomized or treated. This number will be unique across all sites. All enrolled participants will be assigned sequential participant numbers. The participant number may not be used for any other participant. If a potential participant is rescreened, they will be given a new identification number.

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.

8.5.3 Blinding of Study Medication

8.5.3.1 Maintaining the Blind

Blinded treatment assignments will be managed using IRT. All vials (BMS-986263 and placebo) are identical in appearance, and they will be supplied as shown in Table 8. Investigative site staff, sponsor and designee personnel, and participants and their families will remain blinded to treatment assignments.

The investigative site staff will include 2 individuals with well-defined roles, as follows:

- An unblinded study drug administrator, who will be responsible for administering the infusion and/or adjusting the infusion rate and will ensure that the infusion set is concealed with adequate line-cover and bag-cover. This individual will not conduct any patient-facing assessments.
- An assessor, who will be responsible for performing any study-related assessments on study participants including, but not limited to, those pertaining to safety, tolerability, or efficacy.

At all times, every attempt will be made to ensure that the 2 roles are able to function separately to ensure blinding of study treatment.

8.5.3.2 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 principal investigator or designee should only call in for emergency unblinding AFTER the decision to discontinue the participant has been made.

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 IRT Manual. Participant and unblinded treatment information and the reason for the blind being broken must be recorded on the appropriate study status page of the eCRF. After unblinding via IRT, the investigator shall notify the medical monitor.

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.

8.5.4 Study Treatment Preparation, Handling, Storage, and 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]

Please refer to the study Pharmacy Manual for IP and nonIP preparation.

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

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).

Further guidance and information for final disposition of unused study treatment are provided in Appendix 1.

[redacted]

8.5.5 Dose Modification

No reductions or modifications of the total dose are allowed. If a participant interrupts treatment due to an AE, study treatment can be restarted.

8.5.6 Treatment Compliance

As all study medication will be administered by site staff, treatment compliance will not be formally assessed.

8.5.7 Prior and Concomitant Therapy

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

Restrictions and prohibitions on prior and concomitant medications are as follows:

1. Anti-obesity agents (eg, ORLISTAT).
2. Ongoing therapy for HCV or received therapy for HCV within 52 weeks prior to administration of study treatment.
3. Interferon therapy for any disease, or received interferon therapy for any disease within 52 weeks prior to administration of study treatment.

[redacted]

5. Prior exposure to BMS-986263 is prohibited.
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.
7. Other investigational agents. Any other investigational agent must be discontinued at least 12 weeks or 5 half-lives before the first dose of study treatment, whichever is longer.

8.5.8 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 other reasons, 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.

8.6 Efficacy and Safety Assessments

Study procedures and timing are summarized in the Schedule of Activities (Section 1.2). **Waivers or exemptions from protocol-required evaluations are not allowed**.

8.6.1 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 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.

The following procedures or tools will be used to assess participants' fibrotic disease activity during the study (see Schedule of Activities in Section 1.2):

- Liver biopsy assessments (Section 8.6.1.1)
- Other noninvasive measures:
    - Liver stiffness as measured by MRE (Section 8.6.1.2)
    - Liver fibrosis scoring:
        - FibroScan (Section 8.6.1.4)

[redacted]

8.6.1.1 Liver Biopsy

Biopsies performed during screening for purposes of determining eligibility will be assessed by a local pathologist. Participants must have METAVIR Stage 3 or Stage 4 liver fibrosis to be eligible. If pathologic evidence suggesting a cause of liver fibrosis other than HVC-associated fibrosis is observed (eg, NASH), the participant is not eligible. If there is any question about the eligibility of a participant based on locally assessed biopsy results, the investigator should contact the medical monitor prior to randomizing the participant.

Tissue from biopsies performed during the study (or tissue submitted from prior biopsies when appropriate, see Section 8.1.1) will be collected for analysis. All histological assessments related to efficacy of BMS-986263 will be performed by a central reader. Details on the acquisition, quality requirements, histological preparation, and shipping of histological samples are in the Central Laboratory Manual. Due to the delay in assessing tissue samples for study endpoints, a report from the central pathologist will not be provided to the study sites. If

a clinical assessment of the biopsy is required a portion of the sample should be submitted to a local pathologist following the standard procedure utilized by the study site.

No more than 2 study associated biopsies will be conducted within a 48-week period. (Note: In some occasions the first pass for liver biopsy may not result in an adequate quantity of liver tissue, thus demanding for a second pass in order to obtain sufficient amount of liver tissue for analysis. The second pass should not be considered a second biopsy.)

[redacted]

To assess potential HSC suppression, the following assessments will be performed:

- Histology, including changes in hepatic architecture

[redacted]

8.6.1.1.1 Histological Assessment and METAVIR scoring

The METAVIR system is used to assess the extent of inflammation and fibrosis by histopathological evaluation in a liver biopsy of patients with HCV. It assesses liver biopsies for activity grade (A0-A3: A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity) and fibrosis stage (Stage 1 – 4: 1 = portal fibrosis without septa; 2 = portal fibrosis with few septa; 3 = numerous septa without cirrhosis; or 4 = cirrhosis).

8.6.1.1.2 Histological Assessment and Ishak scoring

The Ishak scoring system will also be used to grade fibrosis in the histology samples. The Ishak system (0 through 6 scale) was developed to grade portal-based liver fibrosis associated with viral hepatitis:

- 0: No fibrosis
- 1: Fibrous expansion of some portal areas, with or without short fibrous septa
- 2: Fibrous expansion of most portal areas, with or without short fibrous septa
- 3: Fibrous expansion of most portal areas with occasional portal to portal bridging
- 4: Fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central)
- 5: Marked bridging (portal–portal and/or portal–central) with occasional nodules (incomplete cirrhosis)
- 6: Cirrhosis, probable or definite

8.6.1.1.3 Morphometric Analysis of Collagen Proportionate Area in Stained Tissue

There can be considerable intra- and inter-individual variation in the assessment of liver biopsy to determine fibrosis stage. Assessment of CPA is a method by which the amount (percentage) of collagen in stained tissue sections is analyzed using morphometric image analysis. This technique allows for a quantitative assessment of fibrosis. This morphometric assessment will be performed by a blinded central pathologist.

[redacted]

8.6.1.2 MRE Imaging Assessment

MRE is a noninvasive medical imaging technique approved by FDA in 2009. It quantitatively measures the stiffness of soft tissues by introducing shear waves and imaging their propagation using MRI. MRE has been demonstrated to be accurate and reproducible, and highly concordant compared to histopathology for staging liver fibrosis.[23]

In this study, MRE will be used to quantitate liver stiffness as a surrogate biomarker of liver fibrosis.

MRE assessments should be performed at time points indicated in Schedule of Activities (Section 1.2). MRE should be conducted at the early termination visit only if the participant's prior MRE occurred > 4 weeks prior to termination. The central imaging facility will perform all MRE imaging analyses.

Adequacy of the MRE should be confirmed by the central imaging facility prior to randomization. Image acquisition guidelines and submission processes will be outlined in the IM025006 Imaging Manual, to be provided by the central imaging facility. The clinical sites will be trained in imaging procedures prior to scanning the first study participant. Images will be submitted to the central imaging facility for central review. The site will be informed of quality issues or the need to repeat scanning from the central imaging facility.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the investigator in collaboration with a local radiologist, as per standard medical/clinical judgement.

8.6.1.3 Pharmacokinetic [redacted] Sampling

Blood sampling will be carried out for the analysis of PK [redacted]

8.6.1.4 FibroScan

FibroScan is an ultrasound-based medical device dedicated to the noninvasive measurement of liver stiffness, approved by FDA in 2013. The procedure is painless for the patient, noninvasive, rapid (5-10 minutes), and repeatable. Presently, there are more than 2,000 FibroScan devices available in more than 70 countries in the world. It is widely utilized in hepatologists' offices for the initial evaluation of patients with liver disease before or potentially to forgo liver biopsy.

Multiple studies and meta-analyses have demonstrated that liver stiffness values measured by FibroScan correlate highly with advanced fibrosis in chronic liver diseases.[24-27] Liver stiffness values above 9.6 kPa and 12.5 kPa are indicative of advanced fibrosis (Stage 3) and cirrhosis (Stage 4), respectively.

[redacted] During screening, FibroScan should demonstrate a mean liver stiffness measurement > 5.0 kPa for eligibility.

[redacted]

[redacted]

8.6.2 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 1.2). 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 of BMS-986263 will be assessed by evaluation of the incidence of all AEs and SAEs leading to withdrawal of study medication, [redacted] laboratory data, electrocardiogram (ECG) monitoring, physical examinations, vital signs, [redacted]

The participants must not have documented bone abnormalities at baseline as defined in the Exclusion Criteria (Section 8.4.2). [redacted] Since DXA is required at baseline, the investigator should consider the results of the assessment in determining the eligibility of a potential participant.

8.6.2.1 Adverse Events

The definitions of an AE or SAE can be found in Appendix 2.

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.

The event (term), along with its start and stop dates, maximum intensity (mild, moderate, or severe), seriousness (yes/no), relationship to the IP (yes/no), action taken with regard to the IP, and outcome will be recorded in the eCRF.

Contacts for SAE reporting specified in Appendix 2.

8.6.2.1.1 Time Period and Frequency for Collecting AE and SAE Information

Nonserious AEs will be collected from the time of the first dose of IP through the date of the follow-up or last visit, and at the time points specified in the Schedule of Activities (Section 1.2).

The Reference Safety Information in Sections 5.6.1 and 5.6.2 of the IB should be used to determine the expectedness of SAEs for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs that occur from the time ICF is signed to 30 days after the final dose of the study drug must be reported to PRA Drug Safety. After that time, only SAEs deemed by the investigator to be related to the study drug or a study procedure should be reported.

If applicable, SAEs must be collected that relate to any later protocol-specified procedure.

- 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.
- 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 sponsor or designee within 24 hours, as indicated in Appendix 2.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in 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.

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 2.

8.6.2.1.2 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.

[redacted]

8.6.2.1.3 Follow-up of AEs and SAEs

Nonserious AEs should be followed to resolution, or stabilization, or reported as SAEs if they become serious (Appendix 2).

Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study 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 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 8.4.6.3).

Further information on follow-up procedures is given in Appendix 2.

8.6.2.1.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards 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/EC, if appropriate according to local requirements.

The sponsor or designee will report AEs to regulatory authorities and IECs according to local applicable laws including European Directive 2001/20/EC and FDA CFR 21 CFR Parts 312 and 320. A SUSAR (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.

8.6.2.1.5 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 after product administration, the investigator must immediately notify the medical monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 2.

If the participant becomes pregnant study treatment must be discontinued immediately. Please contact the medical monitor or designee 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.

Any pregnancy that occurs in a female partner of a male study participant should be reported to sponsor or designee. In order for sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this

information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

8.6.2.1.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE eCRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an 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

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

8.6.2.1.7 Potential Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. The study treatment discontinuation criteria are provided in Section 8.4.6.1. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (Appendix 2 for reporting details).

Participants who meet criteria for DILI should have relevant laboratory testing (eg, ALT, AST, and INR levels) repeated at least weekly until abnormalities have resolved. Tests should be repeated within 3 days; then, every 3 days until reversal is noted; and then, every week until normalization. The investigator should make every effort to determine if any other cause for the liver test abnormalities is present.

[redacted]

8.6.2.1.8 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 AEs, as appropriate, and reported accordingly.

8.6.2.2 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (Appendix 2).

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.
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 (determined 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.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

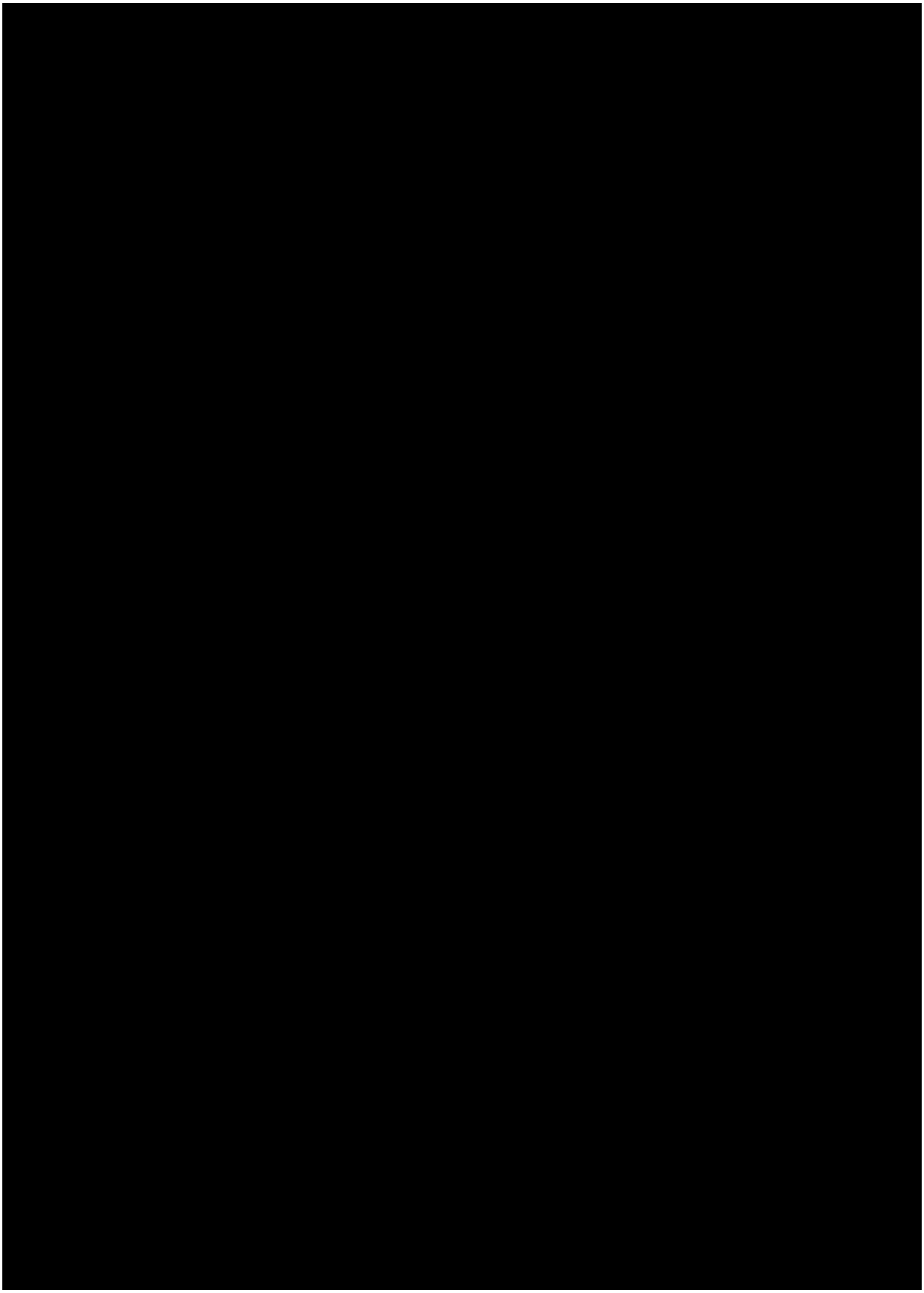
8.6.2.3 Physical Examinations

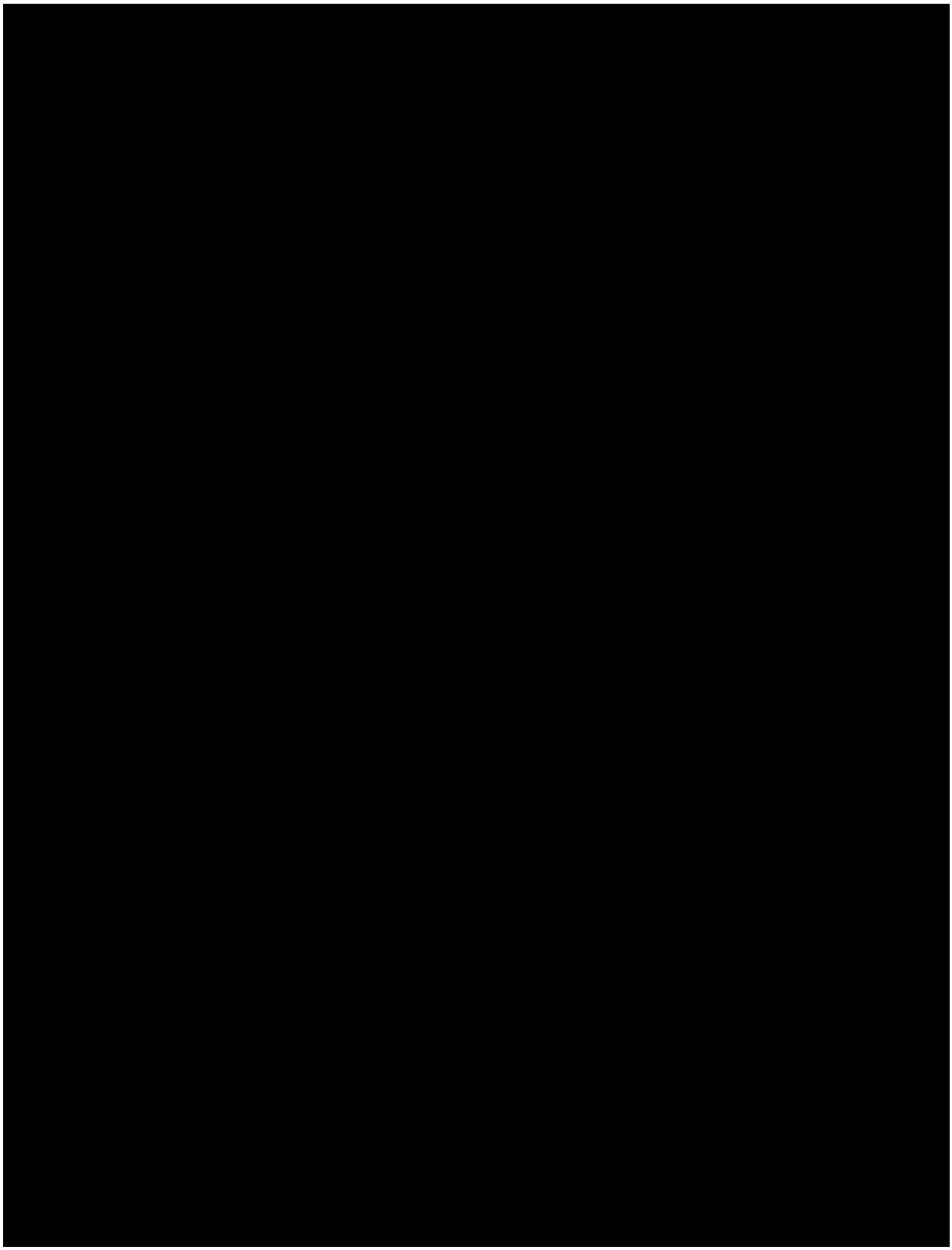
Schedules for physical examinations are provided in Schedule of Activities (Section 1.2). Complete and/or abbreviated physical examinations may be performed by a Doctor of Medicine (MD) or equivalent, or someone who is authorized to perform the examinations by training and has been delegated this task by the principal investigator.

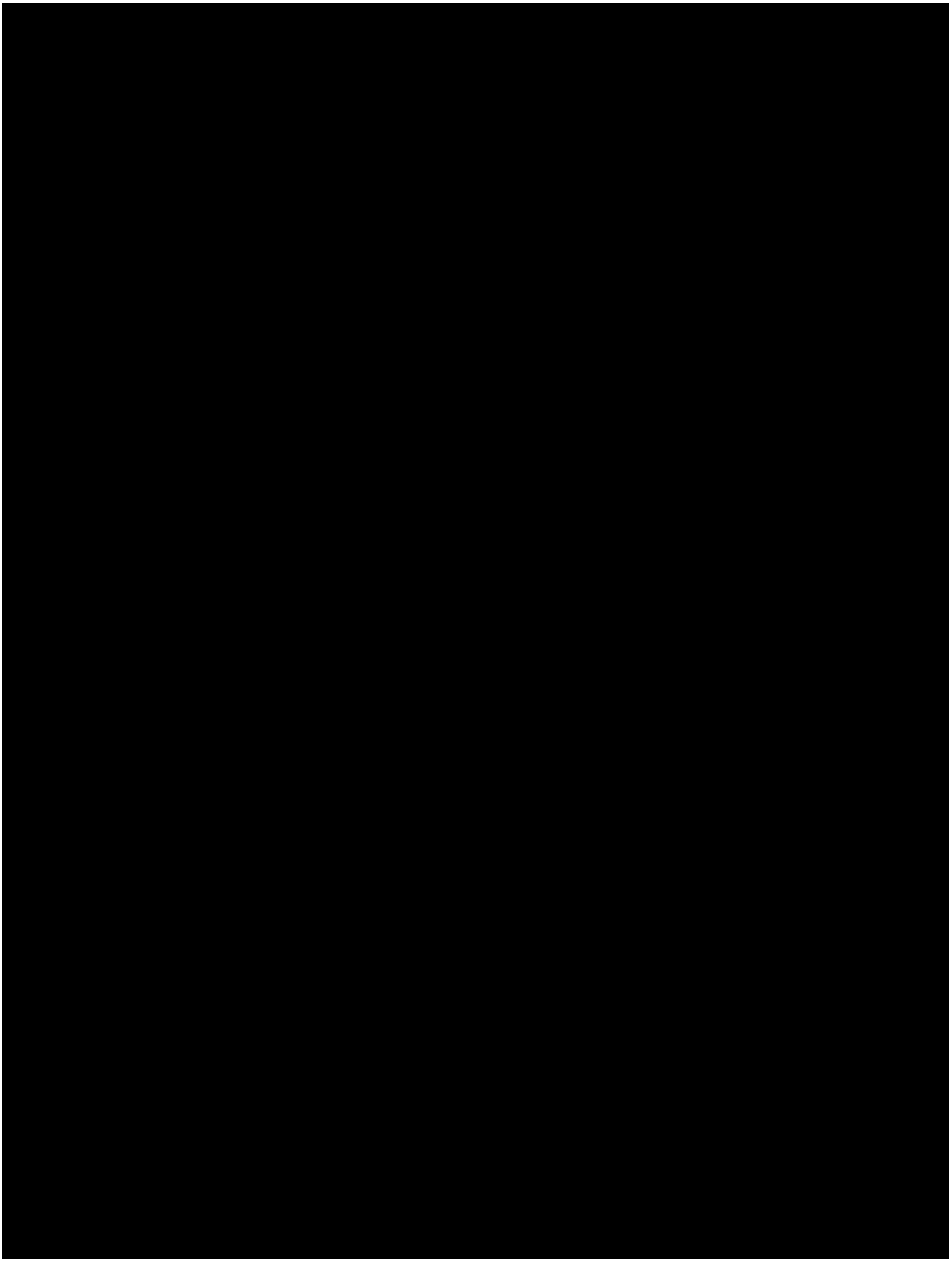
[redacted]

Full physical examinations will be performed at screening and Days 85 and 253 in Part 1 and screening and Days 85, 169, and 253 in Part 2. A full examination will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, height, and body weight.

Abbreviated physical examinations will be performed at the other time points (Schedule of Activities; Section 1.2), which 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.







[redacted]

8.6.2.7 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. Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.

[redacted]

Hematology, serum chemistry and urinalysis assessments are listed below:

Table 11 Hematology, Chemistry, Urinalysis, [redacted] Assessments

Hematology		
• CBC • PT • PTT • INR	• WBC (absolute) • Hemoglobin • Hematocrit • MCV	• MCH concentration • Red cell distribution width • Platelet count
Blood Chemistry		
• AST • ALT • Total bilirubin • Direct bilirubin • ALP • LDH • GGT • Creatinine	• Creatinine clearance • Creatine kinase • BUN • Uric acid • Glucose • PTH • Total protein • Albumin sodium	• Potassium • Chloride • Carbon dioxide • Calcium • Phosphorus • Glomerular filtration rate
Urinalysis		
• pH • Specific gravity • Protein	• Glucose • Ketones • Leukocyte esterase	• Nitrite • Creatinine • Microscopic examination (only to follow-up abnormal findings)
[redacted]		
HbA1C		
[redacted]		
Serology/viral load	• HCV viral load (RNA) • HBsAg	• HbcAb and HBV viral DNA if HbcAb-positive.

[redacted]

Other Analyses		
[redacted]	• FSH • AFP [redacted]	• Illegal drugs of abuse (urine or serum; amphetamine, barbiturate, benzodiazepines, marijuana, cocaine, opiate, or PCP) • pregnancy test (WOCBP only).

AFP = alpha-fetoprotein; ALP = alkaline phosphatase; [redacted] ALT = alanine aminotransferase, AST = aspartate aminotransferase; [redacted] BUN = blood urea nitrogen; [redacted] CBC = complete blood count; [redacted] CVD = cardiovascular disease; DNA = deoxyribonucleic acid; [redacted] GGT = gamma-glutamyl transferase; [redacted] FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HbcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HDL = high-density lipoprotein; INR = international normalized ratio; LDH = lactate dehydrogenase; [redacted] MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MOA = mechanism of action; [redacted] PCP = phencyclidine; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; [redacted] WBC = white blood cell; WOCBP = women of childbearing potential

[redacted]

8.6.2.8 Imaging Safety Assessments – DXA

DXA (femur, hip, and lumbar spine) will be performed at the time points indicated in Schedule of Activities (Section 1.2). DXA is to be scheduled at least 5 days ahead of Day 1 (Randomization) to allow adequate time for results to be analyzed. [redacted]

Image acquisition guidelines and submission processes will be outlined in the IM025006 Imaging Manual, to be provided by the central imaging facility. The clinical sites will be trained in imaging procedures prior to scanning the first study participant. All images will be submitted to the central imaging facility for assessment of the BMD.

Adequacy of DXA should be confirmed by the central imaging facility prior to randomization. The site will be informed of quality issues or the need to repeat scanning from the central imaging facility.

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

8.6.3 Pharmacokinetics

Blood for PK samples for Part 1 will be drawn according to the sampling schedule shown in Table 12. For Part 2, blood for PK samples will be drawn according to the sampling schedule shown in Table 13.

Samples from participants randomized to placebo will not be analyzed.

Table 12 Pharmacokinetic [redacted] Sampling Schedule for BMS-986263 in Part 1

Day[a]	Event	Time[h] (Relative to BMS-986263 Dose) Hour: Min	BMS-986263 Blood Sample for plasma PK
1	pre-infusion	00:00[b,]	X
[redacted]			
1	mid-infusion	00:30[c]	X
1	end-of-infusion	00:00[d]	X
1	postinfusion	01:00[e,]	X
4 (± 1 day)	postinfusion	72:00[f]	X
8	pre-infusion	00:00[b,]	X
[redacted]			
8	mid-infusion	00:30[c]	X
8	end-of-infusion	00:00[d]	X
8	postinfusion	01:00[e,]	X
15	pre-infusion	00:00[b,]	X
29	pre-infusion	00:00[b,]	X
[redacted]			
29	mid-infusion	00:30[c]	X
29	end-of-infusion	00:00[d]	X
29	postinfusion	01:00[e,]	X
36	pre-infusion	00:00[b]	X
43	pre-infusion	00:00[b,]	X
[redacted]			
43	mid-infusion	00:30[c]	X
43	end-of-infusion	00:00[d]	X
43	postinfusion	01:00[e,]	X
46 (± 1 day)	postinfusion	72:00[f]	X
50	pre-infusion	00:00[b]	X
57	pre-infusion	00:00[b,]	X
78	pre-infusion	00:10[b,]	X
[redacted]			
78	mid-infusion	00:30[c]	X
78	end-of infusion	00:00[d]	X
78	postinfusion	01:00[e,]	X
85	postinfusion	168:00 (7 days) [f,]	X
99	postinfusion	504:00 (21 days) [f]	X

PK = pharmacokinetics
[a] The days for PK sampling are indicated in the Schedule of Activities (Section 1.2).
[b] Time is relative to the start of infusion. Samples may be collected up to 120 minutes prior to the start of the infusion.

[c] Time is relative to the start of infusion. Samples should be collected ± 3 minutes within specified timeframe. If infusion is administered at a modified rate, the timing of collection of this sample should correspond to the middle of the modified infusion duration of the total administered dose.
[d] Time is relative to the end-of-infusion. Samples should be collected -2 minutes within specified timeframe. This sample should be taken immediately prior to stopping the infusion. If the end-of-infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.
[e] Time is relative to the end-of-infusion. Samples should be collected ± 3 minutes within specified timeframe.
[f] Time is relative to the end-of-infusion of the previous dosing day. Sample may be collected ± 1 day at the PK visit on Day 4 and Day 46.
[redacted]

**Table 13 Pharmacokinetic [redacted]
Sampling Schedule for BMS-986263 in Part 2**

Day[a]	Event	Time (Relative to BMS-986263 Dose) Hour: Min	BMS-986263 Blood Sample for plasma PK
1	pre-infusion	00:00[b,]	X
[redacted]			
1	mid-infusion	00:30[c]	X
1	end-of-infusion	00:00[d]	X
1	postinfusion	01:00[e,]	X
4 (± 1 day)	postinfusion	72 :00[f]	X
15	pre-infusion	00:00[b]	X
29	pre-infusion	00:00[b,]	X
[redacted]			
29	mid-infusion	00:30[c]	X
29	end-of-infusion	00:00[d]	X
29	postinfusion	01:00[e,]	X
43	pre-infusion	00:00[b,]	X
[redacted]			
43	mid-infusion	00:30[c]	X
43	end-of-infusion	00:00[d]	X
43	postinfusion	01:00[e,]	X
46 (± 1 day)	postinfusion	72 :00[f]	X
57	pre-infusion	00:00[b]	X
71	pre-infusion	00:00[b]	X
85	pre-infusion	00:00[b,]	X
[redacted]			
85	mid-infusion	00:30[c]	X
85	end-of-infusion	00:00[d]	X
85	postinfusion	01:00[e,]	X
99	pre-infusion	00:00[b]	X
113	pre-infusion	00:00[b]	X
127	pre-infusion	00:00[b]	X
141	pre-infusion	00:00[b]	X
141	mid-infusion	00:30[c]	X
141	end-of-infusion	00:00[d]	X
141	postinfusion	01:00[e]	X
155	pre-infusion	00:00[b]	X
169	postinfusion	336:00 (14 days)	X
[redacted]			

PK = pharmacokinetics
[a] The days for PK sampling are indicated in the Schedule of Activities (Section 1.2).
[b] Time is relative to the start of infusion. Samples may be collected up to 120 minutes prior to the start of the infusion.

[c] Time is relative to the start of infusion. Samples should be collected ± 3 minutes within specified timeframe. If infusion is administered at a modified rate, the timing of collection of this sample should correspond to the middle of the modified infusion duration of the total administered dose.
[d] Time is relative to the end-of-infusion. Samples should be collected -2 minutes within specified timeframe. This sample should be taken immediately prior to stopping the infusion. If the end-of-infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.
[e] Time is relative to the end-of-infusion. Samples should be collected ± 3 minutes within specified timeframe.
[f] Time is relative to the end-of-infusion. Sample may be collected ± 1 day at the PK visit on Day 4 and Day 46.

[redacted]

9. STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

This study will enroll a total of 60 participants in Part 1 of the study, randomized via IRT in a 1:2:1 ratio to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, and placebo QW. The sample size for Part1 is not based on formal statistical justification. Part 1 of the study is designed for estimation purposes; no statistical testing will be performed. A 95% confidence interval (CI) for the primary endpoint of proportion of participants with ≥ 1 stage improvement in fibrosis on biopsy after 12 weeks of treatment and odds-ratios between treatment groups will be utilized for this purpose.

In Part 2, approximately 120 participants will be randomized via IRT in a 1:1:1:1 ratio to receive 45 mg BMS-986263 Q2W, 90 mg BMS-986263 Q2W, 90 mg BMS-986263 Q4W, or placebo Q2W in a double-blind manner. The primary endpoint for Part 2 is the proportion of participants with ≥ 1 stage improvement in fibrosis on biopsy after 24 weeks of treatment. For this portion (Part 2) of the study, it is anticipated that approximately 10% of the participants will discontinue (dropout) early from study treatment. Participants who discontinue early 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.

The response rates for the primary liver biopsy endpoint for the 4 treatment groups in Part 2 are assumed to be as follows: placebo Q2W – 20%, 90 mg BMS-986263 Q4W – 30%, 45 mg BMS-986263 Q2W – 35%, and 90 mg BMS-986263 Q2W – 50%. With these assumptions, using a 1-sided 0.05 level of significance, there will be 80% power to detect a trend using a Cochran Armitage trend test in the primary endpoint among the 4 treatment groups with n = 30 in each group.

9.2 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.
[redacted]	
Pharmacokinetic	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.

9.3 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock for the primary efficacy analysis and will provide detailed specifications of the analysis of all efficacy endpoints and safety and will also describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data.

[redacted]

This section provides a summary of planned statistical analyses of the primary and secondary endpoints.

9.3.1 Efficacy

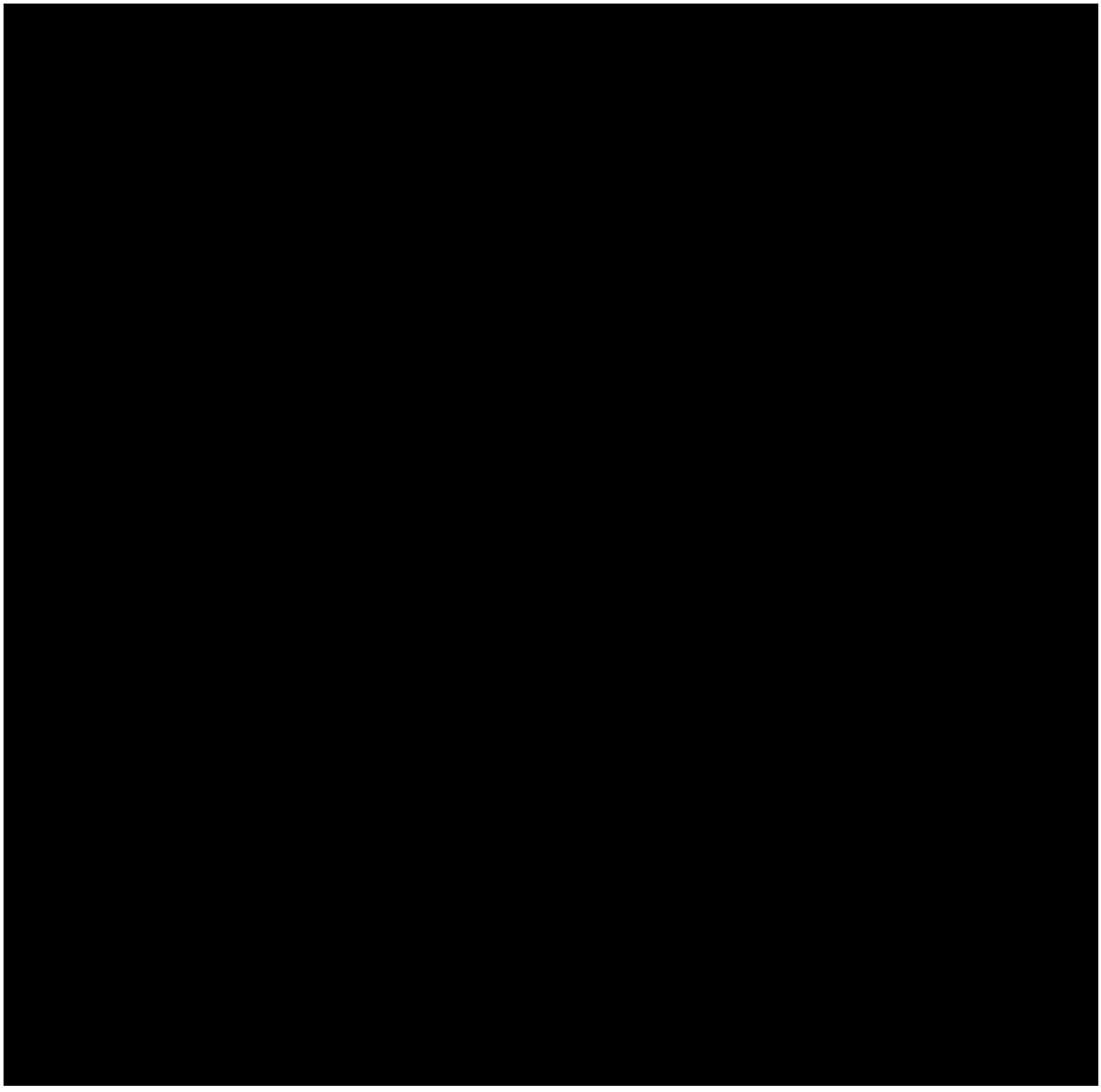
9.3.1.1 Efficacy Endpoints

The primary efficacy endpoint is the proportion of participants who achieve ≥ 1 stage improvement in liver fibrosis (METAVIR score) as determined by liver biopsy after 12 weeks of treatment in Part 1 and after 24 weeks in Part 2.

Secondary efficacy endpoints are as follows:

- Change in CPA, as compared to placebo after 12 weeks of treatment in Part 1 and after 24 weeks of treatment in Part 2

- Proportion of participants with ≥ 1 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment in Part 1 and after 24 weeks of treatment in Part 2
- Proportion of participants with ≥ 2 stage improvement in liver fibrosis (METAVIR score), as compared to placebo after 12 weeks of treatment in Part 1 and after 24 weeks of treatment in Part 2
- Proportion of participants with ≥ 2 stage improvement in liver fibrosis (Ishak score), as compared to placebo after 12 weeks of treatment in Part 1 and after 24 weeks of treatment in Part 2
- Proportion of participants with ≥ 15% decrease from baseline in liver stiffness as measured by MRE at Day 85 in Part 1 and Day 169 in Part 2
- Change from baseline in liver stiffness as measured by MRE Day 85 in Part 1 and Day 169 in Part 2



9.3.1.2 Analysis Methodology

Efficacy analyses will be performed using the modified intent-to-treat (mITT) population. The handling of missing values will be defined in the SAP.

Primary Endpoint Part 1: To evaluate the effect of BMS-986263 (90 mg QW) on METAVIR Fibrosis Stage at Week 12, a 95.0% CI of response rate for treatment vs placebo will be used to estimate the difference between the proportion of participants with ≥ 1 stage improvement in fibrosis on liver biopsy. Additionally, the odds ratio of each treatment will be used to estimate improvement of treatment as compared to placebo for the proportion of participants with ≥ 1 stage improvement in fibrosis on biopsy at Week 12.

Primary Endpoint Part 2: To evaluate the effect of BMS-986263 (45 mg Q2W, 90 mg Q2W, 90 mg Q4W) on METAVIR Fibrosis Stage vs placebo, a stratified Cochran Armitage Trend Test controlling for hepatic fibrosis stage (Stage 3 or Stage 4) will be used to analyze the proportion of participants with ≥ 1 stage improvement in fibrosis on biopsy at Week 24. After the assessment of trend, comparisons of each treatment group with placebo will be performed utilizing a stratified (fibrosis stage) Cochran Mantel-Haenszel test (CMH). All of these analyses will be performed at 1-sided 0.05 level of significance. In addition, 95% CI for the response rates and odds-ratios will be calculated.

A sensitivity analysis using an extended CMH correlation test will be used to assess the trend among the proportions for treatment groups with an adjustment to strata (fibrosis stage).[31] Two-sided 0.10 level of significance will be used.

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.

Continuous endpoints may be analyzed by analysis of covariance methods.

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

Subgroup analyses will be performed including hepatic fibrosis stage.

9.3.2 Safety

Safety assessments 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 incidence of AEs, serious AEs, [redacted]
AEs leading to discontinuation, and death, as well as marked abnormalities in clinical laboratory tests, vital sign measurements, ECGs, physical examinations [redacted]

9.3.3 Other Analyses

[redacted]

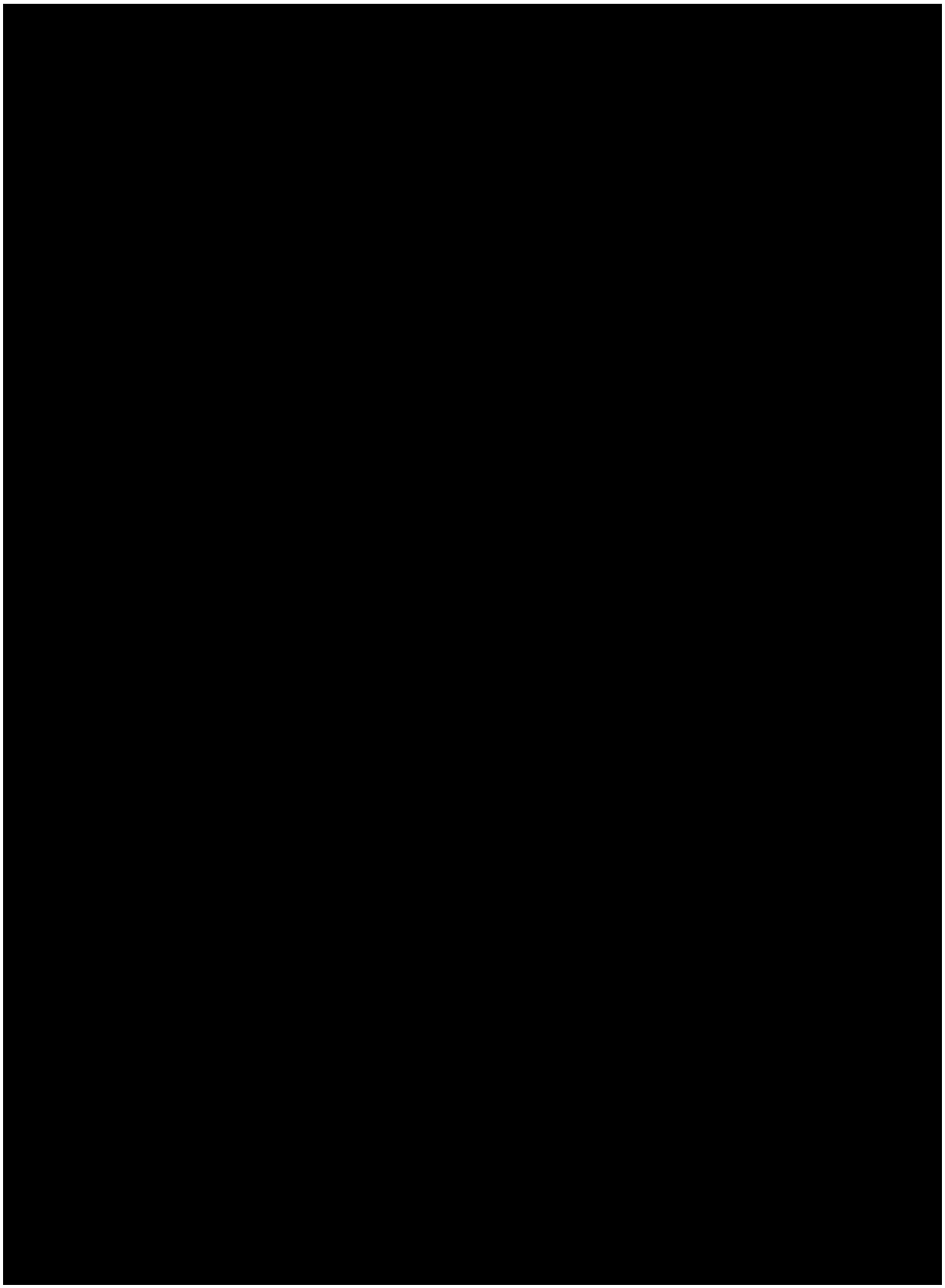
9.3.3.1 Pharmacokinetics

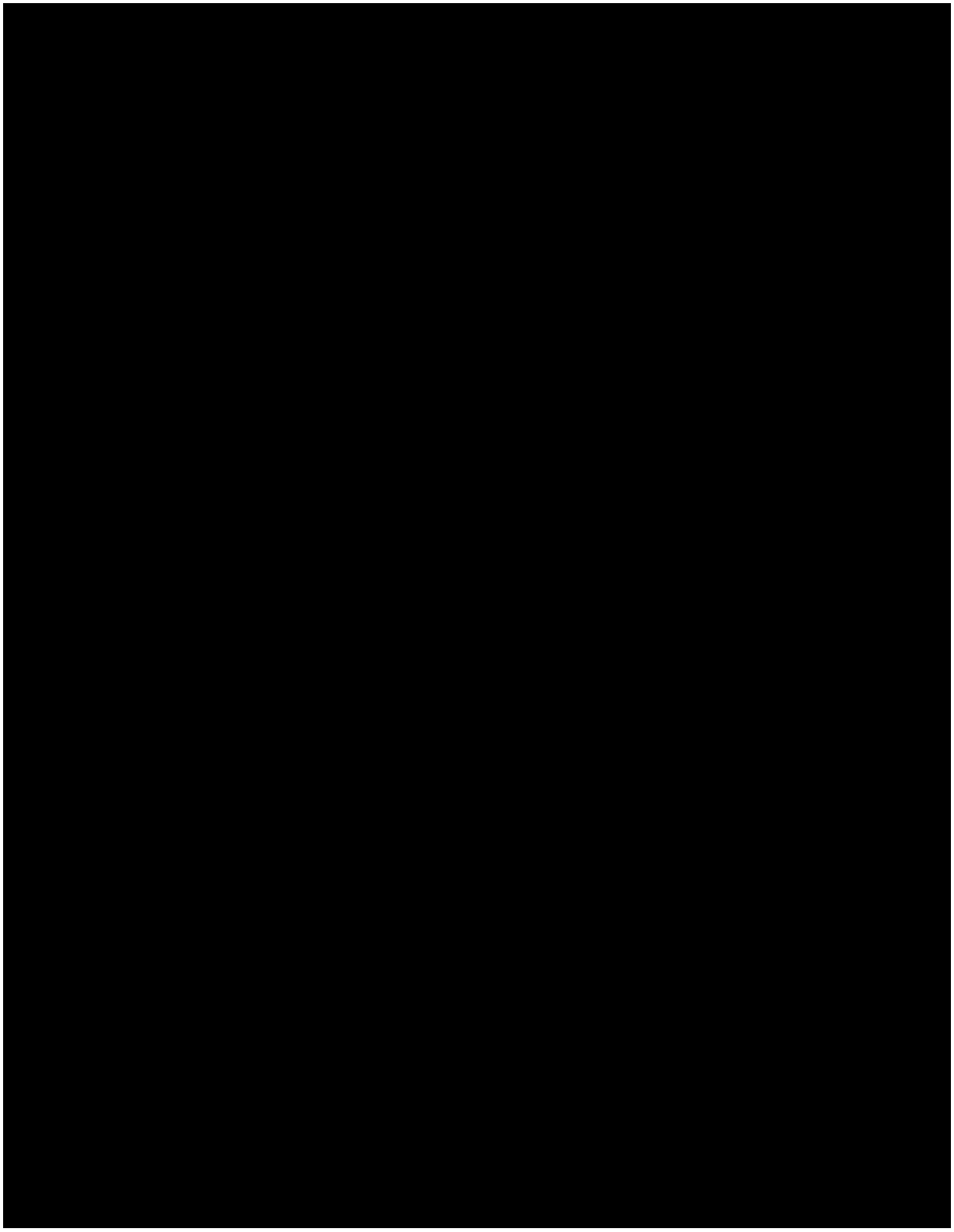
Pharmacokinetics, pharmacodynamics, [redacted] of BMS-986263 will be analyzed based on the time points indicated in the Schedule of Activities (Section 1.2). [redacted]

PK evaluation is a secondary endpoint.

BMS-986263, [redacted] plasma concentrations will be listed and summarized descriptively by dose, day and time.

[redacted]





11. APPENDICES

APPENDIX 1 STUDY GOVERNANCE CONSIDERATIONS

The term 'participant' is intended to refer to a person 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:

- GCP guidelines as defined by ICH guidance
- In accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States (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 IIRB/EC, and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the participants of the study or the scientific value of the study.

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/EC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to 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 participants and any updates.

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

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/EC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study 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 or
- 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 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 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 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 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 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.

Investigators must:

- Provide a copy of the ICF 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 ICF 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 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 ICF 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 participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participants' signed ICF and, in the US, the 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.

Participants unable to give their written consent (eg, those with stroke or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study 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), AE tracking/reporting, protocol-required assessments, and/or drug accountability records).

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

The study personnel will account for all study treatments dispensed to and returned from the participant. Study site personnel will account for all unused study treatments at the site, and unused study medication will be destroyed at the site or returned to the sponsor or designee for appropriate destruction, depending on circumstances. Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records will be reconciled with existing study medication by a study monitor prior to destruction of the product. Certificates of destruction should be signed and will be included in the Trial Master File. 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 (eg, lost, wasted) • amount returned to BMS or designee • 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.

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 eCRF 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. Electronic case report forms 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, eCRFs 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 Pregnancy Surveillance Form, respectively. If an electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific eCRF completion guidelines provided by sponsor or designee.

The confidentiality of records that could identify 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 eCRFs.

The completed eCRF and SAE/pregnancy eCRFs, 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. For eCRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the eCRFs including records of the changes and corrections.

Each individual electronically signing electronic eCRFs must meet sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

Monitoring

BMS [redacted] representatives will review data on-site to identify potential issues to determine a schedule of on-site visits for review of study records.

Representatives of BMS [redacted] 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 BMS [redacted] 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 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 must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator 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 (as applicable; some sites will return unused study treatments depending on circumstances).

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) (eg, study treatments sourced from the site's 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 standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, 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 study 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.

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 and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on one or more of the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

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.

APPENDIX 2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An adverse event (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, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement 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 pre-existing 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).

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

Serious Adverse Event Definition: 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 8.4.6.1 for the definition of potential DILI).

Pregnancy and potential DILI must follow the same transmission timing and processes to BMS as used for SAEs (see Section 8.6.2.1.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Intensity

The intensity of AEs is determined by a physician and will use the following levels:

- Mild: An event that is easily tolerated by the 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.

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 (IB) 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.

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 to PRA Drug Safety within 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: [redacted]

SAE Fax Number:

Americas: [redacted]

Europe/East Asia Pacific: [redacted]

SAE Telephone Contact - For questions on SAE/pregnancy reporting, please call:

Americas: [redacted]

Europe/East Asia Pacific: [redacted]

APPENDIX 3 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Definitions

Woman of Childbearing Potential

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, females must have a serum FSH level > 40 mIU/mL to confirm menopause.

Note: Females 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 periods below are suggested guidelines and the investigators should use their judgement 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.

Contraception Guidance for Female Participants of Child Bearing Potential

One of the contraception methods listed below as "**Highly Effective**" is required to be used during this study and until the end of relevant systemic exposure, defined as 5 days after the end of study treatment, plus 30 days. Hormonal contraception and methods listed as not highly effective or ineffective below are not permitted.

Contraceptive Methods Classified as Highly Effective

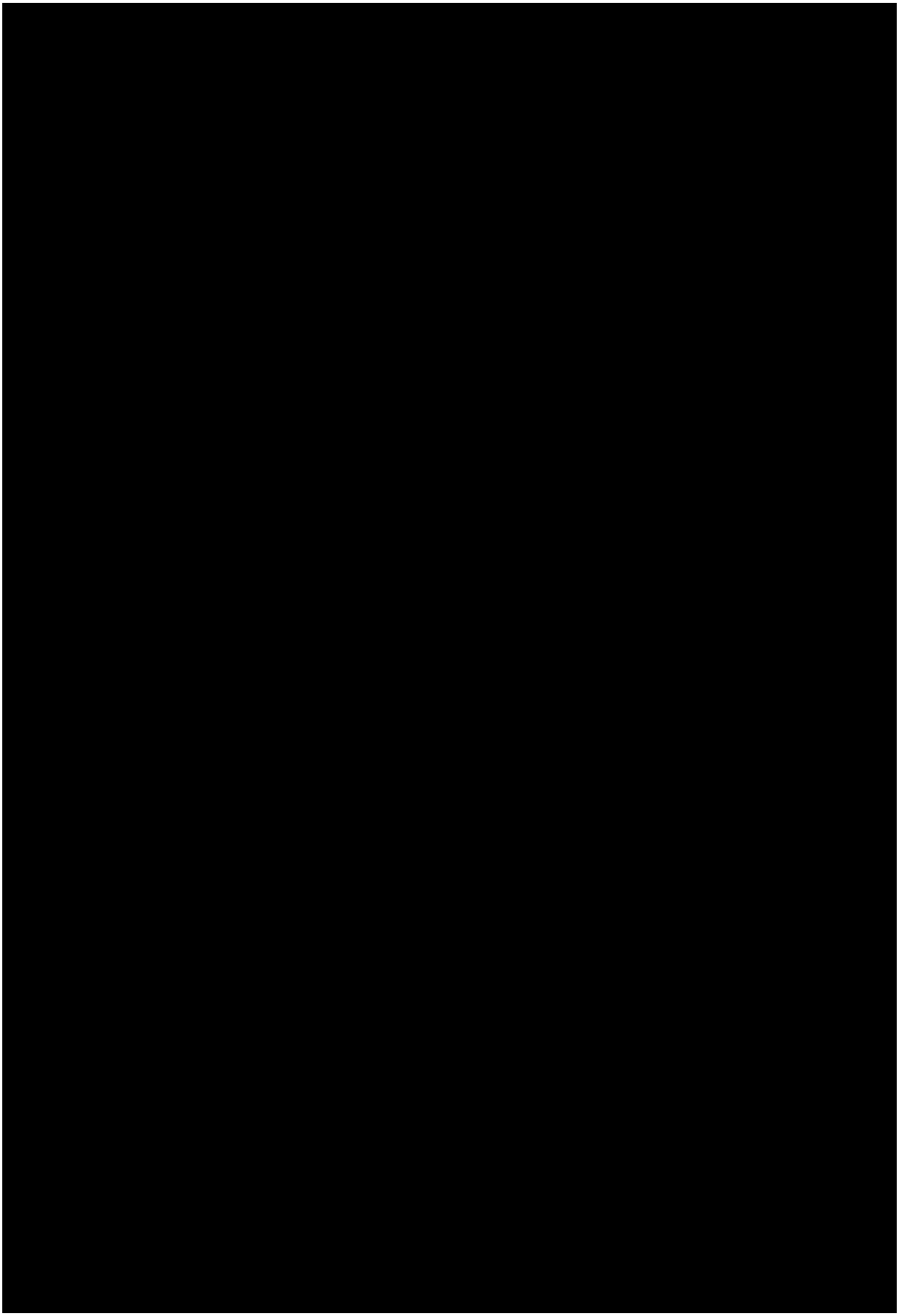
User Independent Methods
• Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• 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.* • 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. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forgo complete abstinence

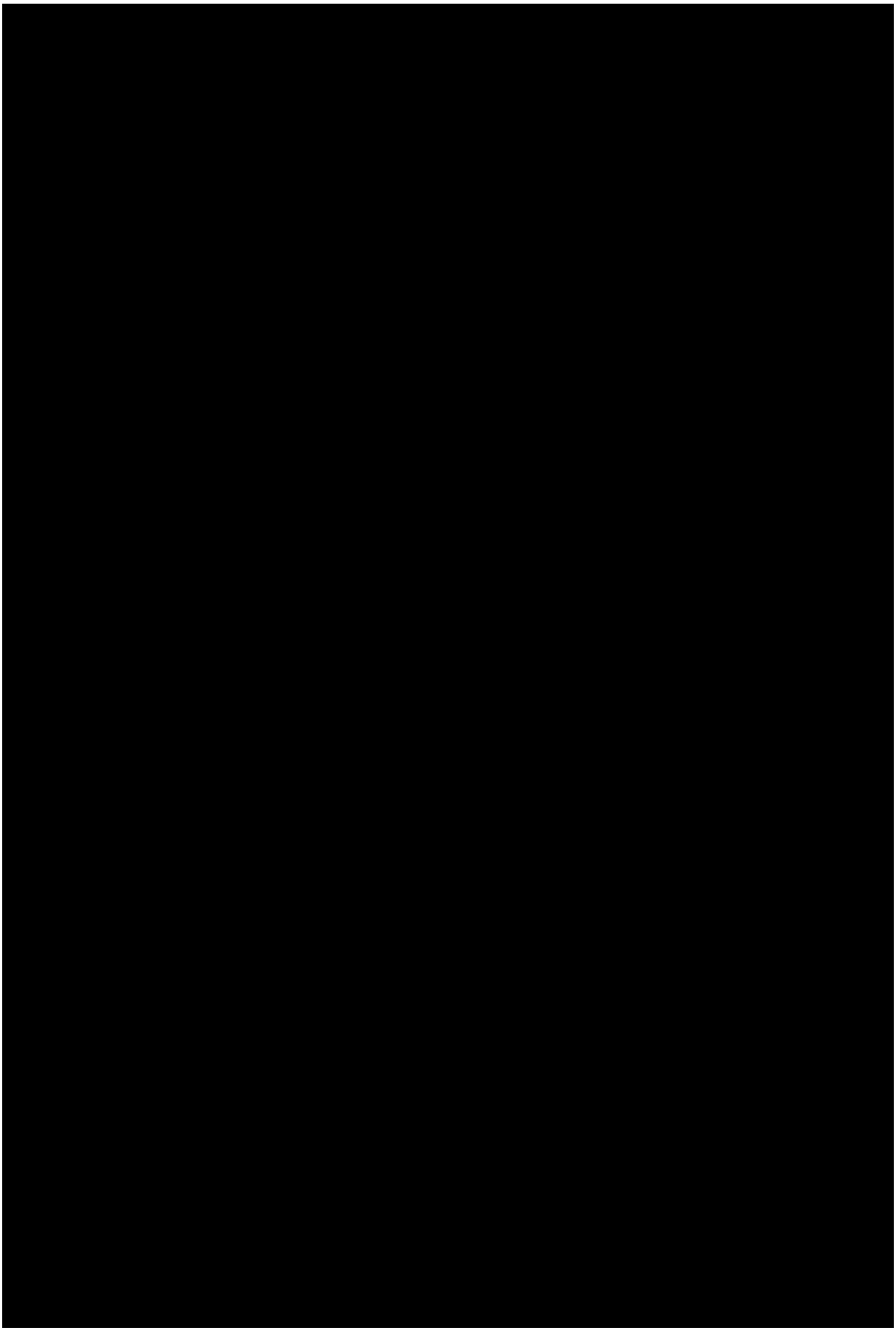
Contraceptive Methods Not Classified as Highly Effective

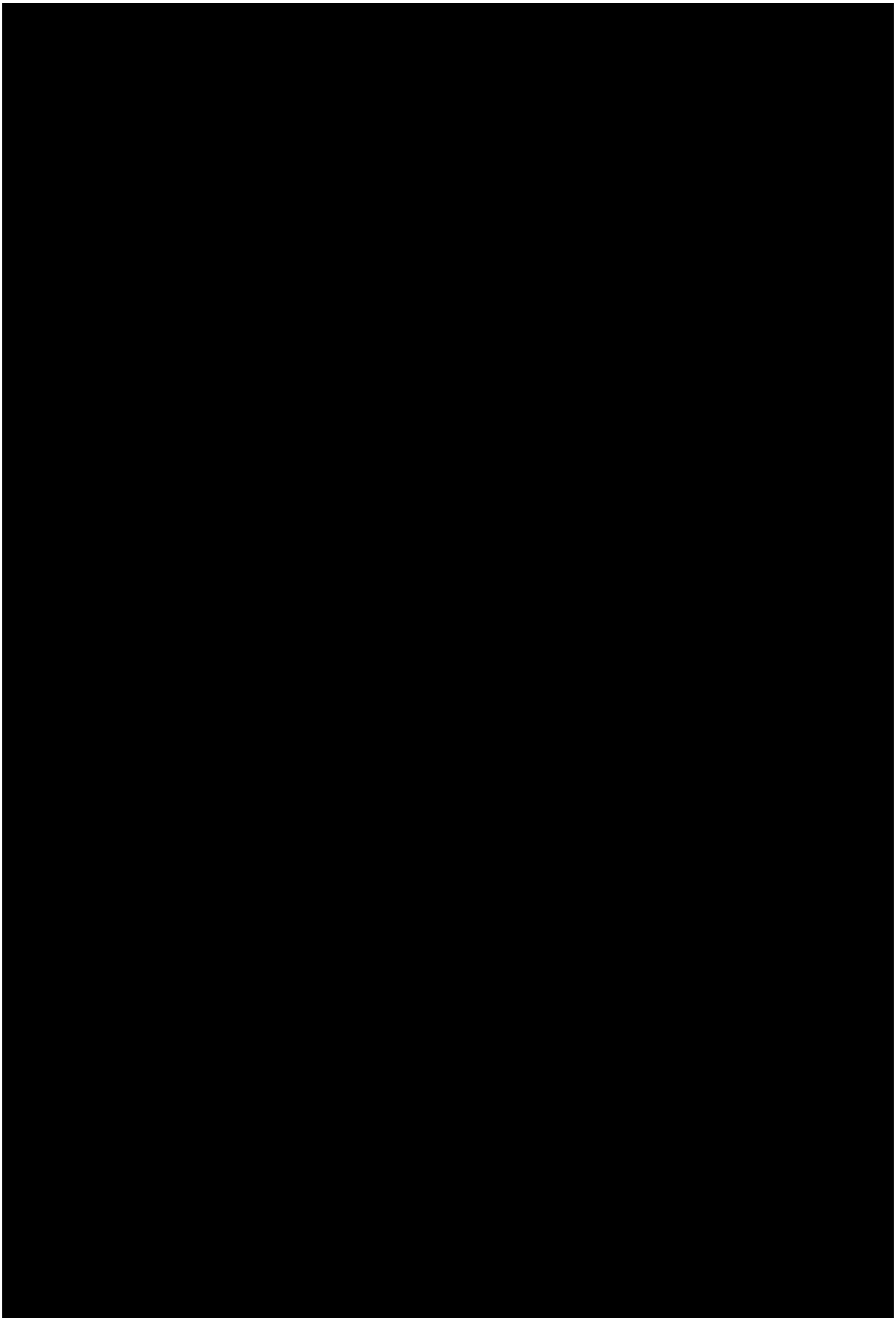
User Dependent Methods *Failure rate of > 1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • Lactation amenorrhea method

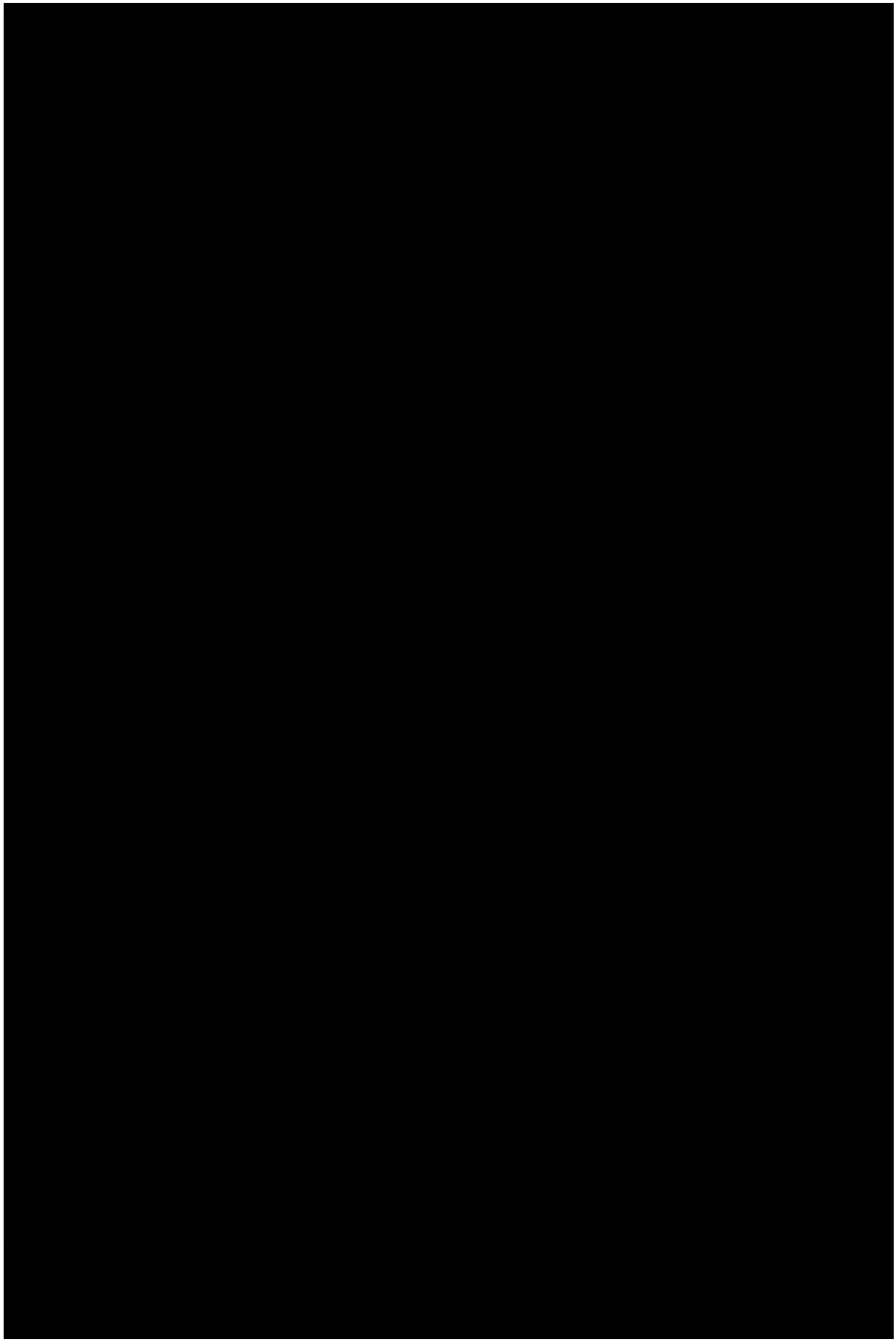
Collection of Pregnancy Information

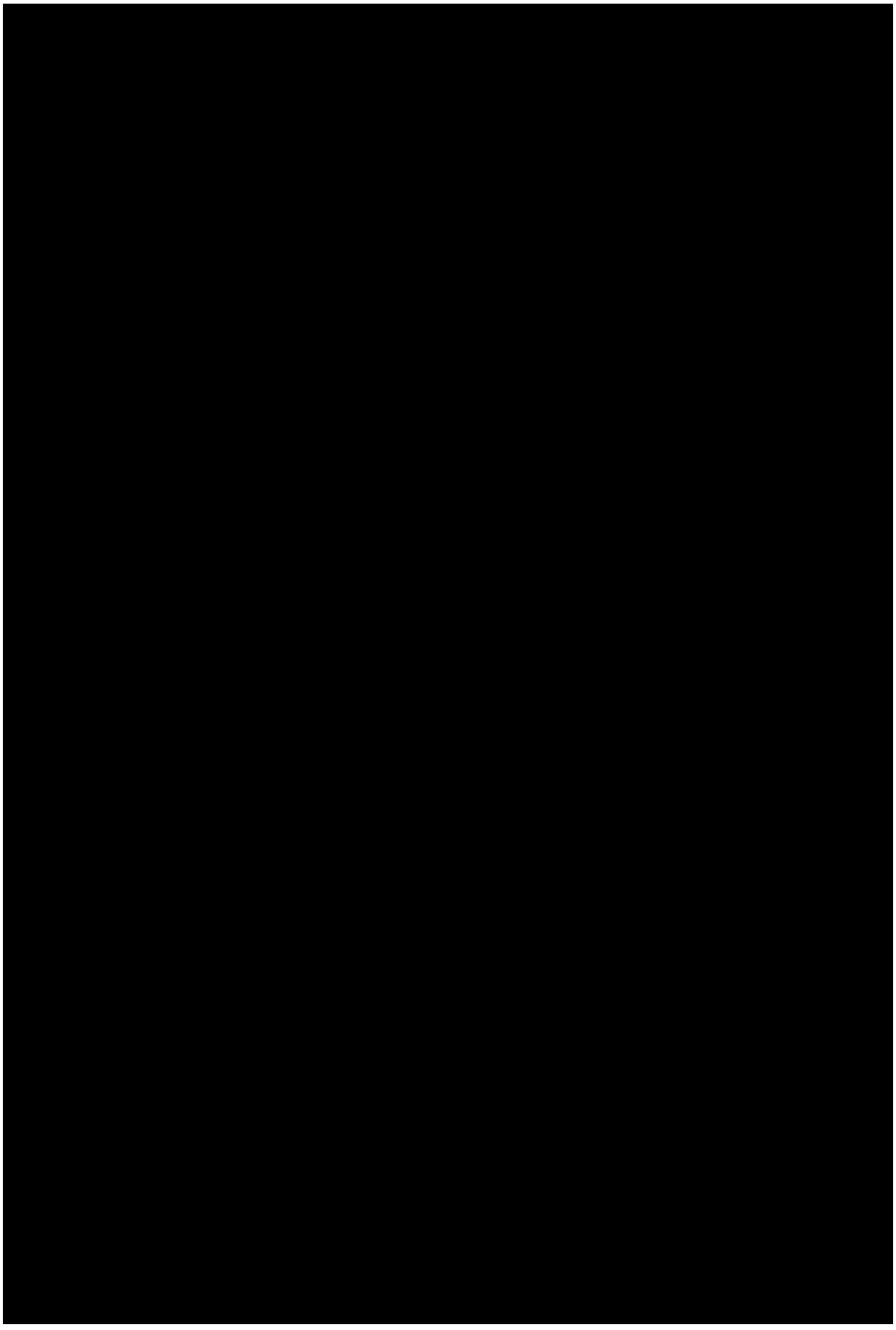
Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 8.6.2.1.5 and the Appendix for AEs and SAEs Definitions and Procedures for Evaluating, Follow-up, and Reporting (Appendix 2).

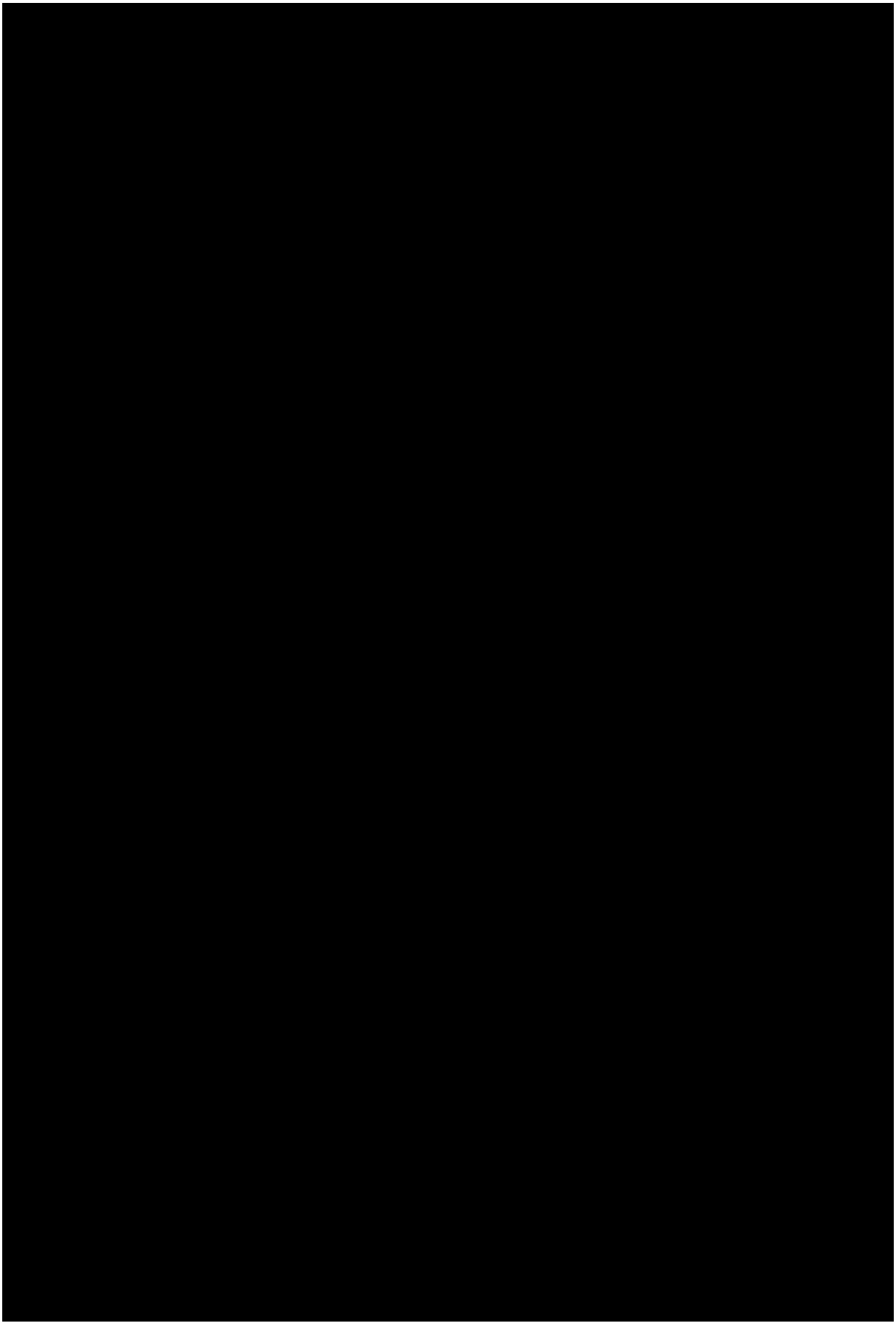


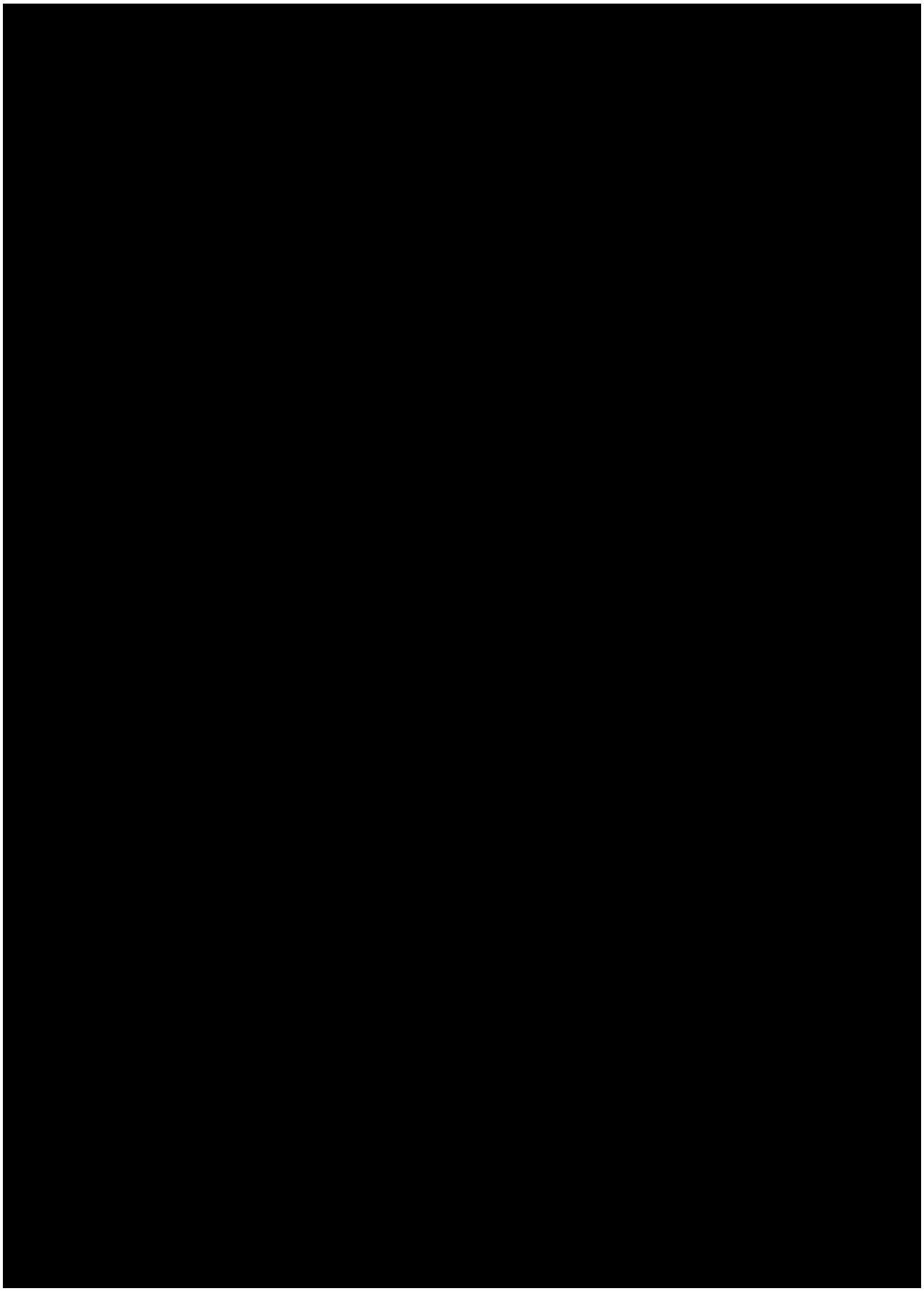


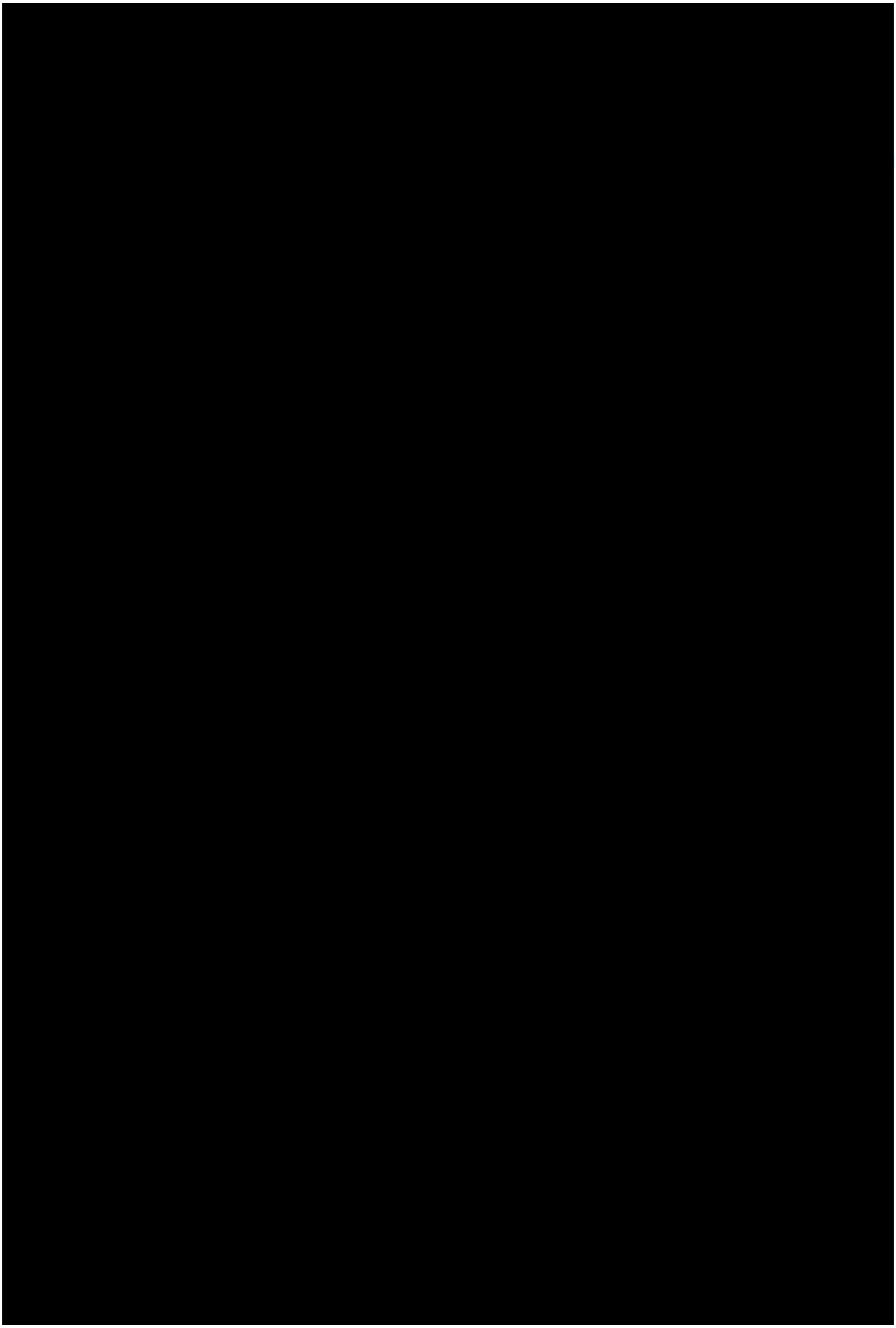


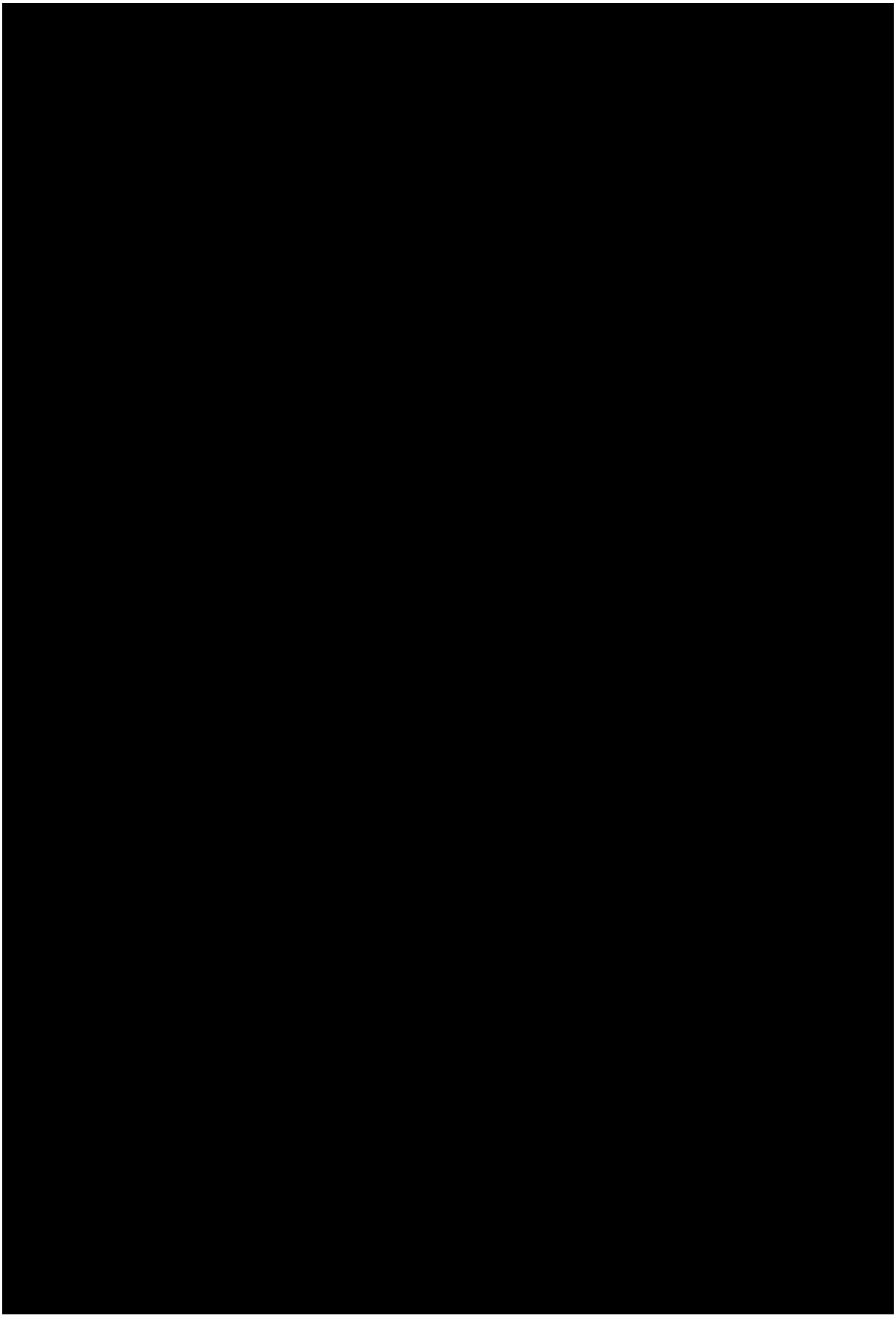


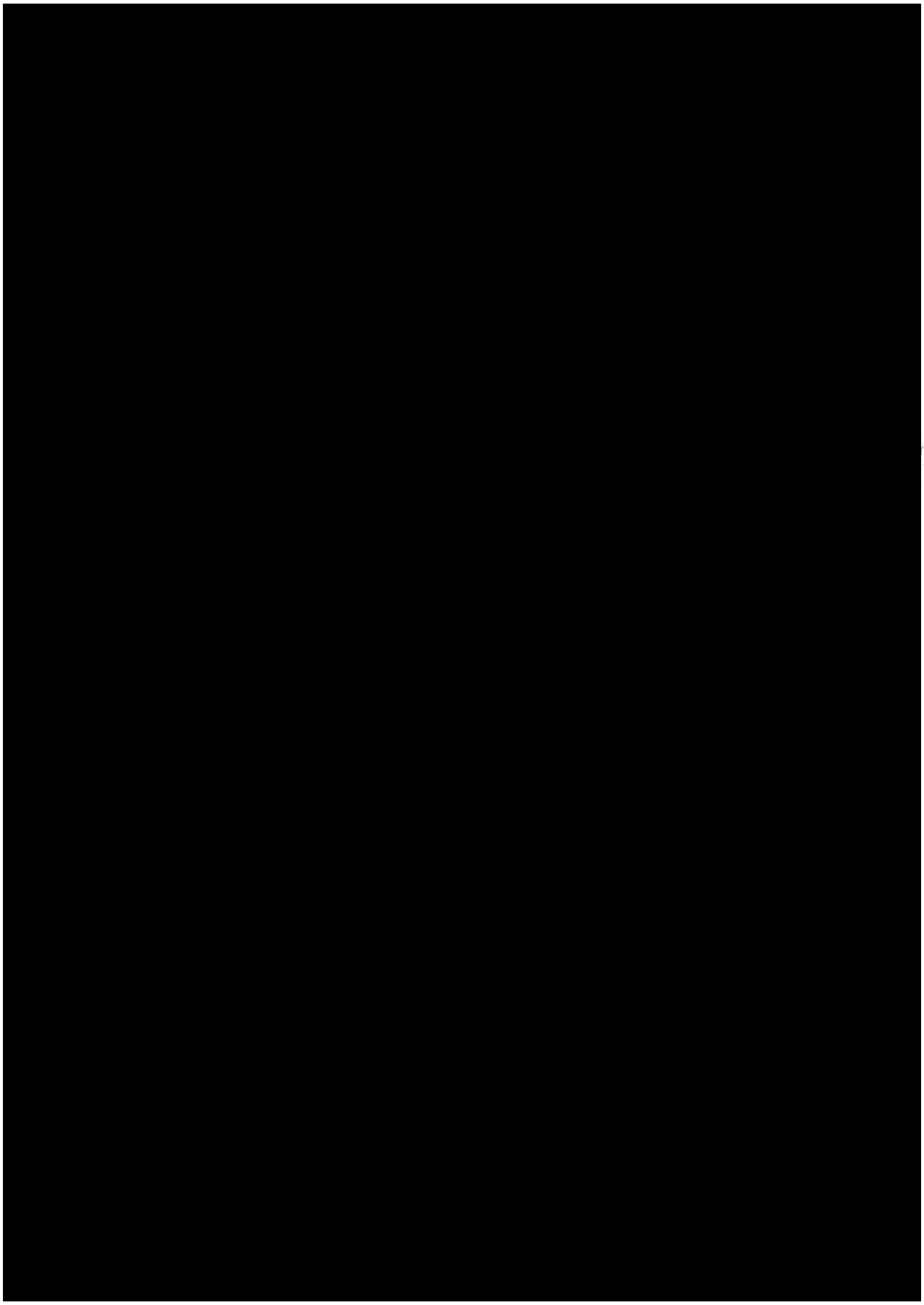










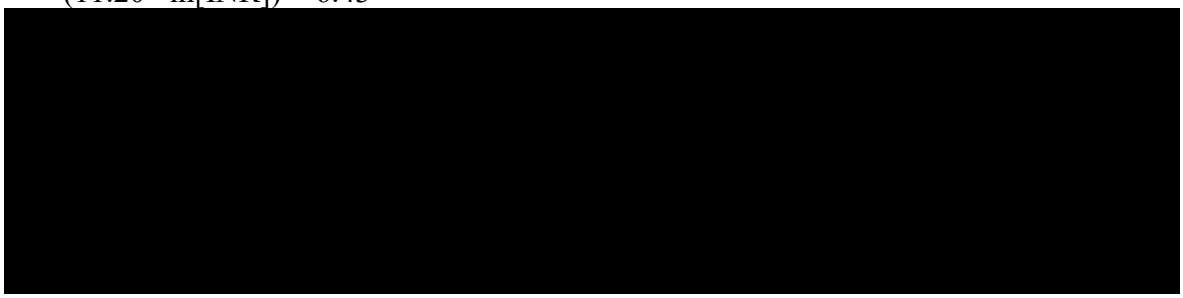


APPENDIX 7 CHILD-PUGH SCORING

Parameter	Classification	Score
Bilirubin (Total)	< 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	> 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	< 1.7	+1
	1.7-2.2	+2
	> 2.2	+3
Ascites	Absent	+1
	Slight	+2
	Moderate	+3
Encephalopathy	No encephalopathy	+1
	Grade 1-2	+2
	Grade 3-4	+3

APPENDIX 8 FORMULAE FOR MEASUREMENTS

- MELD Score = (9.57*ln[creatinine]) + (3.78 * ln[Bilirubin]) + (11.20* ln[INR]) + 6.43



Method of BMI Calculation:

- Use actual height and weight collected on the same day. Whenever possible, body weight should be measured using the same scale throughout the study.
- To calculate BMI:
  - Convert weight pounds to kg (kg = pounds / 2.2)
  - Convert height inches to centimeters (cm = inches × 2.54)
  - BMI = (weight in kg) / (height in cm/100)^2
  - Round to 1 decimal place (if 0.05 or greater, round up)