Official Title of Study:

A Phase 2B Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of BMS-986036 (PEG-FGF21) in Adults with Nonalcoholic Steatohepatitis (NASH) and Compensated Liver Cirrhosis

PROTOCOL MB130-069

NCT Number: NCT03486912

Document Date (Date in which document was last revised): January 30, 2020

A PHASE 2B RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND EFFICACY OF BMS-986036 (PEG-FGF21) IN ADULTS WITH NONALCOHOLIC STEATOHEPATITIS (NASH) AND COMPENSATED LIVER CIRRHOSIS

FALCON 2 Study

Test Drug: BMS-986036 (pegbelfermin)
Protocol Number: MB130-069
IND 125,297
Date and Version: Version 4.0, 30 January 2020

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Approved v4.0 [redacted]

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change	Approvers
Original Protocol	04 January 2018	Not Applicable	[redacted]
Revised Protocol 1 (Final Approved 2.0)	02 March 2018	1. Incorporates changes to multiple Sections of the protocol in response to additional internal review: 2. Revises secondary and exploratory objectives and endpoints 3. Revises the protocol to more clearly define expectations for participants who discontinue study medication or overall study participation 4. Clarifies visit intervals and visit windows for bone mineral density and immunogenicity follow-up visits 5. Clarifies pregnancy reporting requirements 6. Clarifies procedures for collection of serious adverse events and concomitant medications 7. Updated methods of data analysis 8. Provides clarifications to increase consistency within the protocol.	
Revised Protocol 2 (Final Approved 3.0)	20 January 2019	1. Updates the Sponsor's contact information and includes the study name (FALCON 2) and generic name, pegbelfermin, for BMS-986036 2. Updates the screening/rescreening processes and sequence/timing of required testing, e.g., allows	[redacted]

		extension of screening period (from 8 to 12 weeks) if needed 3. Modifies the inclusion criteria of patients with hepatitis C virus sustained viral response (for at least 2 years) 4. Updates inclusion/exclusion criteria for medications 5. Allows inclusion of participants with Grade ≤ 1 varices (from historical esophagogastroduodenoscopy) and updates inclusion/exclusion criteria for Fibroscan elastography and medications [redacted] 7. Provides for the collection of medications that could impact bone mineral density from end of treatment through the 6-month follow-up dual-energy X-ray absorptiometry scan 8. Updates requirements for procedures and testing for subjects prematurely discontinuing study treatment 9. Updates and clarifies study procedures and analysis plans 10. Incorporates editorial updates	
Revised Protocol 3 (Final Approved 4.0)	30 January 2020	1. Updates made throughout the protocol requiring all participants to have sample collection for potential immunogenicity testing during the visit at 6 months after the Week 52 Post-treatment Follow-up (PTFU) Visit. 2. Updated Section 1 Schedule of Activities, Table 1 and Table 2, Clinical Efficacy Assessments, Hepatic Magnetic Resonance Elastography (MRE), participants to fast at least 4 hours prior to assessment to align with instructions in the imaging manual.	[redacted]

		3. Updates the number of randomized participants from approximately 100 to approximately 155 (approximately 38 participants per arm) based on final enrollment. See Section 6.2 for details. 4. Update to Section 1 and Section 8.4.8 to include collection of any other nonalcoholic steatohepatitis (NASH) therapies taken during the post Week 52 follow-up period during the visit at 6 months after the Week 52 PTFU Visit. 5. Updates made throughout the protocol to clarify the exploratory endpoint related to digital pathology assessment of liver biopsies. 6. Update to Section 8.5.1.1 to include handling of incidental findings and blinding of on-treatment biopsy results. 7. Update to Section 9.4.4 to remove endpoints that reference relationships to align with the Statistical Analysis Plan (SAP).	

1. SCHEDULE OF ACTIVITIES

Schedules of procedures and assessments are described in the tables below:

- Table 1 - Screening Period Activities - Study MB130-069
- Table 2 - Double-Blind Treatment Period Activities and Post-Treatment Follow-Up Period Activities - Study MB130-069
- Table 3 - Long-Term Bone Mineral Density and Immunogenicity Follow-Up Period Activities - Study MB130-069

Table 1 Screening Period Activities - Study MB130-069

Procedure/Assessment	Screening Period (up to 8 weeks; see Section 8.1)	Notes Screening Period may be extended to a total of up to 12 weeks upon discussion with the medical monitor
Screening and History Assessments		
Informed consent	X	The approved informed consent form must be signed before completing any protocol-specific procedures
Study enrollment via interactive response technology (IRT)	X	See Section 8.4.3
Inclusion/exclusion criteria	X	See Sections 8.3.1, 8.3.2, 8.3.3, and 8.3.4
Complete medical history	X	See Section 8.3.5, Appendix 4
Surgical history	X	See Section 8.3.5
Diet and exercise history	X	See Section 8.3.5
Prior medications	X	See Section 8.4.8
Dietary and Lifestyle Counseling	X	See Section 8.3.6
Clinical Efficacy Assessments		
Liver biopsy	X	Only to be conducted if no liver biopsy specimen collected within 6 months (26 weeks) prior to informed consent is available and readable by the Central Pathologist. See Section 8.5.1.1.
Hepatic magnetic resonance elastography (MRE)	X	See Section 8.5.1.3. Participants should fast for at least 4 hours prior to assessment
Hepatic magnetic resonance imaging (MRI)	X	See Section 8.5.1.3
Fibroscan® elastography	X	See Section 8.5.1.4
Height and weight for body mass index (BMI) calculation	X	See Section 8.5.1.6
Waist circumference	X	See Section 8.5.1.6
Child-Pugh Turcotte scoring	X	See Section 8.5.1.7, Appendix 5

Procedure/Assessment	Screening Period (up to 8 weeks; see Section 8.1)	Notes Screening Period may be extended to a total of up to 12 weeks upon discussion with the medical monitor
Model for End-Stage Liver Disease (MELD) scoring	X	See Section 8.5.1.8 and Appendix 10
Clinical Safety Assessments		
12-lead electrocardiogram	X	If a participant has a QT interval corrected using Fridericia's formula (QTcF) > 480 msec, it should be confirmed by repeat electrocardiogram 30-60 minutes after the initial electrocardiogram. If the QTcF is confirmed to be > 480 msec, the participant should not be allowed to participate in the study. See Section 8.5.3.5
Vital signs	X	See Section 8.5.3.4
Physical examination	X	Examination will be a full physical examination as described in Section 8.5.3.3
Dual-energy X-ray absorptiometry (DXA) assessment	X	See Section 8.5.3.8
Laboratory Assessments		
Urinalysis	X	Includes assessments listed in Table 8 in Section 8.5.4
Urine for inflammation and kidney markers	X	See Table 8 in Section 8.5.4
Urine drug screen	X	See Table 8 in Section 8.5.4
Serum pregnancy test	X	To be conducted only in women of childbearing potential. See Table 8 in Section 8.5.4
Follicle-stimulating hormone (FSH) testing	X	To be conducted only in postmenopausal women. See Table 8 in Section 8.5.4 and Appendix 2
Hepatitis B assessments	X	See Table 8 in Section 8.5.4 and Appendix 3
Hepatitis C assessments	X	See Table 8 in Section 8.5.4 and Appendix 3
Hematology	X	Includes the assessments listed in Table 8 in Section 8.5.4
Blood chemistry	X	Includes the assessments listed in Table 8 in Section 8.5.4

Procedure/Assessment	Screening Period (up to 8 weeks; see Section 8.1)	Notes Screening Period may be extended to a total of up to 12 weeks upon discussion with the medical monitor
Laboratory metabolic markers	X	See Section 8.5.1.6 and Table 8 in Section 8.5.4. Participants should fast for at least 8 hours prior to the blood collection for these assessments
Serum N-terminal type 3 collagen propeptide (PRO-C3)	X	See Table 8 in Section 8.5.4 Participants should fast for at least 8 hours prior to the blood collection for this assessment
[redacted]		
Adiponectin	X	See Table 8 in Section 8.5.4. Participants should fast for at least 8 hours prior to the blood collection for this assessment
Micro RNA (miRNA)	X	See Table 8 in Section 8.5.4
Whole blood for gene expression assessments	X	See Table 8 in Section 8.5.4
[redacted]		

Table 2 Double-Blind Treatment Period Activities and Post-Treatment Follow-Up Period Activities - Study MB130-069

Procedure/Assessment	Double-Blind Treatment					Follow-Up	
	Day 1 Visit	After Day 1, up to Week 24 Visits every 4 weeks (± 5 days)	Week 24 Visit (± 5 days)	After Week 24, up to Week 48 Visits every 8 weeks (± 5 days)	Week 48 Visit (± 5 days)/ Early Termination (ET)	Week 52/ Post-Treatment Follow-Up Visit (PTFU) (± 5 days)	
Screening and History Assessment Updates							
Inclusion/exclusion criteria	X						Confirm continued study eligibility. See Sections 8.3.1, 8.3.2, 8.3.3, and 8.3.4
Confirm continued eligibility and randomization via interactive response technology (IRT)	X						See Section 8.4.3
Update medical history	X						See Section 8.3.5
Update surgical history	X						See Section 8.3.5
Diet and exercise history	X		X		X		See Section 8.3.5
Prior medications	X						See Section 8.4.8

Procedure/Assessment	Double-Blind Treatment					Follow-Up	
	Day 1 Visit	After Day 1, up to Week 24 Visits every 4 weeks (± 5 days)	Week 24 Visit (± 5 days)	After Week 24, up to Week 48 Visits every 8 weeks (± 5 days)	Week 48 Visit (± 5 days)/ Early Termination (ET)	Week 52/ Post-Treatment Follow-Up Visit (PTFU) (± 5 days)	
Clinical Efficacy Assessments							
Liver biopsy					X		See Section 8.5.1.1 The biopsy should be performed within ± 7 days of the Week 48 Visit. However, if a biopsy cannot be scheduled within the window specified above, the biopsy should be performed as close to schedule as possible Liver biopsy will be performed at the ET Visit if the participant has completed at least Week 20. If a participant discontinues study participation prior to Week 20 they should consider having a liver biopsy at ET
Hepatic magnetic resonance elastography (MRE)			X		X		Assessment window ±7 days. See Section 8.5.1.3. Participants should fast for at least 4 hours prior to these assessments. For participants prematurely discontinuing study medication prior to Week 24, MRE should be conducted at the ET Visit if the date of discontinuation is more than 4 weeks from the date of the previous MRE. For participants prematurely discontinuing study medication after Week 24, MRE should be conducted at the ET Visit if the date of

Procedure/Assessment	Double-Blind Treatment					Follow-Up	
	Day 1 Visit	After Day 1, up to Week 24 Visits every 4 weeks (± 5 days)	Week 24 Visit (± 5 days)	After Week 24, up to Week 48 Visits every 8 weeks (± 5 days)	Week 48 Visit (± 5 days)/ Early Termination (ET)	Week 52/ Post-Treatment Follow-Up Visit (PTFU) (± 5 days)	
							discontinuation is more than 8 weeks from the date of the previous MRE
Hepatic magnetic resonance imaging (MRI)			X		X		Assessment window ± 7 days. See Section 8.5.1.3. For participants prematurely discontinuing study medication prior to Week 24, MRI should be conducted at the ET Visit if the date of discontinuation is more than 4 weeks from the date of the previous MRI. For participants prematurely discontinuing study medication after Week 24, MRI should be conducted at the ET Visit if the date of discontinuation is more than 8 weeks from the date of the previous MRI
Fibroscan® elastography					X		See Section 8.5.1.4
[redacted]							

Procedure/Assessment	Double-Blind Treatment					Follow-Up	
	Day 1 Visit	After Day 1, up to Week 24 Visits every 4 weeks (± 5 days)	Week 24 Visit (± 5 days)	After Week 24, up to Week 48 Visits every 8 weeks (± 5 days)	Week 48 Visit (± 5 days)/ Early Termination (ET)	Week 52/ Post-Treatment Follow-Up Visit (PTFU) (± 5 days)	
Weight for body mass index (BMI) calculation	X		X		X	X	See Section 8.5.1.6. The Screening value for height will be used in the BMI calculation
Waist circumference	X		X		X		See Section 8.5.1.6
Child-Pugh Turcotte scoring	X		X		X		See Section 8.5.1.7, Appendix 5
Model for End-Stage Liver Disease (MELD) scoring	X	X	X	X	X	X	All components of the MELD score should be completed on the same day. If any individual component needs to be repeated on another day, all other components must be repeated as well. See Section 8.5.1.8 and Appendix 10
Liver-related clinical outcome events	X	X	X	X	X	X	See Section 8.5.1.9
3-Level EuroQol 5 Dimension (EQ-5D-3L) quality-of-life questionnaire	X		X		X		See Section 8.5.1.10
36-Question Short Form Health Survey (SF-36) Version 2	X		X		X		See Section 8.5.1.10
Chronic Liver Disease Questionnaire-Nonalcoholic Fatty Liver Disease (CLDQ-NAFLD)	X		X		X		See Section 8.5.1.10
Clinical Safety Assessments							
Adverse events	X	X	X	X	X	X	See Section 8.5.3.1 and Appendix 9
Concomitant medications	X	X	X	X	X	X	See Section 8.3.7

Procedure/Assessment	Double-Blind Treatment					Follow-Up	
	Day 1 Visit	After Day 1, up to Week 24 Visits every 4 weeks (± 5 days)	Week 24 Visit (± 5 days)	After Week 24, up to Week 48 Visits every 8 weeks (± 5 days)	Week 48 Visit (± 5 days)/ Early Termination (ET)	Week 52/ Post-Treatment Follow-Up Visit (PTFU) (± 5 days)	
12-lead electrocardiogram	X		X		X	X	If a participant has a QTcF>480 msec at an on-treatment visit, it should be confirmed by repeat ECG 30-60 minutes after the initial ECG. If the QTcF is confirmed to be >480 msec, the medical monitor should be contacted. See Section 8.5.3.5 and Table 9 in Section 8.5.5
Vital signs	X	X	X	X	X	X	See Section 8.5.3.4
Full physical examination			X		X	X	See Section 8.5.3.3
Abbreviated physical examination	X	X		X			See Section 8.5.3.3
Dual-energy X-ray absorptiometry (DXA)					X		See Section 8.5.3.8. Assessment window ± 7 days Participants will return for a follow-up DXA assessment 6 months after the Week 52/PTFU Visit (see Table 3). One month is defined as 4 calendar weeks. The ET Visit should include a DXA scan only if the participant has completed at least the Week 16 Visit
Laboratory Assessments - On days of study visits, participants will hold their study medication dose until all laboratory samples have been collected.							
Urinalysis	X	X	X	X	X	X	See Section 8.5.4 and Table 8 in Section 8.5.4

Procedure/Assessment	Double-Blind Treatment					Follow-Up	
	Day 1 Visit	After Day 1, up to Week 24 Visits every 4 weeks (± 5 days)	Week 24 Visit (± 5 days)	After Week 24, up to Week 48 Visits every 8 weeks (± 5 days)	Week 48 Visit (± 5 days)/ Early Termination (ET)	Week 52/ Post-Treatment Follow-Up Visit (PTFU) (± 5 days)	
[redacted]							
Serum or urine pregnancy test	X	X	X	X	X	X	To be conducted in women of childbearing potential only. See Table 8 in Section 8.5.4
Enhanced Liver Fibrosis (ELF) Assessment	X		X		X		See Section 8.5.4 and Table 8 in Section 8.5.4. Participants should fast for at least 8 hours prior to the blood collection for this assessment
Hematology	X	X	X	X	X	X	See Section 8.5.4 and Table 8 in Section 8.5.4
Blood chemistry	X	X	X	X	X	X	See Section 8.5.4 and Table 8 in Section 8.5.4
Anti-drug and anti-FGF21 antibodies	X	X	X	X	X	X	See Table 8 in Section 8.5.4. Any participant with anti-drug and/or anti-FGF21 antibodies at Week 52/PTFU or ET who has not demonstrated decreasing anti-drug and/or anti-FGF21 antibody titers will be followed for up to approximately 14 months after Week 52/PTFU as described in Section 8.5.3.6. One month is defined as 4 calendar weeks

Procedure/Assessment	Double-Blind Treatment					Follow-Up	
	Day 1 Visit	After Day 1, up to Week 24 Visits every 4 weeks (± 5 days)	Week 24 Visit (± 5 days)	After Week 24, up to Week 48 Visits every 8 weeks (± 5 days)	Week 48 Visit (± 5 days)/ Early Termination (ET)	Week 52/ Post-Treatment Follow-Up Visit (PTFU) (± 5 days)	
Laboratory metabolic markers	X		X		X		See Section 8.5.1, Section 8.5.4 and Table 8 in Section 8.5.4. Participants should fast for at least 8 hours prior to the blood collection for these assessments
Serum N-terminal type 3 collagen propeptide (PRO-C3)	X	X Samples only to be collected at Week 4, Week 8, and Week 12	X		X	X	See Section 8.5.1, Section 8.5.4, and Table 8 in Section 8.5.4. Participants should fast for at least 8 hours prior to the blood collection for this assessment
[redacted]							

Procedure/Assessment	Double-Blind Treatment					Follow-Up	
	Day 1 Visit	After Day 1, up to Week 24 Visits every 4 weeks (± 5 days)	Week 24 Visit (± 5 days)	After Week 24, up to Week 48 Visits every 8 weeks (± 5 days)	Week 48 Visit (± 5 days)/ Early Termination (ET)	Week 52/ Post-Treatment Follow-Up Visit (PTFU) (± 5 days)	
Adiponectin	X	X Samples only to be collected at Week 4, Week 8, and Week 12	X		X	X	See Section 8.5.1 and Table 8 in Section 8.5.4 Participants should fast for at least 8 hours prior to the blood collection for this assessment
Micro RNA (miRNA)	X	X Samples only to be collected at Week 4, Week 8, and Week 12	X		X	X	See Section 8.5.4 and Table 8 in Section 8.5.4
Whole blood for gene expression assessments	X	X Samples only to be collected at Week 4, Week 8, and Week 12	X		X	X	See Section 8.5.4 and Table 8 in Section 8.5.4
Serum for disease, target and drug effect biomarkers	X	X Samples only to be collected at Week 4, Week 8, and Week 12	X		X	X	See Section 8.5.4 and Table 8 in Section 8.5.4. Participants should fast for at least 8 hours prior to the sample collection

Procedure/Assessment	Double-Blind Treatment					Follow-Up	
	Day 1 Visit	After Day 1, up to Week 24 Visits every 4 weeks (± 5 days)	Week 24 Visit (± 5 days)	After Week 24, up to Week 48 Visits every 8 weeks (± 5 days)	Week 48 Visit (± 5 days)/ Early Termination (ET)	Week 52/ Post-Treatment Follow-Up Visit (PTFU) (± 5 days)	
Plasma for disease, target and drug effect biomarkers	X	X Samples only to be collected at Week 4, Week 8, and Week 12	X		X	X	See Section 8.5.4 and Table 8 in Section 8.5.4. Participants should fast for at least 8 hours prior to the sample collection
[redacted]							
Trough pharmacokinetic (PK) sampling	X	X	X	X	X	X	Trough (predose) samples will be collected at each visit. See Section 8.5.5
[redacted]							

Procedure/Assessment	Double-Blind Treatment					Follow-Up	
	Day 1 Visit	After Day 1, up to Week 24 Visits every 4 weeks (± 5 days)	Week 24 Visit (± 5 days)	After Week 24, up to Week 48 Visits every 8 weeks (± 5 days)	Week 48 Visit (± 5 days)/ Early Termination (ET)	Week 52/ Post-Treatment Follow-Up Visit (PTFU) (± 5 days)	
Study Medication							
Study medication administration training	X						Training maybe repeated as necessary at any study visit at the discretion of the investigator to maintain treatment compliance. See Section 8.4
Dispense study medication	X	X	X	X			See Section 8.4
Study medication return/reconcile		X	X	X	X		See Section 8.4

Table 3 Long-Term Bone Mineral Density and Immunogenicity Follow-Up Period Activities – Study MB130-069

Procedure/Assessment	6 Months After Week 52/PTFU (± 14 days)[a]	9 Months After Week 52/PTFU (± 14 days)[b]	12 Months After Week 52/PTFU (± 14 days)[b]	14 Months After Week 52/PTFU (± 14 days)[b]	Notes: 1 month is defined as 4 calendar weeks.
Concomitant medications since last visit	X				Selected medications that could impact bone mineral density assessment and nonalcoholic steatohepatitis (NASH) therapies taken after the end of study treatment (Section 8.4.8)
Dual-energy X-ray absorptiometry (DXA)	X				See Section 8.5.3.8. For participants who prematurely discontinue study medication, the follow-up DXA scan is not required unless the participant has completed at least Week 16
Anti-drug and anti-FGF21 antibodies	X	X	X	X	See Section 8.5.3.6 and Appendix 11
Blood chemistry				X	See Section 8.5.3.6
Hemoglobin A1c				X	See Section 8.5.3.6
[redacted]					
Serum for disease, target and drug effect biomarkers	X				See Section 8.5.4 and Table 8. Participants should fast for at least 8 hours prior to the sample collection
Plasma for disease, target and drug effect biomarkers	X				See Section 8.5.4 and Table 8. Participants should fast for at least 8 hours prior to the sample collection

[a] Month 6 samples will be collected from all participants.
[b] Performed only in participants for whom Long-Term Immunogenicity Follow-Up Visits are required.

2. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
ABV	alcohol by volume
[redacted]	
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
APRI	AST-Platelet Ratio Index
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMD	bone mineral density
BMI	body mass index
BSAP	bone-specific alkaline phosphatase
[redacted]	
CFR	Code of Federal Regulations
CLDQ-NFLD	Chronic Liver Disease Questionnaire-Nonalcoholic Fatty Liver Disease
CMH	Cochran Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
[redacted]	
CPA	collagen proportionate area
CRN	Clinical Research Network
CTX-1	C-terminal telopeptides type I collagen
[redacted]	
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual 5
DXA	dual-energy X-ray absorptiometry
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture system
EGD	esophagogastroduodenoscopy
eGFR	estimated glomerular filtration rate
ELF	Enhanced Liver Fibrosis
EQ-5D-3L	3-Level EuroQol 5 Dimension (quality-of-life questionnaire)
ET	early termination
FDA	(United States) Food and Drug Administration
FGF	fibroblast growth factor
FGF19	fibroblast growth factor 19

FGF21	fibroblast growth factor 21
FGF23	fibroblast growth factor 23
FGF-R	fibroblast growth factor receptor
FGF-R4	fibroblast growth factor receptor 4
FIB4	Fibrosis 4
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HRQoL	Health-related quality-of-life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
LDL	low-density lipoprotein
[redacted]	
MCD	methionine and choline-deficient
MD	Doctor of Medicine
MELD	Model for End-Stage Liver Disease
miRNA	micro RNA
mITT	modified intent-to-treat
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging-proton density fat fraction
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
NEC	not elsewhere classified
Non-IP	non-investigational product
P1NP	N-terminal propeptide- of type 1 procollagen
[redacted]	
PD	pharmacodynamic
PDFF	proton density fat fraction
PEG	polyethylene glycol

PK	pharmacokinetic
PRO-C3	N-terminal type 3 collagen propeptide
PTFU	Post-Treatment Follow-Up
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
QW	once weekly
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous
SF-36	36-question Short Form quality-of-life questionnaire (Version 2)
T2DM	type 2 diabetes mellitus
TG	triglycerides
TIMP-1	tissue inhibitor of metalloproteinases 1
ULN	upper limit of normal
[redacted]	
WOCBP/WOCBPs	woman/women of childbearing potential

4. ETHICS

This study will be conducted in compliance with the following:

- Institutional Review Board (IRB)/ethics committee (EC) guidelines
- International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- The principles set forth in the Declaration of Helsinki (Fortaleza 2013)
- Applicable regulations regarding clinical safety data management (E2A, E2B[R3]) and scientific integrity (E4, E8, E9, and E10)
- The ICH Note for Guidance on GCP (ICH Harmonised Tripartite Guideline E6 [R1])
- United States Food and Drug Administration (FDA) Code of Federal Regulations (CFR) (21 CFR § 50, 56, 312)

In addition, this study will adhere to all local regulatory requirements, and requirements for data protection.

Details on the ethical conduct of the study, IRB/ECs, and participant consent are in Appendix 1.

5. STUDY ADMINISTRATION AND CONTACTS

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

Additional information regarding vendors and their respective contacts/roles, including central laboratory, central imaging and central pathology, are included in the applicable vendor manuals.

Additional details on the Data Monitoring Committee (DMC) are in the DMC charter.

Study administrative considerations are addressed in Appendix 1.

6. INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in the world today. Nonalcoholic steatohepatitis (NASH), which is the more advanced form of NAFLD, is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning), with or without fibrosis.[1] NASH is associated with increased mortality rates due to cardiovascular-, liver-, and cancer-related deaths.

Currently, there are no approved drugs for the treatment of NASH. With the increasing prevalence of obesity and obesity-related diseases, NASH could soon become the leading indication for liver transplantation and the leading cause of hepatocellular carcinoma (HCC).[2] There is an urgent need to develop safe and effective therapies for NASH.[3]

Fibroblast growth factor 21 (FGF21) is a nonmitogenic hormone that is an important regulator of energy metabolism.[4] FGF21 is a member of a hormone-like subgroup within the fibroblast growth factor (FGF) superfamily. Like other members of this subfamily (i.e., FGF19 and FGF23), FGF21 has low binding affinity for heparin, which allows for transport into the circulation and subsequent action at distant sites. High-affinity binding of FGF21 to FGF receptors (FGF-Rs) occurs only in the presence of the FGF-R co-receptor, β- Klotho; the restricted expression pattern of β-Klotho defines the target tissues for FGF21 activity. FGF-Rs and β-Klotho are co-localized in liver, pancreas and adipose tissue, which are responsible for glucose and fat metabolism.[5] Notably, in contrast to FGF19, FGF21 does not signal through FGF-R4/β-Klotho[6] and, therefore, is not mitogenic, nor does it regulate bile acid metabolism.

FGF21 is most abundantly produced in the liver, where it reduces lipogenesis and glucose production and enhances fatty acid oxidation.[7] In adipose tissue, FGF21 promotes glucose uptake and stimulates secretion of adiponectin, an adipokine with insulin-sensitizing, anti-steatotic, anti-inflammatory, and anti-fibrotic activities. Initial studies in mouse models and primates suggested that FGF21 administration increased energy expenditure, promoted fat utilization and reduced body weight and hepatic steatosis in high fat diet-induced obese mice, and improved lipid profiles, insulin sensitivity, and glycemia in obese, diabetic rhesus monkeys.[8,9] Increases in adiponectin and high-density lipoprotein (HDL) cholesterol and reductions in levels of triglycerides (TGs), low-density lipoprotein (LDL) cholesterol, and insulin have also been reported in a human clinical study with a FGF21 analog.[10] Beneficial changes in circulating factors can be used as biomarkers of FGF21 activity, and they suggest that FGF21 mimetics could be attractive candidates for the treatment of NASH and its metabolic complications.

Serum concentrations of FGF21 are increased in human patients with NAFLD or NASH as well as the methionine- and choline-deficient (MCD) mouse model of NASH.[11,12,13] FGF21 administration to FGF21 knock-out mice, however, has been shown to reverse excessive liver fat accumulation and fibrosis in the mouse MCD NASH model. [13] These data are consistent with the hypothesis that up-regulation of FGF21 seen in human NASH patients or wild-type mice on the MCD diet may be an insufficient compensatory response, and that administration of exogenous FGF21 to achieve supraphysiologic serum concentrations may ameliorate the steatosis and fibrosis associated with NASH.

6.1 Background

BMS-986036, also known by the generic name pegbelfermin, is a polyethylene glycol (PEG)ylated FGF21 analog with potent FGF21 signaling activity. BMS-986036 is a slightly modified version of human FGF21, where the glutamine amino acid at position 108 has been replaced by a novel *para*-acetylphenylalanine residue with a linear 30-kDa PEG attached to improve the pharmacokinetic (PK) properties of the molecule and a methionine residue has been added to the amino-terminus of the protein to enable expression in *Escherichia coli*. Preclinical and clinical studies with BMS-986036 suggest that BMS-986036 is safe and well tolerated, and that it has the ability to increase adiponectin, improve insulin sensitivity, reduce liver fat, reduce liver injury, reduce fibrosis, and improve plasma lipid profiles, making it an attractive candidate for the treatment of patients with NASH who have advanced fibrosis.

Refer to the Investigator's Brochure (IB) for more details on BMS-986036.

6.1.1 Nonclinical Studies

The effects of BMS-986036 treatment have been evaluated in both prevention and therapeutic intervention studies in a mouse model of NASH, in which mice develop a fatty liver at 5 weeks of age, NASH at 7 weeks of age, and liver fibrosis at 9 weeks of age.[14,15]

- In the prevention study, 5-week-old mice treated with BMS-986036 had significantly reduced body weight, liver weight, liver-to-body weight ratio, plasma TGs, and liver TGs. BMS-986036 also significantly decreased histological evidence of hepatic perturbations (NAFLD Activity Score, comprising assessments of steatosis, lobular inflammation, and hepatocyte ballooning) and significantly reduced fibrosis, demonstrating an anti-fibrotic effect of BMS-986036. Consistent with this observed anti-fibrotic effect, BMS-986036 treatment reduced hepatic expression of alpha-smooth muscle actin, tissue inhibitor of metalloproteinases 1 (TIMP-1), and type 1 collagen.
- In the therapeutic intervention study, 9-week-old mice treated with BMS-986036 had statistically significant decreases in liver-to-body weight ratio, blood glucose, plasma alanine aminotransferase (ALT), liver lipid content (TG and cholesterol), as well as histological evidence of hepatic steatosis, hepatocyte ballooning, lobular inflammation, and fibrosis.

BMS-986036 was not genotoxic and had no adverse effects on cardiovascular, respiratory, and/or central nervous systems in rats, dogs, and/or cynomolgus monkeys. BMS-986036 was neither embryo-lethal nor teratogenic in definitive rat or rabbit embryo-fetal development studies.

In repeat-dose toxicity studies in rats and sexually mature monkeys up to 6 months in duration, BMS-986036, administered once daily (QD), was clinically well tolerated and evidence of pharmacology was observed at all doses (changes in adiponectin and other metabolic parameters). Effects on bone (decreases in bone mass, size, mineralization, and strength, as well as changes in formation/resorption biomarkers) were observed, and these

were attributed to pharmacologically mediated body weight loss/reductions and slower overall growth, except at the highest dose tested in monkeys (1 mg/kg/day; 19× area under the concentration-time curve [AUC] multiple).

Expected PEGylated peptide-related effects (injection site inflammation and minimal to moderate tissue vacuolation) were also observed. There was also no indication that PEG- related vacuolation was associated with any apparent degenerative or functional consequences in any cells or tissues, and findings were reversible, except for choroid plexus vacuolation in monkeys at doses ≥ 0.75 mg/kg/day (C-terminal intact BMS-986036 AUC multiple of 8×). PEG-related-findings were consistent with an adaptive response associated with PEG clearance and were not considered adverse.

Most of the observed effects in both studies did not substantially progress with extended duration of dosing and were generally reversible.

The no-observed-adverse-effect level AUC exposure multiples for C-terminal intact BMS-986036 was 0.8× (males) and 2× (females) in rats and 2× in monkeys relative to the highest planned dose of 40-mg once weekly (QW) in this study.

Refer to the IB for more details on these studies.

6.1.2 Clinical Studies

In the first-in-human study (**Study MB130001**), BMS-986036 was administered by subcutaneous (SC) injection in single and multiple doses for up to 14 days to 72 obese, nondiabetic, healthy adult volunteers.[16] C-terminal intact BMS-986036, the active polypeptide, displayed a half-life of approximately 20 - 24 hours and demonstrated a generally linear PK with 2-fold to 3-fold accumulation following QD dosing. Following single dose administration in the range of 1 mg to 60 mg, the drug was slowly absorbed from the SC injection site (abdomen) into the systemic circulation, with median time to maximum concentration ranging from 24 to 33 hours. Following a single weekly dose of 21 mg, the time to maximum concentration was like that of single doses. BMS-986036 in doses of up to 30 mg QD for up to 14 days was well tolerated and safe; adverse events (AEs) were mild and showed no dose-ordered trends. In the multiple-dosing panels, BMS-986036 increased adiponectin levels in a dose-dependent fashion. Adiponectin increased by 41.7% in the BMS-986036 30 mg QD group; in contrast, it decreased by 28.5% in the placebo group. Adiponectin has been shown to inhibit hepatic stellate cell proliferation and hepatic fibrosis in vitro,[17] and higher levels of adiponectin have been shown to correlate with improvements in fibrosis, as well as steatosis and inflammation.[18] It is therefore likely that an increase in adiponectin in response to BMS-986036 would have beneficial anti-steatotic, anti-inflammatory, and anti-fibrotic effects in NASH patients. BMS-986036 also improved insulin sensitivity, promoted favorable lipid changes (decreased TGs, apolipoprotein B, and LDL cholesterol), and reduced body weight compared to placebo.

BMS-986036 was also studied in two Phase 2 studies. **Study MB130002** was a randomized, double-blind, placebo-controlled, parallel-group, multiple-dose study in obese participants with type 2 diabetes mellitus (T2DM). Over 90% of participants had evidence of underlying

fatty liver, based upon the fatty liver index. In this study, participants self-administered BMS-986036 or placebo, SC, for 12 weeks according to one of the following dosing regimens: BMS-986036 (1, 5, or 20 mg QD), BMS-986036 (20 mg QW), or placebo (QD). A total of 96 participants received at least 1 dose of BMS-986036. BMS-986036 treatment improved insulin sensitivity, adiponectin, fasting TGs, LDL cholesterol, HDL cholesterol, apolipoprotein C3, and N-terminal type 3 collagen propeptide (PRO-C3) (a biomarker for type 3 collagen formation, and hence, potentially, fibrosis). Dose-dependent increases in adiponectin were observed in all BMS-986036 dose groups. Meaningful changes in body weight were not observed.[19]

Study MB130045 was a randomized, double-blind, placebo-controlled, parallel-group, multiple-dose study conducted in participants with biopsy-confirmed NASH who had stage 1-3 fibrosis according to the NASH Clinical Research Network (CRN) scoring system. In this study, participants self-administered BMS-986036 or placebo, SC, for 16 weeks according to one of the following dosing regimens: BMS-986036 (10 mg QD), BMS-986036 (20 mg QW), placebo (QD). A total of 50 participants received at least 1 dose of BMS-986036 in the study.[20] Treatment with BMS-986036 for 16 weeks resulted in statistically significant reductions in hepatic fat fraction (as measured by magnetic resonance imaging [MRI]), decreases in ALT and aspartate aminotransferase (AST) (markers of liver injury), increases in adiponectin, and improvements in lipid profiles. Importantly, treatment with BMS-986036 was associated with improvement in fibrosis, as determined by decreases in magnetic resonance elastography (MRE) (an assessment of liver stiffness) and decreases in serum PRO-C3. In particular, BMS-986036 treatment was associated with an increase in the proportion of patients with at least a 15% decrease in MRE-assessed liver stiffness, a reduction that has been previously associated with an improvement in liver fibrosis, as observed on liver biopsy.[21]

Refer to the IB for details on these studies.

6.2 Study Rationale

The current study is designed to confirm and extend the results observed in the Phase 1 and 2a studies with BMS-986036. Specifically, this study aims to demonstrate in participants with NASH and compensated cirrhosis, the efficacy of BMS-986036 using histological and noninvasive endpoints, and the safety of BMS-986036 as assessed by AEs, lab results and bone mineral density (BMD) monitoring.

The protocol was planned to randomize approximately 100 participants to 1 of 4 treatment groups (approximately 25 participants per group). This protocol amendment (Version 4.0) reflects that upon close of enrollment, approximately 155 participants were randomized to treatment (approximately 38 participants per group). The increased number of randomized participants occurred following: 1) unexpectedly high enrollment rate in the final month of the enrollment period; 2) several participants who had initially been enrolled into FALCON 1 (MB130-068) were determined (based on central pathology biopsy results) to qualify for FALCON 2 (MB130-069) during the period between the closure of enrollment and completion of randomization; and 3) an unexpected decrease in the actual screen failure rate for subjects entered in the final month of enrollment.

Based on the unmet medical need for patients, the benefit/risk assessment discussed in Section 6.3, and the strict safety monitoring of all participants, the potential clinical benefit outweighs the risks for those who have chosen to participate in this study. No additional revisions are required in Section 9 due to the increased number of randomized participants.

6.2.1 Scientific Rationale for Study Design

Complete details of the study design are provided in Section 8.1.

Participants having a confirmed diagnosis of NASH and compensated cirrhosis will be enrolled in this multicenter, double-blind, placebo-controlled, randomized, parallel-group study to demonstrate the efficacy and safety of BMS-986036.

NASH patients with compensated cirrhosis have a high unmet medical need for approved therapies and compared to NASH patients with earlier stages of fibrosis, they are more likely to have a favorable benefit/risk profile for treatment with BMS-986036. Compared to NASH patients with stage 1-3 fibrosis, NASH patients with compensated cirrhosis have worsened clinical outcomes and disease-specific mortality.[22,23,24] Moreover, the risk of liver-related mortality increases exponentially with each increase in fibrosis stage.[25] Demonstration of an improvement in fibrosis should be highly predictive of clinical benefit.

NASH grade will be assessed by liver biopsy histology. Fibrosis stage will be assessed by liver histology as well as a number of noninvasive measures. In addition, PRO-C3 levels in participants will be measured during the course of the study in order to collect more data on its potential as a pharmacodynamic (PD) biomarker of fibrosis. The correlation of baseline PRO-C3 levels with response to BMS-986036 will also be assessed. Markers of liver injury, metabolic improvements, and other liver-related outcomes will also be examined. Safety, including hematology and blood chemistry results, electrocardiograms (ECGs), and other potential safety issues (e.g., gastrointestinal AEs, immunogenicity, injection reactions, and effects on bone), will be monitored throughout the study.

PK profiling of BMS-986036 will be performed on all participants based upon trough sampling prior to dosing at each visit. [redacted]

The primary efficacy endpoint of the study will be based on the independent histological evaluation of liver biopsy at 48 weeks – a timepoint at which meaningful clinical benefits in fibrosis and NASH disease activity are expected in the selected patient population treated with BMS-986036.

The design and dose selection of future Phase 3 studies with BMS-986036 will be based upon the totality of the efficacy, safety and PK analyses from this study and from MB130-068, a Phase 2 study of BMS-986036 in participants with NASH and stage 3 liver fibrosis.

6.2.2 Justification for Dose and Regimen

In the present study, weekly SC administration of BMS-986036 (10, 20 or 40 mg, or placebo) will be evaluated for efficacy and safety. Careful examination of the Phase 1 and Phase 2a data, along with insights gleaned from nonclinical studies in animals, support these dosing regimens.

In Study MB130045, BMS-986036 dosed as 10 mg QD or 20 mg QW SC for 16 weeks in NASH participants consistently improved multiple biomarkers associated with steatosis, liver injury, and fibrosis. In addition to significantly decreasing hepatic fat fraction in NASH participants at both doses, improvement relative to placebo was observed for several biomarkers such as serum PRO-C3, liver stiffness (as measured by MRE), adiponectin, hepatic transaminases, and serum lipids. At 16 weeks, the 10 mg QD dose produced effects that were comparable to, albeit modestly higher than, the 20 mg QW dose for several biomarkers (MRI, PRO-C3, LDL cholesterol, and hepatic transaminases).

In addition to data from NASH patients in Study MB130-045, PK and PD data from 2 other randomized, and placebo-controlled studies of BMS-986036 in obese healthy volunteers (MB130-001) and obese T2DM participants (MB130002) were also included and analyzed using population PK-PD analyses.

Population PK-PD models were developed that described the PK-PD relationship between BMS-986036 and several PD responses across these studies, such as increase in adiponectin, reduction of hepatic fat fraction (MRI), reduction of TGs, LDL, and HDL, reduction of liver inflammation, as evidenced by reduction of elevated ALT, and reduction of fibrosis, as noted by improvements in PRO-C3, MRE, and adiponectin. Direct or indirect response PK-PD models were used to describe the relationship between PK and PD. These models were then used to predict biomarker responses at various candidate weekly dosing regimens of BMS-986036.[16,19,20]

Given that only modestly higher PD responses were observed with 10 mg QD dosing relative to the 20 mg QW dose in Study MB130-045, and the consideration that a QW SC dosing regimen is likely to be more acceptable to participants than a daily dosing regimen, and therefore be associated with better compliance, 3 weekly doses were identified -i.e., 10 mg, 20 mg, and 40 mg QW, that are expected to achieve clinically meaningful responses for key biomarkers of NASH, and can be administered in up to 2 injections. Model-predicted percent change from Baseline in key biomarkers for typical NASH study participants are noted in Table 4 below.

Table 4 Model-Predicted Percent Change from Baseline in Key Biomarkers for Typical Participants with NASH

Biomarker	Model-predicted typical % change in response at trough concentrations with various QW doses of BMS-986036		
	10 mg QW	20 mg QW	40 mg QW
Hepatic fat content	−24.8	−29.7	−31.9
Alanine aminotransferase	−16.7	−22.6	−26.7
PRO-C3	−7.0	−12.4	−17.4
Adiponectin	11.4	18.3	24.0

NASH = nonalcoholic steatohepatitis; PRO-C3 = N-terminal type 3 collagen propeptide; QW = once weekly

The safety and PK of 20 mg QW and 40 mg QW dosing regimens for 3 weekly doses has been recently characterized in a Phase 1 study in obese healthy Japanese participants. Preliminary results show that exposure is generally dose proportional between 20 mg and 40 mg QW, and the 40 mg QW dose was safe and well tolerated (refer to IB for additional details). The 40 mg QW dose is hypothesized to provide increased efficacy compared to that of the 20 mg QW dose, but with lower overall BMS-986036 exposure than that of the 10 mg QD dose. Additionally, compared to 10 mg QD, the 40 mg QW dose is expected to provide a higher margin relative to the exposure associated with nonclinical bone-related AEs, and it also provides a lower burden of PEG. Evaluation of the 10 mg QW and 40 mg QW dose regimens is expected to facilitate a more complete evaluation of the dose-response profile of BMS-986036.

6.3 Benefit/Risk Assessment

6.3.1 Summary of Potential Benefits

In obese participants with T2DM (many of whom had underlying fatty liver), treatment with BMS-986036 for 12 weeks improved several metabolic factors (insulin sensitivity, adiponectin, and serum lipids) and led to a reduction in PRO-C3. In participants with NASH, treatment with BMS-986036 for 16 weeks resulted in statistically significant reductions in hepatic fat fraction (measured by MRI), decreases in hepatic transaminases (markers of liver injury), significant increases in adiponectin, significant reductions in PRO-C3, reductions in liver stiffness (measured by MRE), and improvements in lipid profiles.

Thus, clinical data suggest that BMS-986036 has the ability to increase adiponectin, improve insulin sensitivity, reduce liver fat, reduce liver injury, reduce fibrosis, and improve plasma lipid profiles, making it an attractive candidate for the treatment of patients with NASH who have advanced fibrosis. Together, these data support further development of BMS-986036 for the treatment of patients with NASH with compensated cirrhosis.

6.3.2 Summary of Risks

6.3.2.1 Gastrointestinal Events

In Phase 2a studies, the frequency of gastrointestinal AEs in participants treated with BMS-986036 (72%) was higher than that reported in the placebo group (28%). The most frequent gastrointestinal AEs were diarrhea, nausea, aphthous ulcer, constipation, dyspepsia, frequent bowel movements, upper abdominal pain, vomiting, and abdominal pain. When they

occurred, these AEs were of generally mild or moderate intensity; none of these AEs were of severe intensity. There were no discontinuations due to gastrointestinal AEs.

A total of 69 events of diarrhea, nausea, frequent bowel movements, vomiting, abdominal pain, and abdominal pain upper were reported in participants on both placebo and BMS-986036 treated arms. Among the 69 events, 55 events were reported in participants treated with BMS-986036 and 14 events were reported in the placebo group:

- Among the 55 events, there were 3 events for which AE duration was not available for calculation. Therefore, event duration was calculated for 52 events.
- The majority (80.7% [42/52]) of the events were of mild severity (Grade 1), were judged by the investigator to be not related, were resolved in a mean of 6 weeks, and did not require any treatment.
- A smaller percentage (19.2% [10/52]) of the events were of moderate severity; 8 of the moderate grade events (5 events of diarrhea and 1 event each of abdominal pain, vomiting, and frequent bowel movements) did not require any treatment and were resolved quickly (within a mean of 8.7 days). These events were reported as not related by the investigator, except for frequent bowel movements. The remaining moderate severity events (2 events of nausea; 1 related and 1 not related) required treatment and were resolved in a mean of 31 days.

At this time, these events are not explained by the known biological mechanism of PEG-FGF21. Of note, there was no evidence of gastrointestinal AEs in nonclinical models with BMS-986036.

6.3.2.2 Immunogenicity

BMS-986036 is a modified version of human FGF21 and has the potential to be immunogenic; however, the potential safety liability of antibody formation in humans is considered to be low. Most human protein therapeutics can induce a rapid and strong anti-drug antibody (ADA) response in animals, although the presence of ADAs in these species does not necessarily predict immunogenicity in humans.

In the Phase 1 study MB130001, 3 of 72 participants (4%), who received any dose of BMS-986036, developed antibodies to FGF21 and BMS-986036 by the end of the study. An initial assay titer increase was observed, followed by stabilization or decrease in titers, during additional post-study immunogenicity testing over the next 6 months. No participant had persistent positive functional neutralizing ADAs during the Follow-Up Period, although one participant tested positive at 2 nonconsecutive time points. Plasma exposure of BMS-986036 in these 3 participants did not differ from that of other treated participants during the period in which the concentration was detectable. Immunogenicity was not associated with an increased incidence of overall AEs or immunogenicity-related AEs, such as rash or fever, or with altered PK or PD effects.

In Study MB130002, up to Study Discharge (Day 126), anti-BMS-986036 and anti-FGF21 antibodies were detected in 68% and 70%, respectively, of the participants treated with BMS-986036; however, antibody titers were generally low (12.2% and 37%, respectively, had titers ≥ 64), and only 2 participants had neutralizing antibody responses to endogenous

wild-type FGF21. ADAs usually appeared after 8 weeks of dosing and they were not associated with immune-related AEs or injection site reactions. BMS-986036 exposures were similar in participants with ADAs compared with participants without ADAs. During the Follow-Up Period, antibody titers were observed to be either stable or declining in the overwhelming majority of participants, and no participant had neutralizing antibodies.

In Study MB130045, up to Study Discharge (Day 142), anti-BMS-986036 and anti-FGF21 antibodies were detected in 62.5% and 62.5%, respectively, of the participants treated with BMS-986036 20 mg QW; however, antibody titers were generally low (among participants who received BMS-986036 20 mg QW, 4/24 and 0/24, respectively, had anti-BMS-986036 and anti-FGF21 titers ≥ 64). Furthermore, titers were not associated with immune-related AEs or injection site reactions.

6.3.2.3 Injection Reactions

Injection site reactions have been monitored in completed and ongoing studies using the Draize scale, which rates erythema and edema at the injection site on a scale ranging from "none" to "severe." In Phase 1 and Phase 2a studies, injection-related AEs were generally mild, transient, resolved without intervention, and did not lead to discontinuation.

In the single ascending dose portion of Study MB130001, 2 participants (5.6%) who received BMS-986036 and 0 participants in the placebo group developed injection site erythema. In the multiple ascending dose portion of the study, the proportion of participants who developed erythema was well balanced between treatment groups (BMS-986036 at any dose versus placebo). Eleven participants developed injection site erythema (8 participants [22.2%] across all BMS-986036 groups and 3 participants [25.0%] in the placebo group). No participants developed injection site edema.

In Study MB130002, injection site erythema and/or injection site edema were reported in 4 of 96 participants (4.2%) who received BMS-986036 and in 1 of 24 participants (4.2%) who received placebo. One injection site reaction (20 mg QD) was of severe intensity, and the remaining 3 injection site reactions were rated as mild in intensity. Concurrent ADAs were present in 1 participant (10 mg QD) of the 5 participants with injection site erythema and/or edema.

In Study MB130045, injection site erythema was reported in 3 (4.0%) participants, and injection site edema was reported in 1 (1.3%) participant. All AEs of injection site erythema and injection site edema were mild or moderate in intensity. Concurrent ADAs were present in 2 (20 mg QW and 10 mg QD) of the 3 participants with injection site erythema and/or edema.

6.3.2.4 Effects on Bone

In the multiple ascending dose portion of Study MB130001, conducted in healthy participants, all dose panels had a decrease in bone formation markers (bone-specific alkaline phosphatase [BSAP] and N-terminal propeptide- of type 1 procollagen [P1NP]) that was reversible after administration of BMS-986036 had ended. The bone marker values remained within the normal reference range in all participants, and the percent decrease from Baseline

did not differ between treated participants and the pooled placebo group. Similarly, there was no significant change in bone resorption markers in any BMS-986036-treated participants compared to the pooled placebo group.

Analyses from Phase 2 studies (MB130002 and MB130045) in participants with T2DM and in participants with NASH suggest that BMD, as measured by bone densitometry, was not affected by 12 or 16 weeks of dosing with BMS-986036. There were no meaningful differences in population mean BMD change from Baseline at the end of dosing or at 6-months follow-up.

Additionally, in both studies, BMS-986036 had no clinically meaningful impact on biomarkers of bone turnover (BSAP, P1NP, or C-terminal telopeptides type I collagen [CTX-1]) during 12 or 16 weeks of treatment.

Overall, the results from Phase 1 and Phase 2a studies have demonstrated that BMS-986036 was clinically well tolerated in obese participants, in obese participants with T2DM, and in participants with NASH with stage 1-3 liver fibrosis and has an acceptable safety profile to support continued clinical development.

6.3.3 Safety Monitoring

Safety monitoring will be in place during the entire study allowing early detection of any safety signals. Participants will undergo safety evaluations at each clinic visit and the investigator will conduct a thorough safety evaluation before dosing. Safety assessments will be regularly performed and will include assessments for AEs, focused symptom-directed physical examinations, and laboratory measurements.

Study results will be monitored by an independent DMC. The scope of responsibility for the DMC will be comprised of safety monitoring by masked treatment group however, the DMC may request treatment codes and/or efficacy summaries if indicated for safety/benefit assessment (see Appendix 1).

In addition to the DMC, the sponsor (blinded to treatment assignment) will monitor safety. All reported AEs will be assessed, including events of special interest for BMS-986036 (see Section 8.5.3.7). The sponsor has developed a list of events of special interest for the BMS-986036 program based on the known biologic class effects, the mechanism of action, and data from unblinded clinical studies. These will include injection site reactions, gastrointestinal events, and bone-related events. Additionally, BMD and immunogenicity (anti-BMS-986036 and anti-FGF21 antibodies) will be monitored (see Section 8.5.3.6 and Section 8.5.3.8). AEs on or around the time of development of anti-BMS-986036 and/or anti-FGF21 antibodies will be carefully evaluated.

6.3.4 Overall Conclusion

Based on nonclinical data and results available from Phase 1 and Phase 2a studies, the potential benefits of BMS-986036 outweigh the potential risks for patients with NASH and compensated cirrhosis who choose to participate in this study.

7. STUDY OBJECTIVES

The endpoints for the objectives below are described in Section 9.4.1 (efficacy), Section 9.4.2 (safety), Section 9.4.3 (PK), and Section 9.4.4 (exploratory).

The overall study population is restricted to adults with NASH and compensated cirrhosis. Qualifying participants will receive BMS-986036 for 48 weeks. See Sections 8.3.1, 8.3.2, 8.3.3, and 8.3.4 for detailed inclusion and exclusion criteria, respectively.

7.1 Primary Efficacy Objectives

To evaluate the efficacy of BMS-986036 in adults with NASH and compensated cirrhosis based on improvement in fibrosis without worsening of NASH, as determined by liver biopsy at Week 48.

For this protocol, improvement in fibrosis is defined as a decrease of fibrosis by ≥ 1 point, as determined by the NASH CRN Fibrosis Score. Worsening of NASH is defined as an increase of the NAFLD Activity Score (NAS) by ≥ 1 point (see Section 8.5.1.1).

7.2 Secondary Efficacy Objectives

- To evaluate the impact of BMS-986036 on improvement of fibrosis as determined by liver biopsy at Week 48
- To evaluate the impact of BMS-986036 on improvement in fibrosis without worsening of NASH or improvement of NASH as determined by liver biopsy at Week 48
- To evaluate the impact of BMS-986036 on resolution of NASH, as determined by liver biopsy at Week 48
- To evaluate the impact of BMS-986036 on improvement of NASH, as determined by liver biopsy at Week 48
- To evaluate the impact of BMS-986036 on collagen proportionate area (CPA) as determined by liver biopsy at Week 48

7.3 Safety Objective

To demonstrate the safety of BMS-986036 in adults with NASH and compensated cirrhosis throughout the course of the study, including BMD and immunogenicity.

7.4 Pharmacokinetic Objectives

- To determine trough concentrations of BMS-986036 in all participants

[redacted]

7.5 Exploratory Objectives

To explore the impact of BMS-986036 administration on the following parameters:

- Quantitative assessments of fibrosis and fat on biopsy
- NAS
- Digital pathology assessment of NASH

- Hepatic fat fraction by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)
- Noninvasive measures of fibrosis and/or cirrhosis
- Metabolic assessments
- Child-Pugh Turcotte score
- MELD score
- Liver-related clinical outcome events
- Patient-reported outcomes
- Exploratory biomarkers

8. INVESTIGATIONAL PLAN

8.1 Overall Study Design

This will be a multicenter, double-blind, placebo-controlled, randomized, parallel-group study to demonstrate the efficacy and safety of BMS-986036 in the treatment of participants with NASH and compensated cirrhosis. The procedures and assessments to be conducted at each study visit are outlined in the Schedules of Activities tables (Table 1, Table 2, and Table 3 in Section 1) provided at the beginning of this protocol.

A schematic of the study design is in Figure 1 (Screening to Week 52/Post-Treatment Follow-up [PTFU]) and Figure 2 (follow-up visits after the Week 52/PTFU Visit) below.

The study will consist of 4 periods:

- A Screening Period of up to 8 weeks in duration (this period may be extended to a total of up to12 weeks upon discussion with the medical monitor)
- A 48-week, Double-Blind Treatment Period, during which the participants will receive blinded study medication (BMS-986036 10 mg, 20 mg, 40 mg QW or matching placebo QW)
- A 4-week PTFU Period
- A Follow-Up Period of up to 14 months (1 month is defined as 4 calendar weeks) after the Week 52/PTFU Visit for the collection of an additional dual-energy X-ray absorptiometry (DXA) assessment (in all participants), samples for potential immunogenicity testing (in all participants) as well as plasma and serum for biomarkers (in all participants) at 6 months (± 14 days) Post Week 52/PTFU. Subsequent visits at 9, 12, and 14 months after Week 52 or PTFU will be performed in participants for whom Long-Term Immunogenicity Follow-Up Visits are required. See Section 8.5.3.6

At the end of the Screening Period, participants meeting all inclusion and no exclusion criteria will enter the Double-Blind Treatment Period.

Participants will be enrolled and randomized via interactive response technology (IRT) to receive BMS-986036 10 mg QW, BMS-986036 20 mg QW, BMS- 986036 40 mg QW or matching placebo QW in a 1:1:1:1 ratio. A liver biopsy will be performed during Screening (if necessary) and at Week 48 in all participants. A total of approximately 100 participants was planned to be randomized (approximately 25 participants per arm). The final number of participants randomized was approximately 155 (see Section 6.2).

Arm 1: BMS-986036 (10 mg QW)
Arm 2: BMS-986036 (20 mg QW)
Arm 3: BMS-986036 (40 mg QW)
Arm 4: Placebo

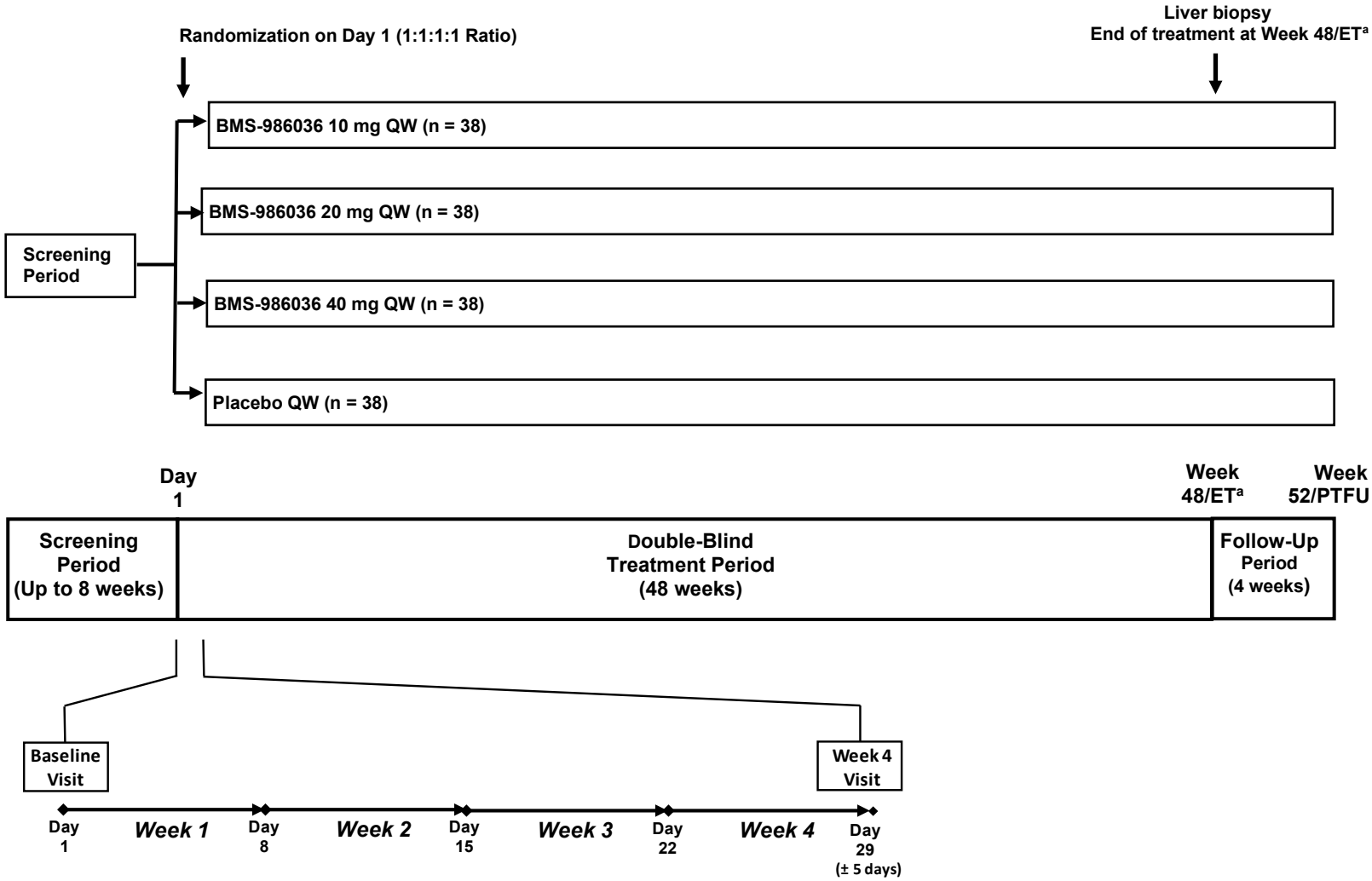
Participants will be stratified at randomization by country (Non-Japan/Japan). Participants in countries other than Japan will be stratified at randomization according to T2DM status (yes/no). Japanese participants will not be further stratified.

Randomized participants will receive their assigned double-blind study medication for a total of 48 weekly doses. The treatment will be administered by SC injection of 2 pre-filled syringes of study medication in the abdomen according to their assigned treatment arm (see Section 8.4.2). During the Double-Blind Treatment Period (Table 2 in Section 1), participants will be evaluated for safety and efficacy every 4 weeks (± 5 days) through Week 24 and every 8 weeks (± 5 days) after Week 24 through Week 48.

Participants will then return at Week 52 (± 5 days) for a PTFU Visit. Participants who discontinue study medication earlier than Week 48 will have an Early Termination (ET) Visit at the time of study medication discontinuation and will return for a PTFU Visit 4 weeks (± 5 days) after the ET Visit.

Participants will return 6 months (± 14 days) (1 month is defined as 4 calendar weeks) after the Week 52/PTFU Visit for DXA to assess BMD and for collection of samples for potential immunogenicity testing as well as serum and plasma biomarker samples (see Table 3 in Section 1). Participants at the Week 52/PTFU Visit may need to return at 9 months, 12 months, and 14 months (± 14 days) (1 month is defined as 4 calendar weeks) after the Week 52/PTFU Visit if required for immunogenicity testing, as described in Section 8.5.3.6 (see Table 3 in Section 1).

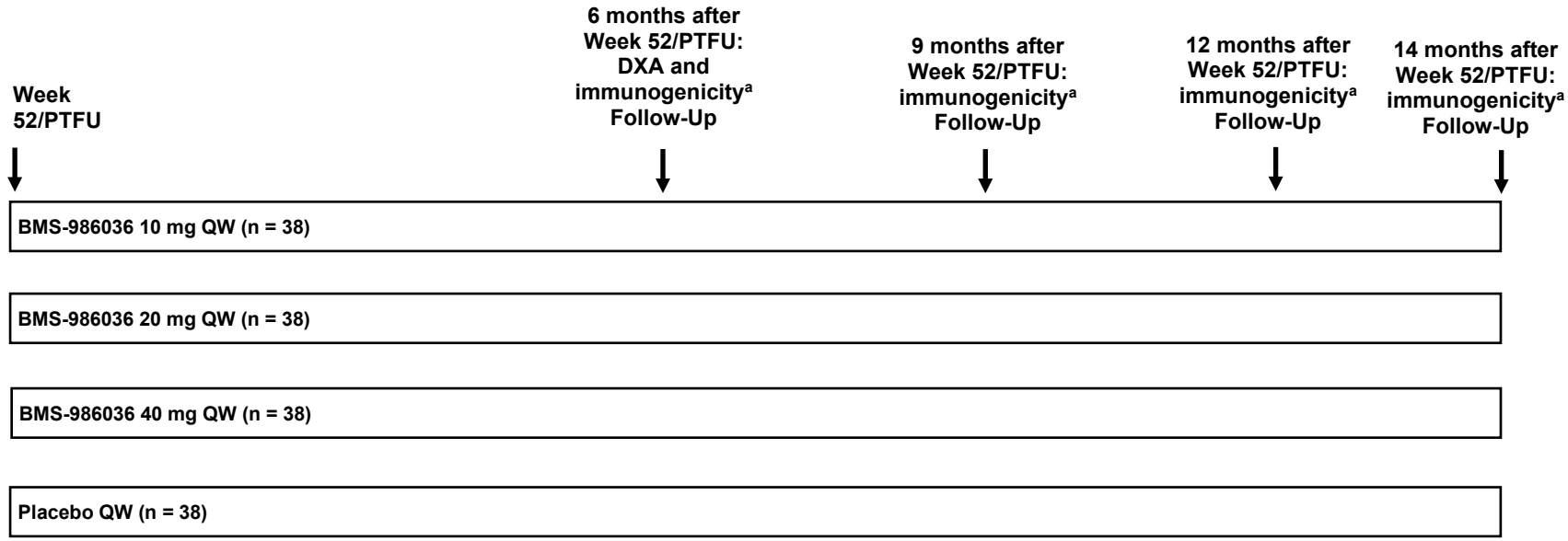
Figure 1 Study Design Schematic – Screening to Week 52/PTFU



ET = early termination; PTFU = Post-Treatment Follow-Up; QW = once weekly

[a] For participants who discontinue study medication prematurely, liver biopsy will be performed at ET if the participant has completed at least Week 20. If a participant discontinues study participation prior to Week 20 they should consider having a liver biopsy at ET.

Figure 2 Study Schematic – Bone Mineral Density and Immunogenicity Follow-Up Visits After the Week 52/PTFU Visit (visit windows ± 14 days) (1 month is defined as 4 calendar weeks)



DXA = dual-energy X-ray absorptiometry PTFU = Post-Treatment Follow-Up; QW = once weekly

[a] All participants will return 6 months (± 14 days) (1 month is defined as 4 calendar weeks) after the Week 52/PTFU Visit for dual-energy X-ray absorptiometry (DXA) to assess bone mineral density (BMD) and for collection of samples for potential immunogenicity testing as well as serum and plasma biomarker samples. Participants will return at 9 months, 12 months, and 14 months (visit windows ± 14 days) (1 month is defined as 4 calendar weeks) after the Week 52/PTFU Visit if required for immunogenicity testing (See Section 8.5.3.6).

8.2 End of Study Definition

The start of the study is defined as the visit at which the first participant signs informed consent. End of study is defined as the last scheduled procedure shown in Table 3 of the Schedule of Activities in Section 1 for the last participant.

For sites and participants, the end of participant participation is defined as the last visit or scheduled procedure shown in the Schedule of Activities (Section 1), including DXA and Immunogenicity Follow-Up Visits after the Week 52/PTFU Visit.

The end of the study for sample analysis is defined as 2 years after final clinical study report.

8.3 Study Population

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and the integrity of the study results. It is imperative that participants meet all eligibility criteria prior to randomization.

To be eligible for the study, participants must meet the criteria in Sections 8.3.1 and 8.3.2.

8.3.1 Inclusion Criteria

1. Signed written informed consent
   a) Participants must be willing to participate in the study and sign the informed consent form(s) (ICF[s])
   b) Participants (and caregivers as applicable) must be willing and able to complete all study-specific procedures and visits
2. Liver biopsy performed within 6 months (26 weeks) prior to the Screening Period. Biopsy performed prior to ICF must be available to the central reader prior to randomization. If historical biopsy is not available, a liver biopsy will be performed during the Screening Period (see Section 8.5.1.1). Biopsy must be consistent with NASH and cirrhosis according to the NASH CRN classification, as assessed by the central reader.
3. Participants taking anti-diabetic, anti-obesity, or anti-dyslipidemic medications must have been on stable regimens for at least 3 months (12 weeks) (6 weeks for statins) prior to and during the Screening Period. The investigator may contact the medical monitor regarding the stability of a participant's regimen when determining eligibility for study participation. Participants taking vitamin E at doses ≥800 IU/day must have been on stable doses for at least 6 months (26 weeks) prior to and during the Screening Period. Vitamin E treatment (≥800 IU/day) must not have been initiated after the qualifying liver biopsy was performed.
4. Age and reproductive status
   a) Men or women 18 to 75 (inclusive) years of age
   b) Women of childbearing potential (WOCBP) must have a negative pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study medication
   c) Women must not be breastfeeding at any time during the study

d) WOCBPs must agree to follow instructions for method(s) of contraception for the duration of treatment (BMS-986036 or placebo) plus 5 half-lives of study medication (5 days) plus 30 days (duration of ovulatory cycle) for a total of 35 days after the end of the Double-Blind Treatment Period
e) WOCBPs who are continuously not heterosexually active are exempt from contraceptive requirements but must undergo pregnancy testing as described in the Schedule of Activities in Section 1

Investigators will counsel WOCBP participants and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of methods of contraception (see Appendix 2).

8.3.2 Exclusion Criteria

1. Other causes of liver disease (e.g., alcoholic liver disease, hepatitis B virus infection (see Appendix 3), chronic hepatitis C virus infection (see Appendix 3), autoimmune hepatitis, drug-induced hepatotoxicity, Wilson disease, α-1-antitrypsin deficiency, iron overload, and hemochromatosis)
2. Current or past history of HCC
3. Medical conditions
   a) Past or current evidence of hepatic decompensation (e.g., ascites, variceal bleeding, hepatic encephalopathy and/or spontaneous bacterial peritonitis) or liver transplantation
   b) Medical history of gastroesophageal varices, except if esophagogastroduodenoscopy [EGD] performed within 12 months prior to the Screening Period has shown ≤ Grade 1 varices and without red wale signs, as assessed by the investigator)[26]
   c) Screening Fibroscan® elastography > 25 kPa (not applicable if EGD performed within 12 months prior to the Screening Period has shown ≤ Grade 1 varices and without red wale signs, as assessed by the investigator)[26]
   d) Recent history (within 2 years prior to the biopsy used to determine eligibility) of drug or alcohol abuse as defined in the Diagnostic and Statistical Manual 5 (DSM-5), Diagnostic Criteria for Drug and Alcohol Abuse (Appendix 4) **OR** in the investigator's judgment, a pattern of excessive alcohol consumption ≥ 30 g/day (males) or ≥ 20 g/day (females). This alcohol consumption is equal to approximately 2 alcoholic drinks per day for males, and approximately 1.5 alcoholic drinks per day for females. One alcoholic drink is equal to 12 ounces (355 mL) of 5% alcohol by volume (ABV) beer, 5 ounces (148 mL) of 12% ABV wine, or 1.5 ounces (44.4 mL) of 40% ABV distilled spirits
   e) Use of illicit intravenous drugs within 5 years prior to or during the Screening Period
   f) A urine drug screen result positive for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, or phencyclidine during Screening, unless a prescribed drug accounts for the positive test
   g) History of bariatric surgery or intestinal bypass surgery within the 5 years prior to informed consent or planned during the conduct of the study

h) History of major surgery (i.e., surgery involving a risk to the life of the patient; specifically, an operation upon an organ within the cranium, chest, abdomen, or pelvic cavity) within 6 weeks prior to or during the Screening Period
i) History of fracture or bone surgery (i.e., hardware placement, joint replacement, bone grafting, or amputation) within 8 weeks prior to or during the Screening Period
j) History of a blood transfusion within 60 days prior to or during the Screening Period
k) History of cancer within the last 5 years (other than treated and believed to be cured basal or squamous cell carcinoma of the skin or resected carcinoma of the cervix)
l) History of weight gain/loss ≥ 10% of body weight within 6 months (26 weeks) prior to or during the Screening Period
m) Uncontrolled hypertension, as defined by systolic blood pressure (SBP) > 160 and/or diastolic blood pressure (DBP) > 100 during Screening, unless discussed with medical monitor. Blood pressure may be rechecked as clinically indicated
n) QT interval corrected using Fridericia's formula (QTcF) > 480 msec on 12-lead ECG during Screening, confirmed by repeat ECG 30-60 minutes after the initial ECG
o) Any acute or chronic cardiovascular condition (e.g., ischemic heart disease, congestive heart failure) considered clinically significant by the investigator
p) Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation, who are known to be positive for human immunodeficiency virus, or who have recurrent or chronic systemic bacterial, fungal, viral or protozoal infections
q) Major episode of infection requiring hospitalization within 4 weeks prior to or during the Screening Period
r) Inability to tolerate SC medication
s) Inability to tolerate venipuncture
t) Women who are breastfeeding

4. Prior and concomitant therapy

a) Participants who have taken systemic corticosteroids at a dose exceeding 20 mg/day prednisone or equivalent for more than 7 consecutive days at any time within 3 months (12 weeks) prior to or during the Screening Period
b) Inability to comply with restrictions and prohibited treatments
c) Prior exposure to BMS-986036 or other FGF21 analogs
d) Other investigational agents must be discontinued at least 4 weeks or 5 half-lives before the first dose of study medication, whichever is longer

5. Physical and laboratory test findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, or clinical laboratory determinations beyond what is consistent with the target population
b) ALT value > 5× the upper limit of normal (ULN) as defined by the central laboratory
c) AST value > 5× ULN as defined by the central laboratory
d) Total bilirubin > 1.5 mg/dL
e) Serum albumin < 3.5 g/ dL
f) Platelet count < $100 \times 10^3/\mu L$
g) International normalized ratio (INR) > 1.4, unless due to therapeutic anticoagulation

h) Fasting plasma glucose < 60 mg/dL (< 3.33 mmol/L) or > 350 mg/dL (> 19.43 mmol/L)
i) Hemoglobin A1c ≥ 10%
j) Fasting TGs > 500 mg/dL
k) Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease equation
l) Evidence of significant worsening of ALT, AST or bilirubin during the Screening Period, in the opinion of the investigator or medical monitor
m) A centrally read DXA BMD T-Score of -2.5 or less at the femoral neck, total hip, or lumbar spine during Screening (exclusionary only if participant is 40 years of age or older)

6. Allergies and adverse drug reactions
   a) History of allergy to FGF21, PEG, or related compounds
   b) History of drug-induced liver injury (DILI)
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 sponsor approval is required
   b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness
   c) Any factor that, in the opinion of the investigator, would jeopardize the evaluation or safety of the participant or be associated with poor adherence to the protocol
   d) Participants who are incapable of completing study-related assessments (i.e., participant questionnaires) as they MUST be completed by the participant

[redacted]

[redacted]

8.3.4 Imaging (MRI/MRE) Contraindications

The imaging specialist at the site's imaging facility will be responsible for determining whether a participant is contraindicated from undergoing these procedures. In addition to the study inclusion and exclusion criteria (Sections 8.3.1 and 8.3.2), the following conditions will exclude the participant from scans:

1. History of claustrophobia, unless controlled with an anxiolytic
2. Physical limitations related to fitting into the bore of the magnet or weight greater than that allowable by the imaging instrument
3. 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
4. Participants with MRI-incompatible cochlear implants
5. Participants with spinal nerve stimulators
6. Participants with a nondetachable infusion pump
7. Participants with known metallic fragments in the body
8. Employment history that involves exposure to welding
9. Participants who have shrapnel anywhere in their body

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 IRB/EC and local institution.

If imaging is contraindicated for a participant, but the participant is otherwise eligible for the study, the participant may still participate in the study.

8.3.5 History: Medical, Surgical, Diet, and Exercise

Medical and surgical history will be collected during Screening and updated on Day 1. Medical history should be complete and comprehensive, including any history of alcohol, marijuana, and caffeine use. Surgical history should include all gastrointestinal and endocrine surgical procedures in the participant's lifetime and all other surgical procedures that occurred in the previous 5 years. Medical history will also include a fall risk assessment at Screening, and a diet and exercise history at Week 24 and Week 48/ET.

8.3.6 Dietary and Lifestyle Counseling

During Screening, after receiving the signed ICF, sites will provide all participants with the following dietary and lifestyle counseling:

- Reduce body weight (if obese or overweight) through diet and exercise
- Follow a balanced diet
- Increase physical activity
- Avoid alcohol as much as possible. However, if alcohol is consumed, do not consume ≥ 30 g/day (males) or ≥ 20 g/day (females) of alcohol during the study. This is equal to approximately 2 alcoholic drinks per day for males, and approximately 1.5 alcoholic drinks per day for females. One alcoholic drink is equal to 12 ounces (355 mL) of 5% ABV beer, 5 ounces (148 mL) of 12% ABV wine, or 1.5 ounces (44.4 mL) of 40% ABV distilled spirits

8.3.7 Concomitant Medication Restrictions

Anti-diabetic, anti-obesity, and anti-dyslipidemic medications are allowed if participants have been on stable dosing regimens for at least 3 months (12 weeks) (6 weeks for statins prior to and during the Screening Period. The investigator may contact the medical monitor regarding the stability of a participant's regimen when determining eligibility for study participation.

During study treatment, participants should refrain from using cannabinoid products.

Vitamin E is allowed; however, vitamin E doses ≥ 800 IU/day are allowed only if participants have been on stable doses for at least 6 months (26 weeks) prior to and during the Screening Period and if vitamin E treatment (≥ 800 IU/day) was not initiated after the qualifying liver biopsy was performed.

Vitamin D and calcium supplementation are permitted per local standard of care. Use of bisphosphonates, selective estrogen receptor modulators, estrogen, or teriparatide for treatment of osteoporosis is permitted if participants have been on stable doses for at least 6 months (26 weeks) prior to and during the Screening Period.

Any change in dose of these medications should be recorded in the electronic case report form (eCRF). Consult with the medical monitor if medications which could impact bone density assessments are to be added during the Double-Blind Treatment Period or during the first 6 months after the Week 52 / PTFU Visit.

Medical or surgical treatments for obesity should not be initiated while the participant is participating in the first 52 weeks of the study (i.e., from the time of informed consent until the participant completes the Week 52/PTFU Visit or discontinues participation in the study, whichever comes first).

Concomitant medications and medical and surgical treatments will not be limited after the Week 52/PTFU Visit.

8.3.8 Screen Failures and Rescreening

Screen failures are defined as participants who consent to take part in the clinical study but are not subsequently randomized. 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 (CONSORT) 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 (SAEs).

8.3.8.1 Retesting During Screening

Laboratory parameters and/or assessments that are included in the Screening procedures (Table 1 in Section 1) may be repeated during the Screening Period in an effort to find all possible qualified participants. Consultation with the medical monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

The most current result prior to randomization is the value by which study inclusion will be assessed, as it represents the participant's most current clinical state.

8.3.8.2 Rescreening

This study will permit the rescreening of a participant who has discontinued the study as a pre-treatment failure (i.e., the participant has not been randomized/has not been treated). Consultation with the medical monitor may be needed to identify whether rescreening is clinically relevant. If rescreened, the participant must sign a new ICF.

In the event that histologic evaluation of the biopsy of an otherwise qualified participant results in a diagnosis of NASH with stage 3 fibrosis, that individual is not eligible for the present study (MB130-069) but may be considered for enrollment under protocol MB130-068 (A Phase 2b Randomized, Double-Blind, Placebo-Controlled Study Evaluating

the Safety and Efficacy of BMS-986036 (PEG-FGF21) in Adults with Nonalcoholic Steatohepatitis [NASH] and Stage 3 Liver Fibrosis). Laboratory parameters and/or assessments that were collected as Screening procedures for this study (MB130-069; Table 1 in Section 1) may be utilized for the same purpose for MB130-068.

Conversely, in the event that histologic evaluation of the biopsy of an otherwise qualified participant for MB130-068 results in a diagnosis of NASH with cirrhosis, that individual is not eligible for the MB130-068 study but can be considered for enrollment under the present study (MB130-069). Laboratory parameters and/or assessments that were collected as Screening procedures for MB130-068 may be utilized for the same purpose (Table 1 in Section 1) in this study (MB130-069).

For participants who are rescreened, consult with the medical monitor to confirm which parameters and/or assessments that were collected as part of the original Screening Period procedures may be utilized.

8.3.9 Withdrawal of Participants

8.3.9.1 Discontinuation of Study Medication

Participants MUST discontinue investigational product (IP) (and non-investigational product [non-IP] at the discretion of the investigator) for any of the following reasons.

- Participant's request to stop study medication. Participants who request to discontinue study medication will be expected to complete an ET (Week 48/ET) Visit and subsequent follow-up visits/procedures per the Schedule of Activities (e.g., Week 52/PTFU; Section 1). The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information. Participants' 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 medication only or also from study procedures and/or Week 48/ET, Week 52/PTFU Visit, etc. (see Section 8.3.9.2)
- 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
- The participant experiences a major bone fracture or is diagnosed with osteoporosis that requires treatment
- Abnormal liver tests as defined in Section 8.5.3.1
- On 2 consecutive visits (at least 2 weeks apart), a participant has an eGFR < 30 mL/min/1.73 m^2, according to the *Modification of Diet in Renal Disease Study* equation
- If there is a significant protocol violation. The violation should be discussed with the medical monitor prior to discontinuing study medication
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease)

illness (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and sponsor approval is required)

- The participant becomes pregnant (study medication must be discontinued immediately)

  In the case of pregnancy (see Section 8.5.3.1), the investigator must immediately notify the medical monitor or designee of this event. In the event a participant becomes pregnant during a clinical study, the study medication must be discontinued immediately. In most cases, the study medication will be permanently discontinued in an appropriate manner. The medical monitor should be contacted within 24 hours of awareness of the pregnancy

- Termination of the study or program by the sponsor
- If a participant loses more than 10% of their total body weight, the investigator should contact the medical monitor. The investigator, together with the medical monitor, will then determine whether the participant should continue to take study medication

If study medication is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate eCRF page. The discontinuation should also be reported via the IRT. As indicated, appropriate follow-up and/or alternate medical care must be arranged for the participant. Please notify the medical monitor as soon as possible when discontinuation of study medication is being considered.

See Section 8.4.6 for details regarding dose modification and/or treatment interruption.

Participants who prematurely discontinue study medication will be expected to complete an ET Visit and subsequent follow-up visits/procedures per the Schedule of Activities, including a Week 52/PTFU Visit (Table 2 in Section 1), DXA and Immunogenicity Follow-Up Visit(s) (Table 3 in Section 1) (see Section 8.5.3.6). The only exception to this requirement is when consent is withdrawn for all study procedures or the participant loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). Participants who discontinue study medication will not be replaced (see Section 8.3.9.4).

8.3.9.2 Discontinuation from Study Participation

When a participant (or caregiver as applicable) requests to discontinue study participation, the participant will undergo an ET Visit as described in Table 2 in Section 1.

The only exception to this requirement is when consent is withdrawn for all study procedures or the participant loses the ability to consent freely (e.g., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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 medication only (see Section 8.3.9.1), or also from study procedures and/or Week 52/PTFU (see Section 1), 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

The following procedures must be followed upon participant withdrawal:

- Assessments for the ET 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 outside of sponsor responsibility
- Participants who discontinue from study participation (yet have not withdrawn consent) may decline further study visits, however, they will be offered additional visits for the purpose of BMD assessment (see Section 8.5.3.8) and immunogenicity testing (see Section 8.5.3.6).

8.3.9.3 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 as 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 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

8.3.9.4 Replacement of Participants

Participants who discontinue from study medication or from study after randomization will not be replaced. Participants who discontinue participation in the study after randomization will not be allowed to reenroll.

8.4 Treatment

Study medication 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.

Each study medication must be listed as either an IP or non-IP.

Study treatment includes both IP and non-IP and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical study.
- Study required premedication
- Other drugs administered as part of the study that are critical to claims of efficacy (e.g., background therapy, rescue medications)
- If specific criteria are required for treatment in a given phase of the study (e.g., extension phase), provide detailed criteria in this Section
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

An IP, also known as investigational medicinal product in some regions, is defined as 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.

Study medication includes both BMS-986036 and placebo and is described in Table 5 below.

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 non-IPs.

Table 5 Study Medications

Product	Potency	IP/Non-IP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per Label)
BMS-986036	10 mg/mL	IP	Blinded	Pre-Filled Syringe	Refer to the label on the container
BMS-986036	20 mg/mL	IP	Blinded	Pre-Filled Syringe	Refer to the label on the container
Placebo	0 mg/mL	IP	Blinded	Pre-Filled syringe	Refer to the label on the container

IP = investigational product; non-IP = non-investigational product

8.4.1 Treatments Administered

The investigator must ensure that the IP will be used only in accordance with the protocol. The study medication doses, dosing frequency and route of administration for each participant are shown in Table 6 below.

Table 6 Study Medication Doses, Dosing Frequency, and Route of Administration

Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Frequency of Administration	Route of Administration
BMS-986036 10 mg arm	1 mL/10 mg/mL BMS- 986036	Once weekly	Subcutaneous
	1 mL placebo		
BMS-986036 20 mg arm	1 mL/20 mg/mL BMS- 986036	Once weekly	Subcutaneous
	1 mL placebo		
BMS-986036 40 mg arm	2 × 1 mL/20 mg/mL BMS-986036	Once weekly	Subcutaneous
Placebo	2 × 1 mL placebo	Once weekly	Subcutaneous

8.4.2 Study Medication Administration

Participants should be instructed to make every effort to administer study medication on the same day each week at approximately the same time of day. Each weekly administration will consist of 2 SC injections.

On Day 1 and at the Week 4, 8, 12, 16, 20, 24, 32, and 40 Visits, study medication will be self-administered by the participant or administered by their designee at the study site as part of the participant's scheduled study visits. At those visits, study medication dosing should be held until all study-related assessments, including participant questionnaires, vital signs, ECG, AE evaluation, physical examinations, and laboratory sample collection (including trough [predose] PK) have been completed. [redacted] If a study visit occurs on a day that is not a planned dosing day, the participant should continue to administer the medication on the planned dosing day; all study-related assessments will continue to be performed at the planned study visit (in-clinic administration of study drug would not occur). [redacted]

Study medication is blinded and is supplied in a pre-filled syringe. Each participant will be dispensed a treatment kit containing 2 smaller boxes (for each weekly administration). Each smaller box will contain 1 prefilled syringe of the medication. Both syringes will be administered in the abdominal area at different locations per training guidelines. Study medication will be assigned by the IRT system.

Guidance and training on administration should be given to the participant (or caregiver, if applicable) prior to the first administration. At a minimum, the first administration should be done by the participant under the supervision of qualified site personnel. Training may be repeated as necessary at any study visit at the discretion of the investigator to maintain treatment compliance. When injections are administered at the site during study visits, site staff may observe the injection to ensure proper technique is being employed. Participants will be required to capture the date, time, and location of each injection on the supplied study medication administration card.

Specific instructions for study medication administration as well as training materials for participants (or caregivers, if applicable) are in the Pharmacy Manual.

8.4.3 Method of Treatment Assignment

After receiving the signed ICF but before any other study-related procedures are performed, the investigative site will access the enrollment option of the IRT system for assignment of a participant number (including participants not subsequently randomized or treated). This number is assigned sequentially by the system and will be unique across all sites. If a potential participant is rescreened, a new identification number will be used.

Randomization will be conducted in the following manner:

- Eligible participants will be randomized by the IRT using a prespecified schedule in a double-blind manner to 10 mg BMS-986036, 20 mg BMS-986036, 40 mg BMS-986036, or placebo arms in a 1:1:1:1 ratio based on the stratification factors specified in Section 8.1
- The IRT will provide study medication kit numbers that contain the appropriate study medication (BMS-986036 or placebo) for dispensation to that participant

At subsequent study visits as listed in the Schedule of Activities (Section 1), the investigator or designee will access the IRT to receive the corresponding kit numbers assigned to the participant for the purpose of dispensing study medication.

8.4.4 Blinding of Study Medication

8.4.4.1 Maintaining the Blind

Blinded treatment assignments will be managed using the IRT. All syringes and syringe contents (BMS-986036 10 mg/mL, BMS-986036 20 mg/mL, and placebo) are identical in appearance. Investigative site staff, sponsor and designee personnel, and participants and their families will remain blinded to treatment assignments. Study medication will be administered in a double-dummy manner as described in Section 8.4.2 in order to maintain the blind.

Sponsor and designee personnel may be unblinded once all participants have completed the Week 52/PTFU Visit and all data have been collected through that time point to facilitate analyses. Designated sponsor staff may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of PK samples and immunogenicity. A

bioanalytical scientist in the sponsor Bioanalytical Sciences department (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.

8.4.4.2 Circumstances for Unblinding

In the event of a medical emergency or pregnancy in an individual participant where knowledge of the study medication is critical to the participant's medical 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 (i.e., that it will alter the participant's immediate management). In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the medical monitor, but the investigator always has ultimate authority for the decision to unblind. The actual TASK of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The principal investigator or appointed designee should only call in for emergency unblinding AFTER the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is through the IRT system. 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.

In cases of accidental unblinding, the site should 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.

8.4.5 Study Medication 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 dispensed only to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product should be stored in a refrigerator (2°C through 8°C [35.6°F through 46.4°F]) and protected from light. If concerns regarding the quality or appearance of the study medication arise, the study medication should not be dispensed, and the sponsor should be contacted immediately.

IP documentation must be maintained. This includes documentation of all processes required to ensure drug is accurately administered, drug storage, administration, and, as applicable, storage temperatures, and use of required processes.

Further details on accountability of study medication are in the Pharmacy Manual.

Further guidance and information on final disposition of unused and returned study medication and study supplies is provided in Appendix 1.

8.4.6 Dose Modification

8.4.6.1 Modification of Dose

No dose reductions or modifications are allowed. If a participant interrupts treatment due to an AE, study medication may be restarted after consultation with the medical monitor.

8.4.6.2 Dose Interruption

If a participant has abnormal laboratory test result(s) and/or clinical AE(s) that, in the judgment of the investigator, could place the participant at risk, study medication administration should be interrupted, and the investigator should notify the medical monitor. Participants may receive further study medication when the AE or abnormal laboratory finding is resolved.

8.4.6.3 Missed Doses

If a participant misses a dose according to the protocol-outlined schedule, the participant (or caregiver, as applicable) should administer the dose as soon as possible and continue on the original schedule with the exception that 2 doses of medication should not be administered less than 48 hours apart.

8.4.7 Treatment Compliance

Study medication compliance will be monitored periodically using standard drug accountability procedures. Drug accountability will be reviewed by the site study staff at each visit to confirm treatment compliance. If a participant misses 2 consecutive doses (not related to an AE/SAE), site staff will discuss discrepancies with the participant at each on-treatment study visit and counsel the participant of the importance of compliance with the assigned regimen. Participants and/or caregivers (as applicable) may be re-trained in study medication administration, if necessary to address study medication compliance issues. If the participant misses 2 more consecutive doses during the study, the investigator should consult with the medical monitor to determine the appropriate course of action for the continued treatment of the participant, which may include withdrawal of study medication.

8.4.8 Prior and Concomitant Therapy

All medications taken from within 3 months (12 weeks) before the Screening Period until the Week 52/PTFU Visit must be recorded on the eCRF. In addition, medications administered between the Week 52/PTFU Visit and the 6 Month Post PTFU Visit that could potentially

impact bone mineral density assessments, as well as other therapies for NASH whether approved or investigational, will be recorded on the eCRF.

Prior medications are defined as medications taken prior to the first dose of study medication and discontinued before the first dose of study medication. Concomitant medications are defined as any medication taken after the first dose of study medication until the Week 52/PTFU Visit. Concomitant medications (e.g., 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 described in Section 8.3.7.

8.4.9 Treatment After the End of the Study

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

The sponsor reserves the right to terminate access to sponsor-supplied study medication if any of the following occur: a) the study is terminated due to safety concerns or other reasons; b) the development of BMS-986036 for treatment of NASH or other indications 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, the sponsor will follow local regulations.

8.5 Efficacy and Safety Variables

Study procedures and timing are summarized in the Schedule of Activities (Section 1). Waivers or exemptions from protocol-required evaluations are not allowed.

8.5.1 Efficacy Assessments

Every effort must be made to ensure that the same evaluator(s) complete 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 evaluation. Documentation of who performed the evaluation is to be recorded in source documents. Assessments should be performed at approximately the same time of day throughout the duration of the study. Baseline assessments must be performed prior to dosing with study medication. 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.

All efficacy assessments will be completed prior to study medication administration. Participant questionnaires will be administered electronically, and information gathered electronically (i.e., electronic patient-reported outcome) will serve as the source document where possible.

The following procedures or tools will be used to assess participant's disease activity during the study (see the Schedule of Activities in Section 1):

- Liver biopsy (see Section 8.5.1.1) submitted to the central pathologist at Screening, and at Week 48 or the ET Visit, if applicable
  - Histological assessments of fibrosis stage and NASH activity
  - Assessments of CPA and fat in stained tissue by morphometry
  - Assessments of fibrosis using digital pathology
- Noninvasive measures of fibrosis and/or cirrhosis
  - Noninvasive scores of hepatic fibrosis (see Section 8.5.1.2) (AST-Platelet Ratio Index [APRI], Fibrosis 4 [FIB4] Index, Enhanced Liver Fibrosis [ELF] Score, NAFLD Fibrosis Score) at Day 1, Week 24, and Week 48/ET
  - Liver stiffness as determined by MRE (see Section 8.5.1.3) at Screening, Week 24, and Week 48/ET
  - Liver stiffness as determined by Fibroscan® elastography (see Section 8.5.1.4) at Screening and Week 48/ET

  [redacted]
- Hepatic fat fraction as determined by MRI-based proton density fat fraction (PDFF) (see Section 8.5.1.3) at Screening, Week 24, and Week 48/ET
- Physical metabolic assessments (see Section 8.5.1.6) at Screening, Day 1, Week 24, and Week 48/ET
  - Body weight
  - Body mass index (BMI)
  - Waist circumference
- Laboratory Metabolic Assessments (see Section 8.5.1.6) at Screening, Day 1, Week 24, and Week 48/ET
  - Lipids (LDL, HDL, TGs)
  - Fasting plasma glucose
  - Fasting plasma insulin
  - Hemoglobin A1c
- Child-Pugh Turcotte Score (see Section 8.5.1.7) at Screening, Day 1, Week 24, and Week 48/ET
- MELD Score (see Section 8.5.1.8) at each visit through Week 52/PTFU
- Liver-Related Clinical Outcome Events (see Section 8.5.1.9) at each visit from Day 1 through Week 52/PTFU
- Exploratory Biomarkers (see Section 8.5.2)
  - Transaminases at each visit through Week 52/PTFU
  - Adiponectin at Day 1, Week 4, Week 8, Week 12, Week 24, Week 48/ET, and Week 52/PTFU
  - PRO-C3 at Day 1, Week 4, Week 8, Week 12, Week 24, Week 48/ET, and Week 52/PTFU

[redacted]

- Health-related quality-of-life (HRQoL) questionnaires (see Section 8.5.1.10) at Day 1, Week 24, and Week 48/ET
  - 3-Level EuroQol 5 Dimension (EQ-5D-3L) questionnaire
  - 36-question Short Form (SF-36) quality-of-life questionnaire
  - Chronic Liver Disease Questionnaire-Nonalcoholic Fatty Liver Disease (CLDQ-NAFLD) questionnaire

8.5.1.1 Liver Biopsy

A liver biopsy will be performed at Screening if no liver biopsy specimen collected within 6 months (26 weeks) prior to informed consent is available and readable by the Central Pathologist.

The on-treatment liver biopsy should be performed within ± 7 days of the Week 48 Visit. However, if a biopsy cannot be scheduled within the window specified above, the biopsy should be performed as close to schedule as possible.

For participants prematurely discontinuing study medication, liver biopsy will be performed at the ET Visit if the participant has completed at least Week 20. If a participant discontinues study participation prior to Week 20 they should consider having a liver biopsy at ET.

Histological assessment of the tissue sample will be conducted by a blinded Central Pathologist. The central reader will be a medical doctor, board certified in pathology, with experience in liver pathology in a clinical study setting.

The on-treatment liver biopsy results will remain blinded to site personnel until after the study database is locked; incidental findings of potential clinical relevance (as determined by the medical monitor) from the central pathologist will be provided to the investigator.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the study should be evaluated and handled by the investigator per the site's standard of care and clinical judgment.

Liver tissue should be collected using a 16 gauge (or larger) cutting needle (e.g., Bard, Microvasive, or TruCut) whenever possible. Use of suction needles (e.g., Menghini, Jamshedi, or Klatskin) are allowed, but may cause fragmentation of fibrotic specimens and impede the evaluation of fibrosis, and should therefore be avoided, if possible. At least 2 cm length of tissue should be obtained.

Additional details on the acquisition, quality requirements, histological preparation, and shipping of histological samples are in the Central Laboratory Manual and the Central Pathology Manual.

Histological Scoring

NASH CRN

For associated primary and secondary endpoints, the NASH CRN system[27] will be used to score the histologic samples and results are reported as the NAFLD Activity Score (NAS) and the NASH CRN Fibrosis Score. The NASH CRN system is based on the concept that necroinflammatory lesions and stage of fibrosis should be evaluated separately; it assesses liver biopsies for degree of steatosis (0-3), lobular inflammation (0-3), hepatocellular ballooning (0-2), and fibrosis (0-4).

NAS

The 3 categories of steatosis, lobular inflammation, and ballooning scores are added together in an unweighted fashion to determine the NAS, which ranges from 0 to 8 (see Table 7 below).

The NAS should not be considered a replacement for the Central Pathologist's diagnosis of NASH.

Table 7 NAS Scoring System

Histology Variable	Grade	Score
Steatosis	< 5%	0
	5% - 33%	1
	> 33% - 66%	2
	> 66%	3
Lobular Inflammation[a]	none	0
	< 2	1
	2 - 4	2
	> 4	3
Ballooning	none	0
	few	1
	many	2

NAS = NAFLD Activity Score

[a] Foci per x200 field

Fibrosis

NASH CRN Fibrosis

Fibrosis is staged separately from NAS on a 0-4 scale: 0 (none); 1 (perisinusoidal or periportal fibrosis); 2 (perisinusoidal and portal/periportal fibrosis); 3 (bridging fibrosis); 4 (cirrhosis).

Ishak

A modified Ishak scoring system will also be used to stage fibrosis in the histologic samples. The Ishak system (0-6 scale) was originally developed to grade portal-based liver fibrosis

associated with viral hepatitis.[28] The modified Ishak system has been adapted to stage central-based liver fibrosis associated with NASH, and it also uses a 0-6 scale:

- 0: No fibrosis
- 1: centrilobular pericellular fibrosis
- 2: centrilobular and periportal fibrosis
- 3: bridging fibrosis (few bridges)
- 4: bridging fibrosis (many bridges)
- 5: early or incomplete cirrhosis
- 6: established or advanced cirrhosis

Morphometric Analysis of CPA and Fat Percentage in Stained Tissue

There is considerable intra- and inter-individual variation of hepatopathologist assessment of fibrosis stage on liver biopsy. Assessment of CPA is a method by which the amount (percentage) of collagen in stained tissue Sections is analyzed using morphometric image analysis. This allows for a quantitative assessment of fibrosis. Percentage of fat in stained tissue Sections is also analyzed using morphometric image analysis. These morphometric assessments will be performed by a blinded Central Pathologist. Additional details on these morphometric assessments are in the Central Pathology Manual.

Assessment of NASH and Fibrosis Using Digital Pathology

Liver biopsy samples will be evaluated using digital pathology, which may include automated techniques.[29]

8.5.1.2 Noninvasive Scores of Hepatic Fibrosis

The ELF, FIB4, APRI, and NAFLD Fibrosis Score are composite indices that have been correlated with fibrosis stage in NASH study participants.[23] [redacted]

ELF assay, FIB4, APRI, and NAFLD Fibrosis Score use a variety of algorithms combining a number of physical attributes and biochemical and hematologic test values to determine the level of the participant's liver fibrosis (see Appendix 10). The scores will be calculated by a computerized system based on laboratory values and nonlaboratory parameters entered into the eCRF by personnel at the site. The sites will not be required to calculate scores.

Details on the collection, processing, and shipping of samples for fibrosis scoring are in the Central Pathology Manual.

- ELF assessment combines hyaluronic acid, procollagen 3 amino terminal peptide, and TIMP-1. A proprietary algorithm is used to evaluate each of these markers by immunoassay, to create an ELF Score
- FIB4 scores fibrosis by combining participant age, ALT, AST, and platelet count. The formula used to calculate the FIB4 score is provided in Appendix 10
- APRI scores fibrosis by combining AST and platelet count. The formula used to calculate the APRI Score is provided in Appendix 10

- The NAFLD Fibrosis Score scores fibrosis by combining participant age, BMI, fasting glucose, presence of diabetes, ALT, AST, platelet count, and albumin. The formula used to calculate the NAFLD Fibrosis Score is provided in Appendix 10

8.5.1.3 Imaging

All participants will have imaging performed unless imaging is contraindicated (see Section 8.3.4). Participants for whom imaging is contraindicated may still participate in the study.

Magnetic Resonance Elastography

MRE is a noninvasive medical imaging technique that measures the stiffness of soft tissues by introducing shear waves and imaging their propagation using MRI. In NASH patients, MRE is reproducible,[33] and it has a higher interobserver agreement for staging fibrosis compared to histopathology.[34] Additionally, an improvement in MRE has been associated with an improvement in liver fibrosis, as observed on liver biopsy.[33,34]

Images will be collected by the site and submitted to a central imaging vendor for evaluation. Sites should be trained and qualified before collecting study images.

Detailed instructions on the conduct of the MRE, and the acquisition and submission of MRE data to the central imaging vendor will be provided in the Imaging Manual.

The on-treatment MRE results will remain blinded to site personnel until after the study database is locked. Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the study should be evaluated and handled by the investigator per the site's standard of care and clinical judgment.

For participants prematurely discontinuing study medication prior to Week 24, MRE should be conducted at the ET Visit if the date of discontinuation is more than 4 weeks from the date of the previous MRE. For participants prematurely discontinuing study medication after Week 24, MRE should be conducted at the ET Visit if the date of discontinuation is more than 8 weeks from the date of the previous MRE.

Magnetic Resonance Imaging

Hepatic MRI is a noninvasive and accurate biomarker utilized for liver fat quantification. In NASH patients, MRI-PDFF accurately classifies grades and changes in hepatic steatosis,[31] and a ≥ 29% reduction in MRI-PDFF has been associated with histological NAS improvement.[32]

Images will be collected by the site and submitted to a central imaging vendor for evaluation. Sites should be trained by the imaging vendor before collecting images.

Detailed instructions on the conduct of the MRI, and the acquisition and submission of MRI data to the central imaging vendor will be provided in the Imaging Manual.

The on-treatment MRI results will remain blinded to site personnel until after the study database is locked. Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the study should be evaluated and handled by the investigator per the site's standard of care and clinical judgment.

For participants prematurely discontinuing study medication prior to Week 24, MRI should be conducted at the ET Visit if the date of discontinuation is more than 4 weeks from the date of the previous MRI. For participants prematurely discontinuing study medication after Week 24, MRI should be conducted at the ET Visit if the date of discontinuation is more than 8 weeks from the date of the previous MRI.

8.5.1.4 Fibroscan® Elastography

Fibroscan® is a noninvasive device that assesses the 'hardness' (or stiffness) of the liver via the technique of transient elastography. Liver hardness is evaluated by measuring the velocity of a vibration wave (also called a 'shear wave') generated on the skin. Shear wave velocity is determined by measuring the time the vibration wave takes to travel to a particular depth inside the liver. Because fibrous tissue is harder than normal liver, the degree of hepatic fibrosis can be inferred from the liver hardness.

With the participant lying supine, an ultrasound-like probe is placed on the skin over the liver area, typically in the right mid-axillary line. The participant will feel a gentle 'flick' each time a vibration wave is generated by the probe. Investigators and site personnel should refer to the equipment manufacturer's information for detailed instructions.

A minimum of 10 valid readings, with at least a 60% success rate of all measurements taken and an interquartile range of ≤ 30% of the median value, are taken with the results expressed in kilopascals (kPa).

[redacted]

[redacted]

8.5.1.6 Metabolic Assessments

Physical Metabolic Marker Assessments

Body weight, waist circumference, and BMI will be monitored as metabolic assessments.

Weight must be recorded using a calibrated scale, preferably the same scale at each clinic visit. The participant should remove shoes and heavy clothing before standing on scale.

Waist circumference will be measured at the natural waist (smallest waist circumference). If there is no natural waist, the measurement should be made midway between the iliac crest and the bottom of the rib with the measuring tape horizontal all the way around the waist. Measurement should be made at the end of normal inspiration with the participant standing. The waist measurement reported on the eCRF should represent the average of at least 2 measurements. The average measurement should agree within 1 cm. If not, additional measurement(s) should be taken.

BMI is used as an index of obesity and is a method of defining normal body weight and excess body fat. It correlates in a population with percent body fat. BMI is determined by weight (kg) divided by height (m) squared.

Note: *All analysis calculations for BMI will be derived internally by the sponsor using height at Screening and weight at the specified time point.*

Laboratory Metabolic Assessments

Blood will be drawn according to the Schedule of Events in Section 1 for the following laboratory metabolic marker assessments. Participants should fast for at least 8 hours prior to collection of the blood samples for these assessments.

- Fasting lipids, including LDL, HDL, and TGs. The HDL/LDL ratio will be calculated using the results of these assessments
- Glucose homeostasis markers including fasting plasma glucose, fasting plasma insulin, and hemoglobin A1c

8.5.1.7 Child-Pugh Turcotte Score

The Child-Pugh Turcotte Score assesses the severity of cirrhosis, and has been shown to be an accurate measure across a broad spectrum of liver disease. It employs numerical scores of 5 measures of liver disease: total bilirubin, serum albumin, INR, ascites, and encephalopathy and is scored according to the scheme in Appendix 5. The sum of scores from each component is the final score.

Blood samples will be collected for the total bilirubin, serum albumin, and prothrombin time assessments used to calculate the Child-Pugh Turcotte Score as part of the hematology and serum chemistry assessments conducted at each visit. The same laboratory will be used for each evaluation. Evaluations of ascites and encephalopathy should be conducted by the same site personnel at each visit wherever possible.

8.5.1.8 MELD Scoring

MELD scoring (see Appendix 10) is a formula for assessing the severity of chronic liver disease that does not include subjective variables such as ascites and encephalopathy. It employs the participant's bilirubin, serum creatinine, and INR.

Blood samples will be taken for bilirubin, serum creatinine, and prothrombin time as part of the hematology and serum chemistry assessments conducted at each visit. The same laboratory will be used for each evaluation. The central laboratory will calculate the MELD Score based on the laboratory values and communicate the score to the site. MELD Scores will be determined at each visit through Week 52/PTFU.

All components of the MELD score should be completed on the same day. If any individual component needs to be repeated on another day, all other components must be repeated as well.

8.5.1.9 Liver-Related Clinical Outcome Events

Participants will be evaluated for the following liver-related clinical outcome events at each visit from Day 1 through Week 52/PTFU:

- All-cause mortality
- MELD Score ≥ 15 (with at least a 2-point increase from Baseline)
- Liver transplant
- Ascites requiring medical intervention
- Hospitalization (≥ 24 hours) for onset of variceal bleed
- Hospitalization (≥ 24 hours) for hepatic encephalopathy
- Hospitalization (≥ 24 hours) for spontaneous bacterial peritonitis
- HCC

If a participant experiences one of the above events, the investigator should contact the medical monitor within 48-72 hours to discuss further participation in the study.

Liver-related clinical outcome events will also be reported as AEs/SAEs, as applicable, as per Section 8.5.3.1 and Appendix 9.

8.5.1.10 Patient-Reported Outcomes (Health-Related Quality-of-Life Questionnaires)

HRQoL questionnaires will be completed electronically by the participant and data transferred as source. Due to potential bias, the questions should not be read to the participant. Participant questionnaires will be assessed at specific visits throughout the study. See Section 1 for details.

The EQ-5D-3L questionnaire (see Appendix 7) is a general quality-of-life instrument that consists of 2 components, health state description and evaluation. The health state description component measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Participants will rate their level of impairment in each dimension using a 3-level scale. In the evaluation component, participants evaluate their overall health status using a visual analog scale.

The SF-36 questionnaire (see Appendix 6) is a commonly used patient-reported outcome instrument used to assess quality of life. The SF-36 is a 36-question instrument, which assesses 8 health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. Each question has 5 answers scored 1 (unable to) to 5 (no difficulty). The scale score of each domain is calculated based on the summed score across items included in the domain and is rescaled to 0 to 100. Version 2 of the SF-36 questionnaire will be used in the study.

The CLDQ-NAFLD questionnaire [30] (see Appendix 8) is a disease-specific quality-of-life instrument for NAFLD and NASH. The CLDQ-NAFLD consists of 36 items in 6 domains: abdominal symptoms, activity, emotional function, fatigue, systemic symptoms, and worry. Each item is on a Likert scale with 1 representing the most impairment and 7 representing the least impairment.

The questionnaires should be administered prior to dosing and before any other study assessments are conducted.

8.5.2 Exploratory Biomarkers

Blood samples will be collected for the assessment of exploratory biomarkers as described in Table 8 in Section 8.5.4. Exploratory biomarkers will include the collection of serum, breath, plasma, [redacted] and whole blood, which will be used to assess markers of fibrosis and associated diseases and pathways (including cardiovascular disease, inflammation, diabetes, and liver disease as well as kidney disease and bone). Work may also include studies on the FGF21 pathway and mechanism of action as well as pathways impacted by BMS-986036. The goal is to better understand NASH and associated diseases/syndromes and the effects of BMS-986036. These studies may include, but are not limited to, assessments listed in Table 8 in Section 8.5.4.

- PRO-C3

- Metabolic biomarkers such as adiponectin

- Serum and plasma biomarkers associated with drug target pathway or pathways impacted by target, liver disease, NASH, fibrosis, apoptosis, diabetes mellitus, metabolic syndrome, inflammation, kidney and bone. Biomarkers may include but are not limited to cluster of differentiation 163 (CD163), C-reactive protein (CRP), pulmonary and activation-regulated cytokine, TIMP-1 and plasminogen activator inhibitor 1 (PAI-1)
- Blood (serum or plasma) samples to develop new or improved assays for pathway and functional markers associated with either the target, fibrosis, NASH, liver or drug
- Ribonucleic acid (RNA) from whole blood and from liver biopsies (when available), for broad gene expression profiling and directed gene analyses. Common RNA technologies may be employed, including but not limited to quantitative polymerase chain reaction, hybridization microarrays, and RNA sequencing. The sponsor has in place a system for restricting access to RNA sequencing data such that only gene expression data are made available

- Micro RNA (miRNA)

Information on the collecting, processing, and submission of samples to the central laboratory is in the Study Laboratory Manual.

8.5.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 1). 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.

Safety will be assessed using incidence of all AEs; the incidence of SAEs; the incidence of AEs leading to withdrawal of study medication; the incidence of AEs of special interest, immunogenicity, laboratory data, ECG monitoring, physical examinations, and monitoring of BMD via DXA.

8.5.3.1 Adverse Events

The definitions of an AE or SAE can be found in Appendix 9.

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 medication or the study, or that caused the participant to discontinue before completing the study.

For weight change (increase or decrease) to be considered an AE, the change should be 10% or more from Baseline that cannot be explained by lifestyle modifications alone.

Contacts for SAE reporting are specified in Appendix 9.

Time Period and Frequency for Collecting AE and SAE Information

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

The collection of nonserious AEs should begin at initiation of study medication and continue until the Week 52/PTFU Visit (Section 1)..

Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study medication, must be collected, including those considered by the investigator to be related to study medication or protocol-specified procedures. All SAEs will be collected through the Week 52/PTFU Visit and will be reported as described in Appendix 9.

The investigator must report any SAE occurring after the Week 52/PTFU Visit that is believed to be related to study medication or a protocol-specified procedure.

- Medical occurrences that begin before the start of study medication 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 9
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of this information 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 medication 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 9.

Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known AEs, when appropriate for the program or protocol.

Follow-Up and Recording of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 9)
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study medication and for those present at the end of study medication, as appropriate
- All nonserious AEs and SAEs must be recorded and described on the corresponding pages of the eCRF. Completion of supplemental eCRFs may be requested for AEs/SAEs and/or laboratory abnormalities that are reported/identified during the course of the study

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 8.5.3.7) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3.9.3).

Further information on follow-up procedures is given in Appendix 9.

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 (e.g., summary or listing of SAEs) from the sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements

Sponsor or designee will be reporting AEs to regulatory authorities and IRB/ECs according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A suspected unexpected serious adverse reaction is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

Pregnancy

Urine or serum samples will be collected at each visit through the Week 52/PTFU Visit for pregnancy testing for WOCBPs. A negative serum pregnancy test is required during Screening. After the Screening Period, urine pregnancy testing will be conducted instead of serum testing at any site where it is allowed by the IRB/EC overseeing study conduct at that site.

Investigators shall counsel WOCBPs on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (i.e., those that have a failure rate of < 1% when used consistently and correctly as discussed in Appendix 2).

If, following initiation of the study medication, 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 (5 days) plus 30 days (duration of ovulatory cycle) for a total of 35 days after the end of the Double-Blind Treatment Period, the investigator must immediately notify the sponsor medical monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the sponsor designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 9.

The study medication will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant safety). Please call the sponsor medical monitor 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 (Appendix 2).

Any pregnancy that occurs in a female partner of a male study participant should be reported to sponsor or designee during at least 5 half-lives after product administration (5 days) plus 30 days (duration of ovulatory cycle) for a total of 35 days after the end of the Double-Blind Treatment Period. In order for the 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.

Laboratory Test Result Abnormalities
The following laboratory test result abnormalities should be captured on the nonserious AE eCRF page or SAE eCRF page, as appropriate. Paper forms are to be used only in the event that 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 medication 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 (e.g., anemia versus low hemoglobin value).

Potential Drug-Induced Liver Injury
Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Appendix 9 for reporting details). **Repeat laboratory testing may be performed locally**, and the results should be promptly communicated to the investigator site.

For the purpose of evaluating a potential DILI, the Baseline value is defined as the mean of the test results from analysis of samples collected during Screening and on Day 1.

Note that the evaluation processes below do not replace SAE reporting per defined criteria in Appendix 9.

Evaluation of Participants with New Elevations of Aminotransferases and/or Total Bilirubin
Repeat laboratory testing (including ALT, AST, fractionated bilirubin and alkaline phosphatase) and physical examination should be performed within 48-72 hours when:

- Participants with normal Baseline aminotransferase (ALT and/or AST) values develop elevations greater than 3× the ULN based upon the central lab, or
- Participants with elevated Baseline aminotransferase values experience additional increases greater than 2× the Baseline (with concomitant elevations of total bilirubin > 2× ULN) AND ALT and/or AST is > 200 U/L.

If the new elevations in aminotransferases persist and the participant is symptomatic, then the drug should be discontinued, and the participant should be evaluated for other causes of liver injury or disease. The medical monitor should be contacted within 48-72 hours.

If the participant is asymptomatic, the participant should be placed under "close observation", defined as physical examination and laboratory evaluation 2-3 times per week.

If close observation is not possible, study medication should be discontinued. The frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study medication has been discontinued and the participant is asymptomatic.

Discontinuation or Temporary Interruption of Study Medication

In addition to the reasons for discontinuation described above, study medication should be discontinued or temporarily interrupted if either of the 2 following scenarios occur:

1) Aminotransferases (ALT and/or AST) > 2× Baseline and aminotransferases > 3× ULN and either:

    i. the increase is accompanied by a concomitant increase in total bilirubin to > 2× Baseline OR the INR concomitantly increases by > 0.2;

    OR

    ii. there are concomitant signs and symptoms of new-onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

2) Total bilirubin increases to > 2× ULN AND:
    i. there are concomitant signs and symptoms of new-onset fatigue nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

    If the above rule is met, a potential DILI work up for competing etiologies (e.g., alcohol use, viral hepatitis, biliary obstruction, autoimmune liver disease) must be performed, and a complete liver profile including INR must be repeated within 48-72 hours. **The medical monitor should be contacted within 48-72 hours.** Study medication can be restarted only if an alternative etiology is definitively identified and liver tests (aminotransferases, total bilirubin and/or INR) have returned to Baseline.

Other Safety Considerations
Any significant worsening noted during interim or final physical exams, ECGs, or any other potential safety assessments required or not required by protocol should also be recorded as a nonserious AE or a serious AE, as appropriate, and reported accordingly. ECGs will be read and interpreted at the site or by a local reader.

8.5.3.2 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 (see Appendix 9).

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 for 14 days after the overdose
3. Obtain a plasma sample for PK analysis within 4 days from the date of the last dose of study medication 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

8.5.3.3 Physical Examinations

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.

Full examinations and abbreviated examinations will be performed as specified in the Schedule of Activities (Section 1).

A full examination will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, and body weight.

Abbreviated examinations will include an abdominal exam 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.

8.5.3.4 Vital Signs

Schedules for vital sign collection are provided in Section 1. Vital signs will include heart rate, respiratory rate, sitting SBP and DBP (to be taken after at least 5 minutes sitting at rest), and oral temperature.

8.5.3.5 Electrocardiograms

Twelve-lead ECGs should be collected at similar times during Baseline and on-treatment visits. ECGs may be collected at any time prior to study medication dosing or PK sample collection. ECGs should be recorded after the participant has been supine for at least 5 minutes. ECG parameters, including QTcF, will be collected on the eCRF.

If a participant has a QTcF > 480 msec during the Screening Period, it should be confirmed by repeat ECG 30-60 minutes after the initial ECG. If the QTcF is confirmed to be > 480 msec, the participant should not be allowed to participate in the study.

If a participant has a QTcF>480 msec at an on-treatment visit, it should be confirmed by repeat ECG 30-60 minutes after the initial ECG. If the QTcF is confirmed to be >480 msec, the medical monitor should be contacted.

8.5.3.6 Immunogenicity

Throughout the study, the potential for immunogenicity of BMS-986036 will be monitored as indicated in the Schedule of Activities (Section 1). In participants that experience immunogenicity, neutralizing activity and exposure-efficacy relationship will be assessed for evidence of a clinical impact on safety and efficacy.

Immunogenicity Assessment Methodology

Participants will be monitored for antibodies to BMS-986036 (drug) using an ADA homogenous bridge assay with electrochemical luminescence detection. Samples will first be screened for potential positive anti-BMS-986036 responses. Then, the samples with positive anti-BMS-986036 responses will be confirmed for specificity using an immunodepletion format with BMS-986036 and nonPEGylated drug. The reactivity of confirmed positive responses will be characterized as "BMS-986036" (specific to the FGF21 region) or "PEG" (specific to the PEGylated region) based on the immunodepletion specificity. Additionally, samples with confirmed positive responses will be titrated to determine the relative positive response.

Participants will also be monitored for antibodies to FGF21 using recombinant Met-FGF21 in a homogenous bridge assay with electrochemical luminescence detection. Samples will first be screened for potential positive anti-FGF21 responses. Then the samples with positive antiFGF21 responses will be confirmed for specificity using an immunodepletion format with wild-type sequence FGF21. Samples with confirmed positive anti-FGF21 responses will be titrated to determine the relative positive response.

Samples positive for anti-BMS-986036 antibodies or positive for anti-FGF21 antibodies will be tested for neutralizing activity in a functional cell based neutralizing antibody assay. The assay measures the ability of an anti-BMS-986036 or anti-FGF21 antibody to inhibit or block Erk1 activation that is induced when FGF21 or drug binds to the β-Klotho and FGF-Rs.

Long-Term Immunogenicity Follow-Up

All participants will have samples collected for immunogenicity at 6 months (± 14 days) after the Week 52/PTFU Visit. Samples collected from participants may not be analyzed if: 1) participant is not on active drug, 2) participant is negative for anti-drug and/or anti-FGF21 antibody titers at the Week 52/PTFU Visit, or 3) participant has evidence of stable or decreasing antibody titers for 2 visits prior to the 6-month posttreatment visit.

Participants with positive anti-drug and/or anti-FGF21 antibodies at the Week 52/PTFU Visit and without evidence of 2 consecutive stable or decreasing antibody titers will be followed for up to 14 months after the Week 52/PTFU Visit (1 month is defined as 4 calendar weeks) until antibody titers decrease for 2 consecutive visits (these additional visits will be conducted at approximately 9 months and 12 months after the Week 52/PTFU Visit). The sponsor or designee will inform the clinical site if a participant needs to return for

immunogenicity follow-up beyond 6 months. If, at 12 months after the Week 52/PTFU Visit, a participant has an increasing titer (compared to the previous titer), an additional follow-up visit will be performed at approximately 14 months (1 month is defined as 4 calendar weeks) after the Week 52/PTFU Visit; at this visit, anti-drug and anti-FGF21 antibodies, as well as additional laboratory assessments (basic metabolic panel, hemoglobin A1c [redacted]), will be collected.

Participants who discontinue from the study prior to the Week 48 Visit will be offered additional Long-Term Immunogenicity Follow-Up Visits, as above. For these participants, prior immunogenicity results will be used to determine whether the participant should be offered Long-Term Immunogenicity Follow-Up Visits beyond the 6-month posttreatment assessment. Additional Long-Term Immunogenicity Follow-Up Visits should occur approximately 9, 12, and 14 months, if applicable (1 month is defined as 4 calendar weeks) after their last study visit.

Refer to the decision tree in Appendix 11 for more details regarding Long-Term Immunogenicity Follow-Up Visits.

8.5.3.7 Adverse Events of Special Interest

The sponsor has developed a list of AEs of Special Interest for the BMS-986036 program based on the known biologic class effects, the mechanism of action, and clinical study data. These will include the following:

- Injection site reactions
- Gastrointestinal events
  - Diarrhea, frequent bowel movements, nausea, vomiting, abdominal pain
- Bone-related events
  - Osteoporosis, osteopenia, bone and joint injuries, fractures (except tooth fracture), endocrine abnormalities of gonadal function not elsewhere classified (NEC), hyperparathyroid disorders, hypoparathyroid disorders, parathyroid disorders NEC, parathyroid analyses, metabolic bone disorders, vitamin D abnormal, vitamin D decreased, vitamin D deficiency, and miscellaneous events related to bone density

8.5.3.8 Bone Safety by DXA

Potential effects of BMS-986036 on BMD will be evaluated by DXA scans of the hip (including femoral neck) and spine that will be performed during the Screening Period and at the Week 48 Visit (or ET, if applicable) as indicated in the Schedule of Activities (Section 1). Participants will return for a follow-up DXA assessment 6 months (1 month is defined as 4 calendar weeks) after the Week 52/PTFU Visit. DXA may be performed within a window of ± 7 days of the scheduled Week 48/ET Visit and within a window of ± 14 days of the scheduled 6-month follow-up visit. DXA scans will be evaluated by central reading. Acquisition guidelines, instructions on calibration and the handling and submission of DXA scans are included in the Imaging Laboratory Manual. Note that at least one of the requested anatomic sites (hip [including femoral neck] or spine) must be evaluable for participants to be eligible for the study (See Section 8.3.2).

For participants prematurely discontinuing study medication DXA scans should be conducted at the ET Visit only if the participant has completed at least the Week 16 Visit. If a participant has not completed at least Week 16, the follow-up DXA scan at 6 months after PTFU Visit should also not be performed.

8.5.4 Laboratory Assessments

Participants should not administer study medication on the days of clinic visits until after all laboratory samples have been collected (see Table 8 below). Blood samples will be collected according to the schedule in Section 1. In addition, a number of hematology and blood chemistry values collected as part of the safety laboratory assessments will also be used to determine FIB4 index, APRI, and NAFLD Fibrosis Scores according to the schedule in Section 1.

Safety (hematology, blood chemistry, and urinalysis), efficacy, and exploratory laboratory assessments to be conducted during the study are listed in Table 8 below. The schedule for collection of samples for each assessment is in Section 1. Laboratory assessments will be conducted by central or specialty laboratories. Additional details on the collection, processing, and submission of samples for laboratory assessments are in the Study Laboratory Manual. If clinically indicated, repeat laboratory testing may be performed at a local lab.

Investigators must document their review of each laboratory safety report. A central laboratory will perform the safety analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed during Screening must be available prior to dosing.

In addition to those detailed assessments outlined in Table 8 below, serum, plasma and urine may be assayed for exploratory markers associated with liver, fibrosis, [redacted] or metabolic syndrome disease including markers associated with the BMS-986036 target pathway or with organs or pathways impacted by FGF21.

Urine or serum samples will be collected for pregnancy testing for WOCBPs. A negative serum pregnancy test is required during Screening. After the Screening Period, urine pregnancy testing will be conducted instead of serum testing at any site where it is allowed by the IRB/EC committee overseeing study conduct at that site. Women who are considered postmenopausal will have follicle-stimulating hormone testing performed during Screening.

Urine samples to test for drugs of abuse will be collected during Screening.

Repeat assessments for any laboratory assessment will be permitted according to the investigator's clinical judgment.

Table 8 Laboratory Assessments

ELF Assay (to be collected at Day 1, Week 24, and Week 48/ET). Participants will fast for 8 hours prior to collection of blood samples for these assessments:

- Hyaluronic acid
- Procollagen 3 amino terminal peptide
- Tissue inhibitor of metalloproteinases 1 (TIMP-1)

Laboratory Metabolic Markers (to be collected at Screening, Day 1, Week 24, and Week 48/ET). Participants will fast for 8 hours prior to collection of blood samples for these assessments:

- Low-density lipoprotein cholesterol
- High-density lipoprotein cholesterol
- Triglycerides
- Plasma glucose – *Also used for NAFLD Fibrosis Score*
- Plasma insulin
- Hemoglobin A1c – *also to be collected at Long-Term Immunogenicity Follow-Up Visits as applicable (see Section 8.5.3.6)*

Hepatitis Assessments (to be collected at Screening only- see Appendix 3 for diagnosis and exclusion criteria):

- Hepatitis B core antigen antibody
- Hepatitis B surface antigen antibody
- Hepatitis B surface antigen
- Hepatitis B virus DNA
- Hepatitis C virus antibody
- Hepatitis C virus RNA

Pregnancy Testing (to be collected at each visit through the Week 52/PTFU Visit):

- Serum or urine β-HCG. Women of childbearing potential only. Serum β-HCG to be collected at Screening and serum or urine β-HCG to be collected thereafter according to local laws and regulations and Institutional Review Board/Ethics Committee requirements)
- Follicle-stimulating hormone (Screening only for postmenopausal women)

Hematology (to be collected at each visit through the Week 52/PTFU Visit):

- Complete Blood Count
  - White blood cells, including differential
  - Red blood cells
  - Hemoglobin
  - Hematocrit
  - Platelet count – *Also used for FIB4, APRI, and NAFLD Fibrosis Score*
  - Mean corpuscular hemoglobin (MCH)
  - Mean corpuscular hemoglobin concentration (MCHC)
  - Red cell distribution width (RDW)
- Prothrombin time
- Partial thromboplastin time
- International normalized ratio – *Also used in MELD and Child-Pugh Turcotte scoring*

Blood Chemistry (to be collected at each visit through Week 52/PTFU and at Long-Term Immunogenicity Follow-Up Visits as applicable [see Section 8.5.3.6]):

- AST – *Used as both safety and efficacy endpoints. Also used for FIB4, APRI, and NAFLD Fibrosis Score*
- ALT – *Used as both safety, efficacy endpoints, and for FIB4, APRI, and NAFLD Fibrosis Score*
- Serum glucose
- Total bilirubin
- Indirect bilirubin
- Alkaline phosphatase
- Lactate dehydrogenase
- Creatinine
- Blood Urea Nitrogen
- Uric acid
- Total Protein
- Albumin – *Also used for NAFLD Fibrosis Score.*
- Sodium
- Potassium
- Chloride
- Carbon dioxide
- Calcium
- Phosphorus
- Glomerular filtration rate

Urinalysis (to be collected at each visit through the Week 52/PTFU Visit):

- pH
- Specific gravity
- Protein [redacted]
- Glucose
- Ketones
- Blood
- Leukocyte esterase
- Nitrite
- Creatinine [redacted]
- Albumin [redacted]
- Microscopic examination (only to follow-up abnormal findings)
- Drug Screen (Screening only)

Immunogenicity (to be collected at Day 1 and each subsequent visit through the Week 52/PTFU Visit and at Long-Term Immunogenicity Follow-Up Visits as applicable [see Section 8.5.3.6]):

- Serum anti-BMS-986036 antibody
- Serum anti-FGF21 antibody

PRO-C3 (to be collected at Screening, Day 1, Week 4, Week 8, Week 12, Week 24, Week 48/ET, and Week 52 [PTFU]). Participants will fast for 8 hours prior to collection of blood samples for these assessments:

- N-terminal type 3 collagen propeptide (PRO-C3) – Will include blood collection for additional serum for new or improved assays

[redacted]

Adiponectin (to be collected at Screening, Day 1, Week 4, Week 8, Week 12, Week 24, Week 48/ET, and Week 52/PTFU). Participants will fast for 8 hours prior to collection of blood samples for these assessments

[redacted]

Plasma and Serum for disease, target and drug effect biomarkers (to be collected at Day 1, Week 4, Week 8, Week 12, Week 24, Week 48, ET [if applicable], Week 52/PTFU, and 6 months after Week 52/PTFU). Participants will fast for 8 hours prior to collection of these samples

Gene Expression (to be collected at Screening, Day 1, Week 4, Week 8, Week 12, Week 24, and Week 48/ET and Week 52/PTFU):

- Whole blood for RNA analysis (broad and/or directed gene expression profiling)

[redacted]

Micro RNA (miRNA) (to be collected at Screening, Day 1, Week 4, Week 8, Week 12, Week 24, Week 48/ET, and Week 52/PTFU)

[redacted]

[redacted] ALT = alanine aminotransferase; APRI = AST-Platelet Ratio Index; AST = aspartate aminotransferase; DNA = deoxyribonucleic acid; β-HCG = beta human chorionic gonadotropin; ELF = Enhanced Liver Fibrosis; ET = early termination; FGF21 = fibroblast growth factor 21; FIB4 = Fibrosis 4 Index; NAFLD = nonalcoholic fatty liver disease; NAS = NAFLD Activity Score; NASH = nonalcoholic steatohepatitis; PTFU = Post-Treatment Follow-up; RNA = ribonucleic acid; [redacted]

8.5.5 Pharmacokinetics

8.5.5.1 All Participants

Serum concentrations of BMS-986036 will be derived from trough (predose) blood samples collected from each participant before the administration of BMS-986036 dosing at each visit. Participants will be instructed to not administer study medication on the days of clinic visits until the trough PK sample has been collected.

[redacted]

Table 9 Timing of Pharmacokinetic and Electrocardiogram Assessments

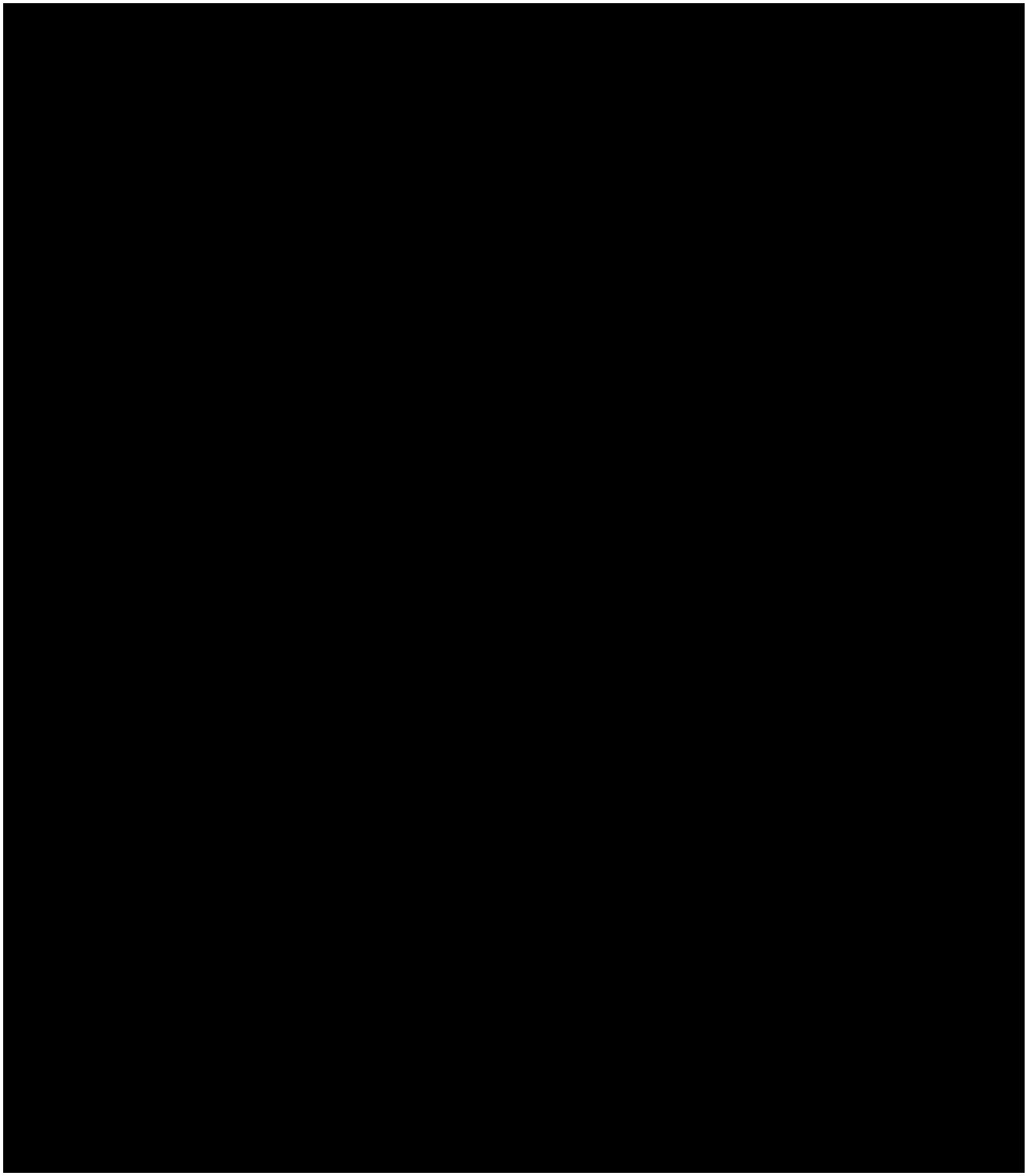
Study Day	Event	Time Postdose (sample window)	Pharmacokinetic Sample	Electrocardiogram
Assessments Associated with the Day 1 Visit				
Day 1 (Day of Week 1 dose)	Predose	0 h	X	X
Day 1	Dose			
[redacted]				
Day 8 (Day of Week 2 dose)	Predose	0 h	X	
Day 8	Dose			
Assessments Associated with the Week 24 Visit				
Day 169 (Day of Week 25 dose)	Predose	0 h	X	X
Day 169	Dose			
[redacted]				
Day 176 (Day of Week 26 dose)	Predose	0 h	X	
Day 176	Dose			

[redacted]

Pharmacokinetic samples should be taken after the electrocardiogram assessments are performed at times where both pharmacokinetic samples and electrocardiograms are to be collected.
Day 1 is defined as the day of administration of the first dose of study medication.

BMS-986036 concentrations will be evaluated by a central laboratory. Further details of sample collection, processing, submission and storage are provided in the Study Laboratory Manual.

[redacted]



9. STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

The primary efficacy endpoint is the proportion of participants with a ≥ 1-stage improvement in fibrosis (as defined by NASH CRN Fibrosis Score) without worsening of NASH (as defined by the NAFLD Activity Score) at Week 48, as determined by liver biopsy.

It is planned to randomize approximately 100 participants to 1 of the 4 treatment groups (approximately 25 participants per group), BMS-986036 10 mg QW, BMS-986036 20 mg QW, BMS-986036 40 mg QW or matching placebo QW in a 1:1:1:1 ratio.

A Cochran-Armitage trend test of proportions, with an estimated response rate of 15% for the primary endpoint for placebo and response rates for BMS-986036 10 mg QW, BMS-986036 20 mg QW, and BMS-986036 40 mg QW of 20%, 30%, and 40%, respectively, would provide at least 70% power at a 1-sided $\alpha = 0.05$ (based on original sample size estimate of approximately 100 participants). The final sample size was approximately 155 participants (see Section 6.2).

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, analyzed as per randomized treatment.
Modified intent-to-treat (mITT)	All participants who are randomized and receive at least 1 dose of study medication, analyzed according to randomized treatment. All primary efficacy analyses will be conducted using this population.
As treated (Safety)	All participants who are randomized and receive at least 1 dose of study medication, analyzed according to treatment actually received. This population will be essentially the same as the mITT unless a participant received an incorrect treatment, i.e., a treatment different from what he/she was randomized to. All safety analyses will be conducted using this population.

9.3 Stratification

Randomization of participants will be stratified by country (Non-Japan/Japan). For participants in countries other than Japan, the randomization will be further stratified according to T2DM status (yes/no).

9.4 Endpoints

9.4.1 Efficacy Endpoints

9.4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of participants who achieve a ≥ 1-stage improvement in fibrosis (as defined by NASH CRN Fibrosis Score) without worsening of NASH (as defined by the NAFLD Activity Score) at Week 48, as determined by liver biopsy.

For this protocol, improvement in fibrosis is defined as a decrease of fibrosis by ≥ 1 point, as determined by the NASH CRN Fibrosis Score. Worsening of NASH is defined as an increase of the NAFLD Activity Score (NAS) by ≥ 1 point. (see Section 8.5.1.1).

9.4.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are as follows:

- Proportion of participants with Ishak Score improvement at Week 48
- Proportion of participants who achieve a ≥ 1-stage improvement (as defined by NASH CRN Fibrosis Score) in fibrosis without worsening of NASH or NASH improvement (reduction of NAFLD Activity Score by ≥ 2 points with contribution from > 1 NAS component) at Week 48 as determined by liver biopsy
- Proportion of participants who achieve a ≥ 1-stage improvement (as defined by NASH CRN Fibrosis Score) in fibrosis
- Proportion of participants with a decrease in CPA at Week 48
- Proportion of participants with NASH resolution (NAS component of ballooning = 0 and inflammation = 0-1) at Week 48
- Proportion of participants with NASH improvement (reduction of NAFLD Activity Score by ≥ 2 points with contribution from > 1 NAS component) at Week 48

9.4.2 Safety Endpoints

Safety will be assessed by the following:

- Incidence and frequency of treatment-emergent AEs and SAEs
- ECGs at Week 24, and Week 48
- Vital signs at each visit
- Physical examinations (full or abbreviated as shown in Section 8.5.3) at each visit through Week 52/PTFU
- Laboratory evaluations at each visit through Week 52/PTFU
- BMD as measured by DXA Week 48/ET, and 6 months (1 month is defined as 4 calendar weeks) after the Week 52/PTFU Visit
- Anti-BMS-986036 antibodies at each visit with follow-up for up to 14 months (1 month is defined as 4 calendar weeks) after the Week 52/PTFU Visit as described in Section 8.5.3.6
- Anti-FGF21 antibodies at each visit with follow-up for up to 14 months (1 month is defined as 4 calendar weeks) after the Week 52/PTFU Visit as described in Section 8.5.3.6

9.4.3 Pharmacokinetic Endpoints

- Trough (predose) BMS-986036 concentrations from samples collected at each visit

[redacted]

9.4.4 Exploratory Endpoints

- Quantitative measurements of fibrosis and fat on biopsy
  - Assessment of NASH CRN Fibrosis Score at Week 48
  - Assessment of Ishak Fibrosis Score at Week 48
  - Assessment of fibrosis using digital pathology at Week 48
  - Assessment of CPA at Week 48
  - Assessment of fat in stained tissue by morphometry at Week 48
  - Assessment of alpha smooth muscle actin at Week 48
- Assessment of NAS at Week 48
- Assessment of NASH using digital pathology at Week 48
- Hepatic fat fraction as measured using MRI-PDFF at Week 24 and Week 48
- Noninvasive measures of fibrosis and/or cirrhosis
  - Liver stiffness as determined by MRE at Week 24 and Week 48
  - Fibroscan elastography results at Week 48

    [redacted]
  - Noninvasive scores of hepatic fibrosis (APRI, FIB-4, ELF, and NAFLD Fibrosis Score) at Week 24 and Week 48
- Metabolic assessments at Week 24 and Week 48
  - Physical assessments (body weight, waist circumference, and BMI)
  - Serum lipids (LDL, HDL, and TGs)
  - Plasma glucose
  - Plasma insulin
  - Hemoglobin A1c
- Child-Pugh Turcotte Score at Week 24 and Week 48
- MELD Score at each visit through Week 52/PTFU
- The event rate for any one (first occurrence) of the liver-related clinical outcome events described in Section 8.5.1.9 by Week 48
- Patient-reported outcomes at Week 24 and Week 48
  - EQ-5D-3L questionnaire
  - SF-36 questionnaire
  - CDLQ-NAFLD questionnaire
- Exploratory biomarkers
  - Transaminases
    - ALT normalization (ALT ≤ ULN) at Week 24 and Week 48
    - AST normalization (AST ≤ ULN) at Week 24 and Week 48

- ALT at each visit through Week 52/PTFU
- AST at each visit through Week 52/PTFU
- Change from Baseline (Day 1 predose) ALT levels at each visit through Week 52/PTFU Visit
- Change from Baseline (Day 1 predose) AST levels at each visit through Week 52/PTFU Visit

o PRO-C3
- Assessment of PRO-C3 levels at each visit through Week 52/PTFU
- Change from Baseline (Day 1 predose) in PRO-C3 levels at each visit through Week 52/PTFU Visit

[redacted]

o Assessment of adiponectin at each visit through Week 52/PTFU

[redacted]

9.5 Statistical Analyses

A full Statistical Analysis Plan (SAP) will be developed that will provide more details for the statistical analysis methods to be used. The SAP will be finalized before database lock for the Week 52 analysis and will provide detailed specifications of the analysis of all efficacy endpoints and safety. The SAP will also provide more details on the definition of analysis populations to be used in the analyses and procedures for accounting for missing data. The following provides a summary of planned statistical analyses of the primary and secondary endpoints; exploratory analyses will be described in the SAP.

9.5.1 Demographic and Baseline Characteristics

A description of the participant population will be included in a statistical output report, including subgroups of age, gender and race.

Demographic and Baseline characteristics will be summarized using frequency distributions and descriptive statistics using the Randomized Participants and modified intent-to-treat (mITT) populations. No statistical analyses will be performed to compare treatment groups at Baseline.

9.5.2 Efficacy Analyses

Efficacy analyses will be performed using the mITT population unless otherwise specified below.

9.5.2.1 Primary Endpoint

The primary endpoint is the proportion of participants who achieve a ≥ 1-stage improvement in fibrosis (as defined by NASH CRN Fibrosis Score) without worsening of NASH (as defined by the NAFLD Activity Score) at Week 48, as determined by liver biopsy.

For this protocol, improvement in fibrosis is defined as a decrease of fibrosis by ≥ 1 point, as determined by the NASH CRN Fibrosis Score. Worsening of NASH is defined as an increase of the NAFLD Activity Score (NAS) by ≥ 1 point (see Section 8.5.1.1).

A Cochran-Armitage trend test with a one-sided 0.05 level of significance will be used to examine the linear trend among the proportions across treatment groups. Also, 95% confidence intervals for the odds-ratio of each BMS treatment group to placebo will be provided.

A sensitivity analysis using an extended Cochran Mantel-Haenszel (CMH) correlation test[37] will be used to assess the trend among the proportions for treatment groups with an adjustment to strata. A two-sided 0.10 level of significance will be used.

Since this is a Phase 2 study, no adjustment for multiplicity will be applied.

[redacted]

All participants who prematurely discontinue from treatment without a biopsy at Week 48 (or ET, if applicable) or otherwise have a missing Week 48 (or ET, if applicable) biopsy result will be considered nonresponders for the primary analysis of the primary efficacy endpoint. In addition, a completer analysis of the primary endpoint will be performed excluding participants without a Week 48 biopsy.

9.5.2.2 Secondary Efficacy Endpoints

Secondary endpoints will be analyzed using methodology consistent with that of the primary endpoint unless otherwise specified in the SAP.

Further details of the primary and secondary analyses, any additional sensitivity analyses and data handling details regarding issues such as missing data will be provided in the SAP.

9.5.2.3 Methods for Handling Treatment Discontinuations and Other Causes of Missing Data

Participants who prematurely discontinue study medication will be expected to complete an Early Termination visit (Week 48/ET) and must continue to be followed for follow-up visits/procedures per the Schedule of Activities (e.g., Week 52/PTFU; Section 1).

Primary efficacy analyses will include all data that are collected on a participant during the study even after treatment discontinuation. All primary efficacy analyses will be performed with the mITT population, analyzed according to randomized treatment.

Additional details for handling of missing data will be provided in the SAP.

9.5.3 Safety Analyses

Safety analyses will be performed using the As Treated population. For analysis, all treatment-emergent (i.e., occurring after the first dose of study medication) AEs, SAEs, and AEs of special interest will be summarized by system organ class, preferred term, and treatment. Vital signs, immunogenicity, BMD, and laboratory data will be summarized by treatment. ECG abnormalities, physical examination abnormalities, if present, will be summarized.

Responses of anti-BMS-986036 antibodies and anti-FGF21 antibodies will be listed and tabulated by treatment and study day. [redacted]

9.5.4 Pharmacokinetic Analysis

Trough BMS-986036 serum concentrations (in all participants at all visits) [redacted] will be summarized by treatment and visit.

The PK data obtained in this study may be combined with data from other studies of BMS-986036 to develop a population PK/PK-PD model. This model will be used to evaluate the effects of intrinsic and extrinsic (if applicable) covariates (e.g., immunogenicity and renal function) on the PK of BMS-986036 and to determine measures of individual exposure (such as peak, trough, and time-averaged concentration following a single dose) of BMS-986036. Model determined exposures will be used for exposure-response analyses of selected efficacy and safety endpoints, as appropriate. Details of the planned population PK and exposure-response analyses will be covered in a separate pharmacometric analysis plan and the results of the population PK and exposure-response analyses presented in a pharmacometric report, separate from the clinical study report.

9.5.5 Analyses of Exploratory Endpoints

Analyses for the exploratory efficacy endpoints will be described in the SAP, which will detail the derivation of the endpoints and associated statistical methods and models.

10. REFERENCE LIST

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11. APPENDICES

Appendix 1 Study Administrative 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 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 IRB/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 (e.g., 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 (e.g., advertisements), and any other written information to be provided to participants. The investigator or sponsor should also provide the IRB/EC 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 (e.g., 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/EC
- 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/EC(s) and if applicable, also by local health authority must be sent to the sponsor.

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/EC(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/EC(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.

The sponsor or designee will provide the investigator with an appropriate (i.e., 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.

[redacted]

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/EC'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 United States, the participants' signed Health Insurance Portability and Accountability Act Authorization.

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

Participants unable to give their written consent (e.g., 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 study 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, 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 Medication Records

The study personnel will account for all study medications dispensed to and returned from the participant. Study site personnel will account for all unused study medications 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 medications (whether supplied by the sponsor, its vendors, or the site) must substantiate study medication 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 sponsor/designee or a health authority.

If	Then
Supplied by the sponsor (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount returned to the sponsor 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.

The sponsor 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. eCRFs 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 (EDC) tool, eCRFs will be prepared for all data collection fields with the exclusion of data collection associated with pregnancy, which will be reported on the Pregnancy Surveillance Form. 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. Subinvestigators in Japan may not be delegated the eCRF approval task. For eCRFs, review and approval/signature should be completed electronically through the study EDC 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 study EDC tool using the unique user account provided by sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

Monitoring

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

Representatives of the sponsor or designee 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 the sponsor or designee internal auditors and government inspectors who must be allowed access to case report forms, source documents, other study files, and study facilities. The sponsor audit reports will be kept confidential.

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

Records Retention

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

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

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

Return of Study Medication

For this study, study medications (those supplied by the sponsor, a vendor, or sourced by the investigator) such as partially used study medication containers and syringes may be destroyed on site (as applicable; some sites will return unused study medications depending on circumstances).

If …	Then
Study medications supplied by the sponsor (including its vendors)	Any unused study medications supplied by the sponsor can only be destroyed after being inspected and reconciled by the responsible study monitor unless study medications containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics). If study medications will be returned, the return will be arranged by the responsible study monitor.

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 the sponsor 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 (e.g., 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 study 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 medications provided by the sponsor (or its vendors). Destruction of nonstudy medications sourced by the site, not supplied by the sponsor, is solely the responsibility of the investigator or designee.

For sites that will not destroy study medication on site, it is the investigator's or designee's responsibility to arrange for disposal of all empty study medication 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 medications supplied by the sponsor 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
- Participant recruitment (e.g., among the top quartile of enrollers)
- Involvement in study design
- Regional representation (e.g., 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.

Data Monitoring Committee

This study will utilize a DMC for the duration of the study. Additional details can be found in the DMC charter and will be provided upon request.

Appendix 2 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 WOCBPs:

- 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 under the age of 55 years must have a serum follicle stimulating hormone (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 judgment in checking serum FSH levels.

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

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

Contraception Guidance for Female Participants of Child Bearing Potential

At minimum, one of the **highly effective** methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, as defined in Section 8.3.1.

Local laws and regulations may require use of alternative and/or additional contraception methods (e.g., one highly effective method plus another method).

Contraceptive Methods Classified as Highly Effective

User Dependent Methods

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[b]
  - oral
  - injectable

User Independent Methods

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b]
- Intrauterine device (IUD)[c]
- Intrauterine hormone releasing system (IUS)[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 medication. 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.
- WOCBPs 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 chooses to forego complete abstinence.

NOTES:

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

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

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

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, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method

Methods of Contraception Not Considered Effective in Japan

- Diaphragm with spermicide*
- Cervical cap with spermicide*
- Vaginal Sponge with spermicide*
- Male condom with spermicide* or male condom without spermicide or male condom applied spermicide
- Female condom with spermicide* or without spermicide*

* These methods are not approved or certified in Japan.

Appendix 3 Criteria for Diagnosis and Exclusion of Participants with Hepatitis B Virus (HBV) and Chronic Hepatitis C (HCV) Infection

HBV Infection

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

(a) Perform HBV DNA:
- If HBV DNA is **detected**, then participant must be excluded.
- If HBV DNA is **not detected**, then the participant may be considered eligible for enrollment based on the investigator's judgment and after discussion with the study medical monitor.

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

HCV Infection

A participant who is HCV Ab positive must be excluded unless:

- The participant has a history of HCV sustained viral response (undetectable HCV RNA) for at least 2 years prior to biopsy confirming study eligibility.

Appendix 4 DSM-5 Criteria for Drug And Alcohol Abuse

Diagnostic Criteria for Psychoactive Substance

Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by 3 (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
   a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect,
   b) Markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal, as manifested by either of the following:
   a) The characteristic withdrawal syndrome for the substance,
   b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking) or recover from its effects.
6. Important social, occupational or recreational activities are given up or reduced because of substance use.
7. The substance use is continued despite knowledge of having a persistent or recurring physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption.)

Criteria for Severity of Psychoactive Substance Dependence:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others.

Moderate: Symptoms or functional impairment between “mild” and “severe”.

Severe: Many symptoms in excess of those required to make the diagnosis, and the symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.

In Partial Remission: During the past 6 months, some use of the substance and some symptoms of dependence.

In Full Remission: During the past 6 months, either no use of the substance, or use of the substance and no symptoms of dependence.

Diagnostic Criteria for Psychoactive Substance Abuse

A. A maladaptive pattern of psychoactive substance use, leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring at any time in the same 12-month period:
    1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school, neglect of children or household).
    2. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use).
    3. Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct).
    4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights).
B. The symptoms have never met the criteria for substance dependence for this class of substance.

Appendix 5 Child-Pugh Turcotte 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 6 SF-36 (Version 2) Questionnaire

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 7 EQ-5D-3L Questionnaire

Health Questionnaire

English version for the UK
(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

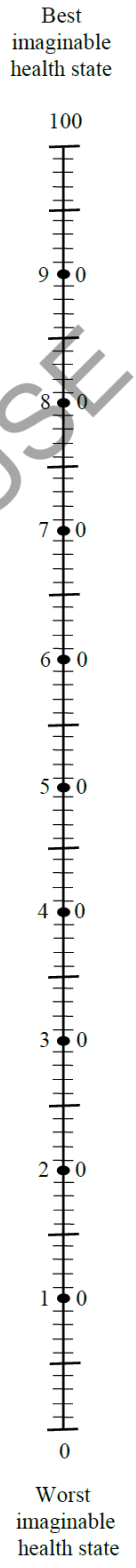
Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 8 CLDQ-NAFLD

The Chronic Liver Disease Questionnaire for NAFLD (CLDQ-NAFLD)

This questionnaire is designed to find out how you have been feeling during the last two weeks. You will be asked about your symptoms related to your fatty liver disease, how you have been affected in doing activities, and how your mood has been. Please complete all of the questions and select only **one** response for each question.

1. How much of the time during the last two weeks have you been troubled by a feeling of abdominal bloating?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

2. How much of the time have you been tired or fatigued during the last two weeks?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

3. How much of the time during the last 2 weeks have you experienced bodily pain?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

4. How often during the last two weeks have you felt sleepy during the day?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

5. How much of the time during the last two weeks have you experienced abdominal pain?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

6. How much of the time during the last two weeks has shortness of breath been a problem for you in your daily activities?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

7. How much of the time during the last two weeks have you not been able to eat as much as you would like?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

8. How much of the time in the last two weeks have you been bothered by having decreased strength?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

9. How often during the last 2 weeks have you had trouble lifting or carrying heavy objects?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

10. How often during the last two weeks have you felt anxious?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

11. How often during the last 2 weeks have you felt a decreased level of energy?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

12. How much of the time during the last two weeks have you felt unhappy?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

13. How often during the last two weeks have you felt drowsy?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

14. How much of the time during the last two weeks have you been bothered by a limitation of your diet?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

15. How often during the last two weeks have you been irritable?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

16. How much of the time during the last two weeks have you had difficulty sleeping at night?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

17. How much of the time during the last two weeks have you been troubled by a feeling of abdominal discomfort?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

18. How much of the time during the last two weeks have you been worried about the impact your liver disease has on your family?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

19. How much of the time during the last two weeks have you had mood swings?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

20. How much of the time during the last two weeks have you been unable to fall asleep at night?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

21. How often during the last two weeks have you had muscle cramps?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

22. How much of the time during the last two weeks have you been worried that your symptoms will develop into major problems?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

23. How much of the time during the last two weeks have you had a dry mouth?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

24. How much of the time during the last two weeks have you felt depressed?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

25. How much of the time during the last two weeks have you been worried about your condition getting worse?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

26. How much of the time during the last two weeks have you had problems concentrating?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

27. How much of the time have you been troubled by itching during the last two weeks?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

28. How much of the time during the last two weeks have you been worried about never feeling any better?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

29. How much of the time during the last two weeks have you been concerned about the availability of a liver if you need a liver transplant?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

30. How much of the time during the last two weeks have you had trouble walking two blocks or climbing two flights of stairs because of your health?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

31. How much of the time during the last two weeks have you had trouble bending, lifting, or stooping?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

32. How much of the time during the last two weeks have you had a feeling like you may die earlier because of your fatty liver?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

33. How much of the time during the last two weeks have you felt distressed by having fatty liver?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

34. How much of the time during the last two weeks have you not enjoyed life?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

35. How much of the time during the last two weeks have you felt the need to take naps (5 min or longer) during the day?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

36. How much of the time during the last two weeks have you been experiencing joint pain?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

Appendix 9 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up and Reporting

Adverse Events

Adverse Event Definition:
An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant after initiation of study medication (BMS-986036 or placebo) 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 medication, whether or not considered related to the study medication.

Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in sponsor 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 (e.g., 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

Results in persistent or significant disability/incapacity
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 [e.g., 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. Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential DILI is defined as: • ALT or AST > 3× ULN AND • Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) AND • No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

Suspected transmission of an infectious agent via the study medication is an SAE.

Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs.

Evaluating AEs and SAEs

Assessment of Intensity
The intensity of AEs is determined by a physician and will use the following level: • 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 even; and both AEs and SAEs can be assessed as severe.

Assessment of Causality

The causal relationship to study medication is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study medication administration and the AE.

Not related: There is not a reasonable causal relationship between study medication administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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 medication or if new information becomes available, the SAE report must be updated and submitted within 24 hours to the sponsor (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 medication, and pregnancies must be reported to [redacted] Drug Safety within 24 hours of awareness of the event.

SAEs must be recorded on the SAE Report Form. For studies capturing SAEs through EDC, 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 10 Formulae for Measurements

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

- ELF assay combines hyaluronic acid, procollagen 3 amino terminal peptide, and tissue inhibitor of metalloproteinase 1. An algorithm is used to evaluate each of these markers by immunoassay, to create an ELF Score.

- FIB4 score = (age [years] × AST level [U/L])/(platelet count [x10^9/L] × square root of ALT [U/L])

- APRI score = ([AST divided by AST Upper Limit of Normal]/platelet count [x10^9/L]) × 100

- NAFLD Fibrosis Score = -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × fasting glucose/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet count – 0.66 × albumin (g/dL)

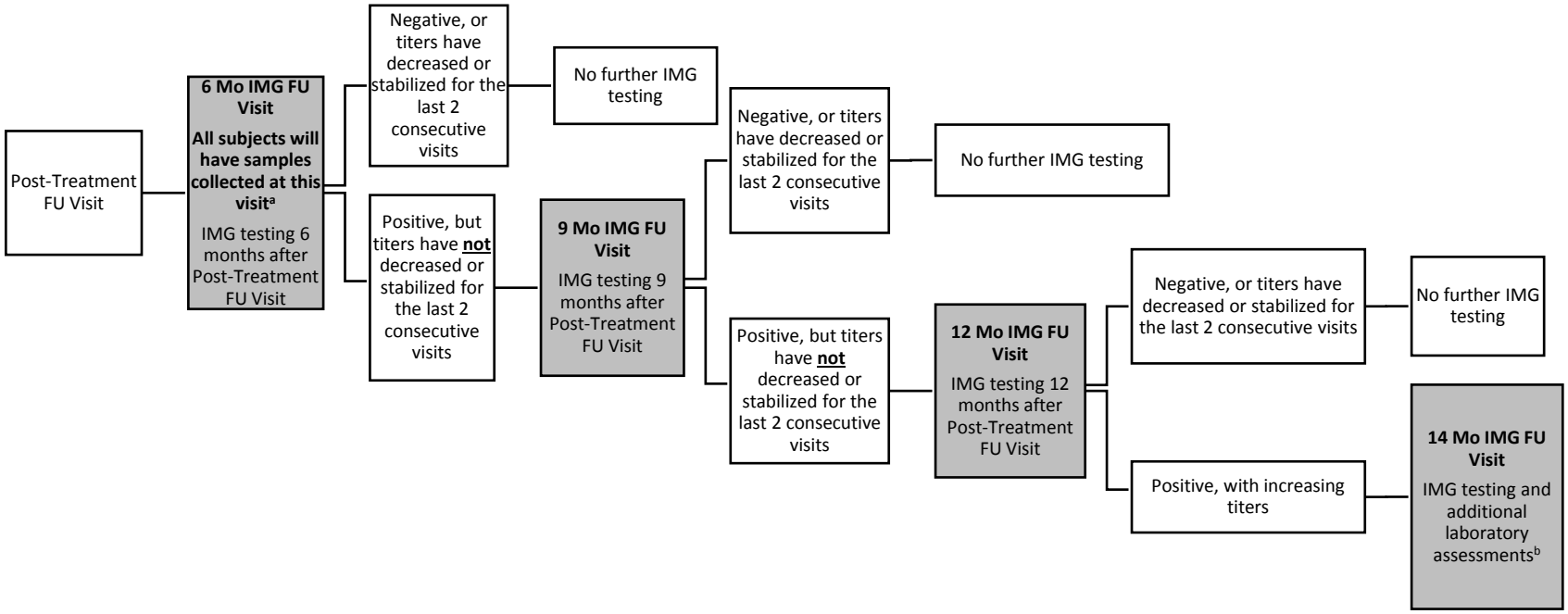
Method of BMI Calculation:

- 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)

Appendix 11 Decision Tree for Long-Term Immunogenicity Follow-Up Visits After the Week 52/PTFU Visit

Participants who discontinue study medication prior to Week 48 are expected to complete an ET Visit and to remain in the study and continue to have immunogenicity monitored according to the Schedule of Events in Section 1.

Participants who discontinue study participation will be offered immunogenicity follow-up visits, as per the diagram. All participants will have immunogenicity samples collected at 6 months after the Week 52/PTFU Visit. Additional immunogenicity follow-up visits may occur approximately 9, 12, and 14 months, if applicable, (visit window ± 14 days) (1 month is defined as 4 calendar weeks) after the last completed study visit.



FU = Follow-Up; IMG = Immunogenicity (anti-drug and anti-FGF21 antibodies); Mo = month (defined as 4 calendar weeks)

[a] All participants will have samples collected for immunogenicity at 6 months (± 14 days) after the Week 52/PTFU Visit. Samples collected from participants may not be analyzed if: 1) participant is not on active drug, 2) participant is negative for anti-drug and/or anti-FGF21 antibody titers at the Week 52/PTFU Visit, or 3) participant has evidence of stable or decreasing antibody titers for 2 visits prior to the 6-month posttreatment visit

[b] Additional assessments include: basic metabolic panel, hemoglobin A1c [redacted]