Official Protocol Title:	A Phase 2b Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-3655 in Individuals With Pre-cirrhotic Nonalcoholic Steatohepatitis
NCT number:	NCT04583423
Document Date:	24-Aug-2022

Title Page

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Protocol Title: A Phase 2b Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-3655 in Individuals With Pre-cirrhotic Nonalcoholic Steatohepatitis

Protocol Number: 001-05

Compound Number: MK-3655

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	134888
EudraCT	2019-003048-63

Approval Date: 24 August 2022

Sponsor Signatory

Typed Name:
Title:

Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 05	24-AUG-2022	This amendment was created to harmonize follow-up safety monitoring of all study participants through Week 64 (previously only WOCBP were followed through Week 64).
Amendment 04	01-JUN-2022	This amendment was created primarily to modify the IA futility criterion based on an updated assessment of the minimum LFC response supportive of study continuation.
Amendment 03	22-SEP-2021	This amendment was created primarily to expand the participant population to include premenopausal women.
Amendment 02	05-MAY-2021	This amendment was created primarily to enhance operational efficiency of this study.
Amendment 01	19-FEB-2021	This amendment was created primarily to transition the committee used to supplement the routine study monitoring conducted in this study from the Sponsor's siDMC to an eDMC. Additional changes included corrections and clarifications to the protocol language.
Original Protocol	30-JUL-2020	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendments:

To harmonize follow-up safety monitoring of all study participants through Week 64 (previously only WOCBP were followed through Week 64).

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Primary Change		
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities (SoA) 4.1 Overall Design 4.3.3 Rationale for Dose Interval and Study Design 8.1.8.8 Telephone Contact 8.3.10 Pregnancy Testing 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Revised the approximate duration of participation of all participants in the study from 64 weeks to 72 weeks.	To harmonize follow-up safety monitoring of all study participants through Week 64 (previously only WOCBP were followed through Week 64).

Section # and Name	Description of Change	Brief Rationale
8.11.6 Participants Discontinued From Study Intervention but Continuing to Be Monitored in the Study 8.11.7 Post-Treatment Visit and Telephone Contacts 9.6.2 Analysis Methods for Safety Analyses		
Additional Changes		
5.2 Exclusion Criteria	Added GLP-1 agonists under weight loss medication in Table 1 Stability Definitions for Medications and Other Substances.	To indicate approval of GLP-1 agonists for the treatment of obesity.
8.3.10 Pregnancy Testing	Clarified pregnancy testing.	Clarification
8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events	Removed "AE and/or" from the sentence discussing medication error, misuse, or abuse.	To align with the EU CTR.
Throughout document	Minor editorial changes.	To provide clarity.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2b Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-3655 in Individuals With Pre-cirrhotic Nonalcoholic Steatohepatitis

Short Title: Phase 2b Study of MK-3655 in Individuals with Pre-cirrhotic NASH

Hypotheses, Objectives, and Endpoints:

In males and females aged 18 to 80 years (in Japan and Taiwan, aged 20 to 80 years [Appendix 7]) with pre-cirrhotic NASH:

Primary Objectives	Primary Endpoints
To evaluate the effect of each dose of MK-3655 versus placebo on the proportion of individuals with NASH resolution without worsening of fibrosis after 52 weeks. Hypothesis (H1): At least 1 dose of MK-3655 is superior to placebo with respect to the proportion of individuals with NASH resolution without worsening of fibrosis after 52 weeks.	- NASH resolution (defined as a score of 0-1 for inflammation, 0 for ballooning, and any grade of steatosis) without worsening of fibrosis assessed with the NASH CRN scoring system (evaluated by BICR)
To evaluate the safety and tolerability of MK-3655 compared with placebo.	- AEs - Discontinuation of study intervention due to AEs
Secondary Objectives	Secondary Endpoints
To evaluate the effect of each dose of MK-3655 versus placebo on mean percent relative reduction from baseline in LFC after 24 weeks.	- LFC (%) measured by MRI-PDFF (evaluated by BICR)
To evaluate the effect of each dose of MK-3655 versus placebo on the proportion of individuals with ≥1 stage improvement in fibrosis without worsening of steatohepatitis after 52 weeks.	- ≥1 stage improvement in fibrosis without worsening of steatohepatitis (defined as no increase in the ballooning, inflammation, or steatosis scores) assessed with the NASH CRN scoring system (evaluated by BICR)

To evaluate the effect of each dose of MK-3655 versus placebo on the proportion of individuals with ≥2 point improvement in the NAS without worsening of fibrosis after 52 weeks.	- ≥2 point improvement in the NAS with ≥1 point improvement in inflammation or ballooning without worsening of fibrosis assessed with the NASH CRN scoring system (evaluated by BICR)

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Treatment of individuals with pre-cirrhotic NASH.
Population	Males and females aged 18 to 80 years (in Japan and Taiwan, aged 20 to 80 years [Appendix 7]) with pre-cirrhotic NASH, Stage 2 or 3 liver fibrosis, and a NAS ≥4 with a score ≥1 point in each component (ie, lobular inflammation, ballooning, and steatosis).
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Participant or Subject Investigator Sponsor Care Provider
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 45.5 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 328 participants will be randomized.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>Participants will be randomized in a 1:1:1:1 ratio and dosed Q4W.
<table>
<tr><th>Intervention Group Name</th><th>Drug (Conc)</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin</th><th>Treatment Period (V5 to V15)</th><th>Use</th></tr>
<tr><td rowspan="2">Group 1</td><td>MK-3655 (33.3 mg/mL)</td><td>50 mg</td><td>1 × 1.5 mL injection Q4W</td><td>SC</td><td>Double-Blind Treatment Period</td><td>Test Product</td></tr>
<tr><td>MK-3655 Matching Placebo</td><td>0 mg</td><td>1 × 1.5 mL injection Q4W</td><td>SC</td><td>Double-Blind Treatment Period</td><td>Placebo</td></tr>
<tr><td>Group 2</td><td>MK-3655 (33.3 mg/mL)</td><td>100 mg</td><td>2 × 1.5 mL injections Q4W</td><td>SC</td><td>Double-Blind Treatment Period</td><td>Test Product</td></tr>
<tr><td>Group 3</td><td>MK-3655 (100 mg/mL)</td><td>300 mg</td><td>2 × 1.5 mL injections Q4W</td><td>SC</td><td>Double-Blind Treatment Period</td><td>Test Product</td></tr>
<tr><td>Group 4</td><td>MK-3655 Matching Placebo</td><td>0 mg</td><td>2 × 1.5 mL injections Q4W</td><td>SC</td><td>Double-Blind Treatment Period</td><td>Placebo</td></tr>
<tr><td colspan="7">admin=administration; conc=concentration; Q4W=once every 4 weeks; SC=subcutaneous; V=visit.</td></tr>
</table>
Other current or former name or alias for the study intervention is NGM313.</td></tr>
<tr><td>Total Number of Intervention Groups/Arms</td><td>4</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 72 weeks, from the time the participant provides documented informed consent through the final contact.

After a staged screening period (Visit 1 through Visit 3) of approximately 6 weeks (±28 days), each eligible participant will enter a 2-week, single-blind placebo run-in period (Visit 4 up to Visit 5/Randomization). On completion of the placebo run-in, eligible participants will be randomized to receive assigned double-blind intervention and participate through Visit 15/Week 52. A post-treatment follow-up visit (Visit 16) will occur 4 weeks after Visit 15. Post-treatment follow-up telephone contacts will be performed at Weeks 60 and 64.</td></tr>
</table>

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	Yes
Study governance considerations are outlined in Appendix 1. The Data Monitoring Committee for this study is an eDMC.	

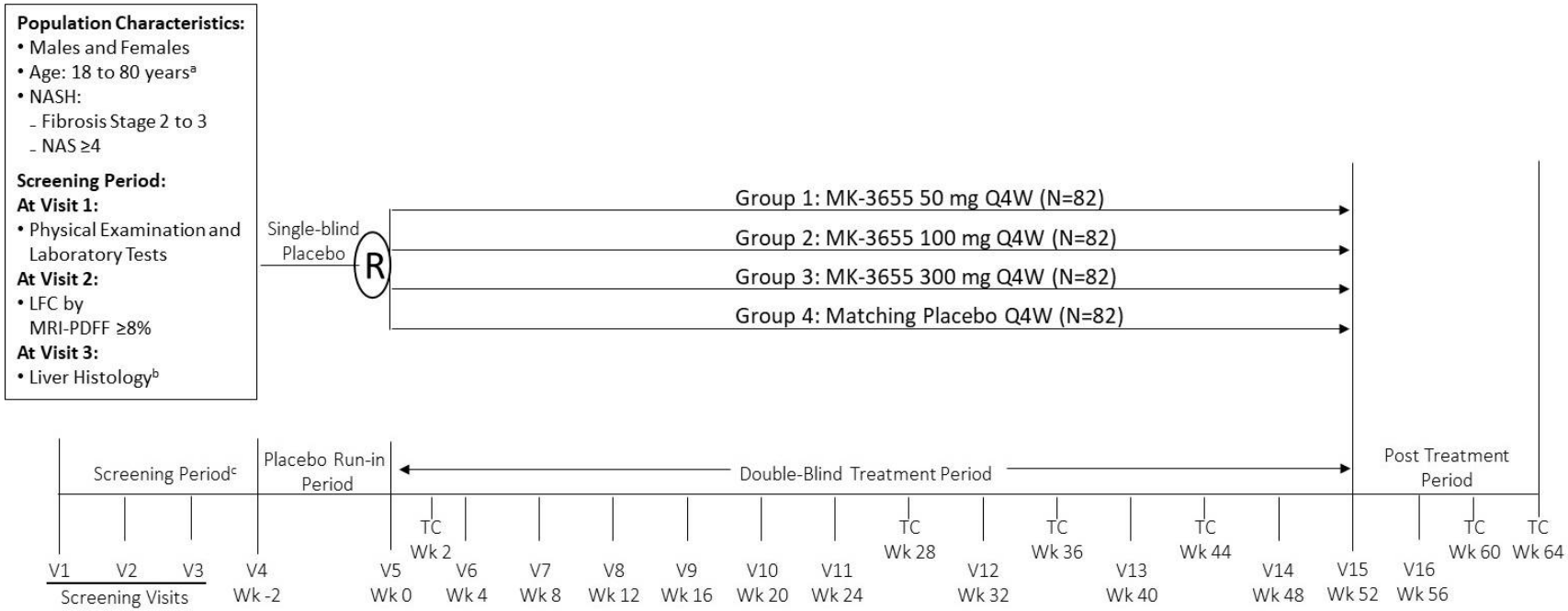
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 15.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



D=Day; LFC=liver fat content; MRI-PDFF=magnetic resonance imaging-proton density fat fraction; NAS=nonalcoholic fatty liver disease (NAFLD) activity score; NASH=nonalcoholic steatohepatitis; R=randomization; Q4W=once every 4 weeks; T2DM=type 2 diabetes mellitus; TC=telephone contact; V=visit; Wk=week.

[a] For participants in Japan and Taiwan, the population age will be from 20 to 80 years.
[b] Participants with a liver biopsy performed within 6 months of Visit 1/Screening will have their biopsy slides read centrally by a pathologist to confirm eligibility for study randomization.
[c] The interval between Visit 1 and Visit 4 for eligible participants will be approximately 6 weeks.

1.3 Schedule of Activities (SoA)

Study Period	**Screening**			**Placebo Run-in**	**Double-Blind Treatment**											**Post-Treatment Follow-up**			**Notes**
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**DC**	**16**	**TC**	**TC**	**For participants who DC study intervention early, see Section 8.11.6.**
Scheduled Week	**-8 to -2**			**-2**	**0 D1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**	**N/A**	**56**	**60**	**64**	
Visit Window Guideline (Days):	**±28**			**±3**								**±5**				**-**	**+7**			
Administrative and General Procedures																				
Informed Consent	X																			Informed consent must be documented before any study procedures are performed and may be completed before V1.
Informed Consent for FBR	X																			Participation in FBR is not required for participation in the main study.
Inclusion/Exclusion Criteria	X			X	X															Alcohol consumption assessed as part of exclusion criterion #11 (see Section 5.2).
Participant Identification Card	X				X															At the time of randomization (V5), the site will add the treatment/randomization number to the participant identification card.
Medical History	X																			
Prior and Concomitant Medication Review	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Assignment of Screening Number	X																			
Contact IVRS	X			X	X	X	X	X	X	X	X	X	X	X	X	X				

Study Period	**Screening**			**Placebo Run-in**	**Double-Blind Treatment**											**Post-Treatment Follow-up**			**Notes**
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**DC**	**16**	**TC**	**TC**	**For participants who DC study intervention early, see Section 8.11.6.**
Scheduled Week	**-8 to -2**			**-2**	**0 D1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**	**N/A**	**56**	**60**	**64**	
Visit Window Guideline (Days):	**±28**			**±3**								**±5**				**-**	**+7**			
Treatment Randomization					X															Participants will be randomized after confirmation of eligibility and before D1 procedures/assessments.
Diet and Activity Counseling/ Monitoring				X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Assessment of alcohol consumption					X	X	X	X	X	X	X	X	X	X	X	X	X			Assessment will be performed before administration of study intervention.
Self-Injection Training - Participant and/or Caregiver				X	X															Retraining will be performed by site personnel at subsequent visits, as needed. In Japan, administration of study intervention is not allowed by a caregiver (see Appendix 7).
Witness Dose of Study Interventions				X	X	X	X	X	X	X	X	X	X	X						Performed after all procedures/assessments are complete.
Placebo Dispensing (For Run-in Period)				X																

Study Period	**Screening**			**Placebo Run-in**	**Double-Blind Treatment**											**Post-Treatment Follow-up**			**Notes**
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**DC**	**16**	**TC**	**TC**	
Scheduled Week	**-8 to -2**			**-2**	**0 D1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**	**N/A**	**56**	**60**	**64**	**For participants who DC study intervention early, see Section 8.11.6.**
Visit Window Guideline (Days):	**±28**			**±3**								**±5**				**-**	**+7**			
MK-3655/Matching Placebo Dispensing (For Double-Blind Treatment Period)					X	X	X	X	X	X	X	X	X	X						
Dispense Participant Diary				X																
Review Participant Diary (Date and location of injection and experience)				X	X	X	X	X	X	X	X	X	X	X	X	X				Participants will be directed to bring diaries back at **ALL** visits for review by site personnel.
Investigational Product Accountability												X	X	X	X	X				Participants will be directed to return all vials (used and unused) for visual inspection by site personnel.

Study Period	**Screening**			**Placebo Run-in**	**Double-Blind Treatment**											**Post-Treatment Follow-up**			**Notes**
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**DC**	**16**	**TC**	**TC**	
Scheduled Week	**-8 to -2**			**-2**	**0 D1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**	**N/A**	**56**	**60**	**64**	**For participants who DC study intervention early, see Section 8.11.6.**
Visit Window Guideline (Days):	**±28**			**±3**								**±5**				**-**	**+7**			
Telephone Contact	X---------X (Within 3 days before V2 and V3)				X-----X (Wk 2)						X----------X (Wks 28, 36, & 44)							X	X	Telephone contact by the investigator/qualified designee or site staff will be made: (1) within the 3 days before V2 and V3 to assess for concomitant medications and AEs as well as remind participants about their upcoming appointments, (2) at Wk 2 to perform a C-SSRS assessment, (3) at Wks 28, 36, and 44 to assess for AEs and concomitant medications, record body weight, assess pregnancy status (if applicable), and to assess compliance with study intervention administration, and (4) at Wks 60 and 64 to assess for AEs and pregnancy status (if applicable).

Study Period	Screening			Placebo Run-in	Double-Blind Treatment											Post-Treatment Follow-up				Notes
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**DC**	**16**	**TC**	**TC**	**For participants who DC study intervention early, see Section 8.11.6.**
Scheduled Week	**-8 to -2**			**-2**	**0 D1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**	**N/A**	**56**	**60**	**64**	
Visit Window Guideline (Days):	**±28**			**±3**								**±5**				**-**	**+7**			
Efficacy Procedures																				
MRI-PDFF		X									X					X[a]				Assessed by BICR.
Liver Biopsy			X												X	X[b]				For management of participants with historical liver biopsies, see Section 8.11.3.3.1. Assessed by BICR.
A1C	X				X			X			X		X		X	X				
Fasting Plasma Glucose	X				X	X	X	X			X		X		X	X				
Fasting Lipid Profile, apoB, and apoA1	X				X			X			X				X	X				Lipid profile includes total cholesterol, non-HDL-C, HDL-C, LDL-C, and TG. apoB and apoA1 will not be collected at V1.
Patient-Reported Outcomes																				
CLDQ NAFLD-NASH					X										X	X				Perform PROs in the order listed in Column 1 of the SoA.
PGI-S					X										X	X				
EQ-5D-5L					X										X	X				
Safety Assessments/Procedures																				
Complete Physical Examination	X														X	X				
Directed Physical Examination					X			X			X		X							
Height	X																			

Study Period	**Screening**			**Placebo Run-in**	**Double-Blind Treatment**											**Post-Treatment Follow-up**				**Notes**
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**DC**	**16**	**TC**	**TC**	**For participants who DC study intervention early, see Section 8.11.6.**
Scheduled Week	**-8 to -2**			**-2**	**0 D1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**	**N/A**	**56**	**60**	**64**	
Visit Window Guideline (Days):	**±28**			**±3**								**±5**				**-**	**+7**			
Body Weight Assessment and Monitoring	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X			At V11 participants will be provided digital scales to assess body weight at home at Wks 28, 36, and 44.
BMI	X																			
MELD-Na score	X																			
12-lead ECG	X														X	X				Performed after 10 minutes in a supine position and before BP and HR assessments.
Vital Signs (HR, BP, and Temperature)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X			HR and BP will be collected at all scheduled visits. Temperature will be collected at V5. HR and BP performed after a 10-minute resting period.
DXA				X											X	X[c]				BMD and body composition.

Study Period	**Screening**			**Placebo Run-in**	**Double-Blind Treatment**											**Post-Treatment Follow-up**				**Notes**
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**DC**	**16**	**TC**	**TC**	**For participants who DC study intervention early, see Section 8.11.6.**
Scheduled Week	**-8 to -2**			**-2**	**0 D1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**	**N/A**	**56**	**60**	**64**	
Visit Window Guideline (Days):	**±28**			**±3**								**±5**				**-**	**+7**			
Urine Pregnancy Test (if applicable)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collect predose (except at DC and V16). At V11, V12, and V13 WOCBP will be provided pregnancy test kits to assess pregnancy status at home at Wks 28, 36, and 44 (see Section 8.3.10). At V16 WOCBP will be provided pregnancy test kits to assess pregnancy status at home at Wks 60 and 64 (see Section 8.3.10). Serum hCG will be performed when a pregnancy is suspected.
FSH	X																			If applicable.
PT and INR	X																			
Hepatitis B (HBsAg) and Hepatitis C (anti-HCV)	X																			For Argentina-specific requirements see Appendix 7.
ACTH					X		X		X		X	X	X	X	X	X				Samples should be collected between 7 AM and 10 AM.

Study Period	**Screening**			**Placebo Run-in**	**Double-Blind Treatment**											**Post-Treatment Follow-up**				**Notes**
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**DC**	**16**	**TC**	**TC**	**For participants who DC study intervention early, see Section 8.11.6.**
Scheduled Week	**-8 to -2**			**-2**	**0 D1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**	**N/A**	**56**	**60**	**64**	
Visit Window Guideline (Days):	**±28**			**±3**								**±5**				**-**	**+7**			
Bedtime Salivary Cortisol	X				X		X		X		X	X	X	X	X	X				Salivary cortisol test kits will be provided to participants at the visit prior to the required sample collection timepoint (except V1). Participants are to collect bedtime salivary cortisol at home between 9 PM and midnight the evening before the study visit. The sample should be returned to the site the following day (no later than 72 hours from the time of collection).
TSH	X				X			X			X		X		X	X				
FT4	X				X			X			X		X		X	X				
IGF-1	X				X			X			X		X		X	X				
Hematology	X				X	X		X			X		X		X	X				
Chemistry Panel	X				X	X		X			X		X		X	X				
Serum Ketones					X	X		X			X		X		X	X				Includes acetoacetate acid and beta-hydroxybutyrate.
Urinalysis	X														X	X				
Bone Biomarkers (Serum P1NP and CTX)					X						X				X	X				

Study Period	**Screening**			**Placebo Run-in**	**Double-Blind Treatment**											**Post-Treatment Follow-up**				**Notes**
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**DC**	**16**	**TC**	**TC**	**For participants who DC study intervention early, see Section 8.11.6.**
Scheduled Week	**-8 to -2**			**-2**	**0 D1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**	**N/A**	**56**	**60**	**64**	
Visit Window Guideline (Days):	**±28**			**±3**								**±5**				**-**	**+7**			
C-SSRS: Screening Version	X																			
C-SSRS: Since Last Visit Version				X	X	X	X	X	X	X	X	X	X	X	X	X	X			An additional C-SSRS assessment will be performed at 2 wks after randomization by telephone contact.
PHQ-9	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
AE Monitoring	X----------X				X	X												X	X	
Immunogenicity/PK/PD/Biomarkers																				
Immunogenicity Assay (ADA)					X	X		X			X				X	X	X			Collect predose (except at DC and V16).
MK-3655 PK Blood Sample					X	X	X	X			X				X	X	X			Collect predose (except at DC and V16).
Adiponectin					X						X				X	X				Collect predose (except at DC).
Fasting Insulin					X						X				X	X				Collect predose (except at DC).
HOMA-IR					X						X				X	X				
Fasting FFA					X						X				X	X				Collect predose (except at DC).
FIB-4					X						X				X	X				
NFS					X						X				X	X				
APRI					X						X				X	X				
Pro-C3					X						X				X	X				Collect predose (except at DC).
Blood for Serum Biomarkers	X				X	X		X			X				X	X				Collect predose (except at DC).

Study Period	Screening			Placebo Run-in	Double-Blind Treatment											Post-Treatment Follow-up				Notes
Visit Number/Title	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**DC**	**16**	**TC**	**TC**	**For participants who DC study intervention early, see Section 8.11.6.**
Scheduled Week	**-8 to -2**			**-2**	**0 D1**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**	**52**	**N/A**	**56**	**60**	**64**	
Visit Window Guideline (Days):	**±28**			**±3**								**±5**				**-**	**+7**			
Blood for Plasma Biomarkers	X				X	X		X			X				X	X				Collect predose (except at DC).
Blood for Genetic Analysis					X															Collected from randomized participants only. See Section 8.9.1.

A1C=glycated hemoglobin; ACTH=adrenocorticotropic hormone; ADA=anti-drug antibodies; AE=adverse event; apoA1=apolipoprotein A1; apoB=apolipoprotein B; APRI=AST/platelet ratio index; BICR=blinded independent central review; BMD=bone mineral density; BMI=body mass index; BP=blood pressure; CLDQ NAFLD-NASH=chronic liver disease questionnaire for nonalcoholic fatty liver disease – nonalcoholic steatohepatitis; C-SSRS=Columbia-Suicide Severity Rating Scale; CTX=collagen type 1 cross-linked telopeptide; D=Day; DC=discontinuation; DXA=dual-energy x-ray absorptiometry; ECG=electrocardiogram; FBR=future biomedical research; FFA=free fatty acid; FIB-4=fibrosis-4; FSH=follicle stimulating hormone; FT4=free thyroxine; HBsAg=Hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=Hepatitis C virus; HDL-C=high density lipoprotein-cholesterol; HOMA-IR=homeostatic model assessment-insulin resistance; HR=heart rate; ICF=Informed Consent Form; IGF-1=insulin-like growth factor-1; INR=international normalized ratio; IVRS=interactive voice response system; LDL-C=low density lipoprotein-cholesterol; MELD-Na=model for end-stage liver disease-sodium score; MRI-PDFF=magnetic resonance imaging-estimated proton density fat fraction; NFS=NAFLD fibrosis score; P1NP=procollagen type 1 N-terminal propeptide; PD=pharmacodynamics; PGI-S=Patient Global Impression of Severity; PHQ-9=Patient Health Questionnaire – 9; PK=pharmacokinetic; PRO=patient-reported outcomes; Pro-C3=propeptide of type III collagen; PT=prothrombin time; TC=telephone contact; TG=triglycerides; TSH=thyroid-stimulating hormone; V=visit; Wk=week; WOCBP=woman/women of childbearing potential.

[a] For participants who discontinue study intervention **AND** where at least 4 wks have passed since the first dose of study intervention, the end of study MRI-PDFF should be performed as part of the DC visit procedures. See Section 8.11.6.
[b] For participants who discontinue study intervention **AND** where at least 12 wks have passed since the first dose of study intervention, the end of study liver biopsy should be performed as part of the DC visit procedures. See Section 8.11.6.
[c] For participants who discontinue study intervention **AND** where at least 24 wks have passed since the first dose of study intervention, the end of study DXA procedure should be performed as part of the DC visit procedures. See Section 8.11.6.

2 INTRODUCTION

2.1 Study Rationale

MK-3655 is a humanized mAb that selectively activates the FGFR1c/KLB receptor complex. MK-3655, formerly NGM313, was initially discovered by NGM Biopharmaceuticals, Inc (NGM). In Phase 1 single and multiple ascending dose testing, MK-3655 demonstrated good safety and tolerability, a PK profile potentially supporting monthly dosing by subcutaneous administration, and biomarker confirmation of robust on-target pharmacology. In a Phase 1b study (MK-3655 P005 [NGM 17-0202]; N=25) in obese, insulin-resistant, nondiabetic male and female participants, a single dose of MK-3655 resulted in a significant reduction in LFC assessed by MRI-PDFF and improved insulin sensitivity assessed by hyper-insulinemic, euglycemic clamp. These data support the further development of MK-3655 as a NASH therapeutic agent.

The principal goals of this Phase 2b study are to assess whether the pharmacological effects observed in earlier studies are seen in the target population of NASH patients with Stage 2 and 3 fibrosis, to assess whether MK-3655 treatment can achieve histologic improvement of NASH activity and fibrosis, to expand the safety and tolerability characterization of MK-3655, and to identify optimal doses for further development.

2.2 Background

Refer to the IB for detailed background information on MK-3655.

2.2.1 Pharmaceutical and Therapeutic Background

NAFLD is a condition of increased accumulation of fat (triglycerides) in hepatocytes. NAFLD is primarily a consequence of obesity-related insulin resistance, resulting in increased trafficking of fatty acids from adipose to liver and de novo hepatic lipogenesis [Fabbrini, E., et al 2010]. NAFLD encompasses a spectrum of disease, ranging from simple steatosis to gradual development of chronic inflammation (steatohepatitis or NASH), fibrosis, and ultimately cirrhosis. Approximately 3% of the NAFLD population will transition to cirrhosis with a mean follow-up of 7.6 ± 4.0 years (range, 0.1 to 23.5 years) [Adams, L. A., et al 2005]. Additionally, some patients develop hepatocellular carcinoma without cirrhosis [Stine, J. G., et al 2018] [Perumpail, R. B., et al 2015]. In general, patients with NASH are diagnosed between the ages of 40 and 60 years, and have associated metabolic comorbidities that include obesity, dyslipidemia, T2DM, and MetS [Younossi, Z. M., et al 2016] [Younossi, Z., et al 2018] [Chalasani, N., et al 2018] [Tholey, D. 2020]. Globally, the estimated prevalence of NAFLD is approximately 25% of the adult population and an increasing proportion of these cases will be NASH; rising from 20% to 27% between the years 2015 and 2030 [Friedman, S. L., et al 2018]. Additionally, NASH has been recognized as one of the leading causes of cirrhosis in adults in the US, and NASH-related cirrhosis is currently considered the second most common indication for liver transplants in the US [Younossi, Z. M., et al 2016].

NAFLD patients are typically asymptomatic; therefore, more likely to initially be identified based on risk factors (obesity, MetS, T2DM) and/or abnormal liver tests without alternate explanation. The presence of steatosis may be assessed through imaging (ultrasound, MRI). In patients with confirmed steatosis, the risk for NASH and advanced fibrosis can be further assessed through laboratory panels and imaging-based assessments of liver stiffness. These diagnostics cannot definitively diagnose NASH or fibrosis stage but are useful in assessing risk of advanced fibrosis. The liver biopsy remains the gold standard against which noninvasive methods are judged for definitive diagnosis and/or intervention [Rockey, D. C., et al 2009] [Chalasani, N., et al 2018].

Lifestyle modification directed at weight loss and exercise remain the most recommended treatment for NAFLD; however, even in well-organized settings, only a minority of patients achieve and sustain weight loss. Presently, there are no agency approved medications for the treatment of NASH. According to evidence-based practice guidelines, pioglitazone and high dose vitamin E (800 IU/day) are now recommended as pharmacotherapies for biopsy-proven NASH patients with and without diabetes, respectively [Sumida, Y. 2018]. However, neither pioglitazone nor vitamin E have demonstrated in the NASH population a robust histological efficacy, been studied long-term to assess impact on liver-related outcomes or have fully characterized safety. The absence of well-characterized, safe, and highly effective NASH treatments is a significant unmet medical need recognized by both medical societies and regulatory agencies [Friedman, S. L., et al 2018] [Food and Drug Administration 2018] [Chalasani, N., et al 2018].

The focus of this study is to evaluate MK-3655, a humanized mAb that selectively activates the FGFR1c/KLB receptor complex that mediates most or all the metabolic benefits of FGF21 and its pharmacologic analogs including insulin sensitization, lipid profile improvements, and liver fat reduction [Owen, B. M., et al 2015] [Sanyal, A., et al 2018]. FGFR1c/KLB is also considered the principal target mediating the robust anti-steatotic effect reported for a FGF19 analog [Owen, B. M., et al 2015] [Harrison, S. A., et al 2018]. Unlike FGF21 and FGF19 analogs, MK-3655 selectively activates only FGFR1c/KLB, which may confer an optimal therapeutic profile through avoidance of unfavorable effects potentially mediated by activation of other FGFR/KLB complexes. FGF21-mediated activation of FGFR2/KLB and FGFR3/KLB may potentially contribute to unfavorable effects which have been associated with FGF21s including effects on the hypothalamic-pituitary axis, bone, heart rate, blood pressure, glucocorticoids, and female reproductive function [Wei, W., et al 2012] [Talukdar, S., et al 2016] [Kim, A. M., et al 2017] [Owen, B. M., et al 2015] [Owen, B. M., et al 2013] [Singhal, G., et al 2016]. FGFR4/KLB-mediated modulation of bile acid metabolism is presumed to be responsible for the substantial LDL-C elevation seen with administration of an FGF19 analog [Harrison, S. A., et al 2018].

Given the central role of insulin resistance in the pathogenesis of NAFLD/NASH, a well-tolerated insulin-sensitizing agent with beneficial effects on steatosis and other aspects of MetS would be a potentially compelling therapeutic option for the dysmetabolic NASH population.

2.2.2 Preclinical and Clinical Studies

Toxicology and clinical data are briefly summarized below. Refer to the MK-3655 IB for a more extensive summary of the preclinical and clinical data available for MK-3655.

2.2.2.1 MK-3655 Preclinical Overview

The preclinical safety profile of MK-3655 has been assessed in 3 GLP-toxicology studies in NHP of up to 28-weeks in duration. MK-3655 does not bind to FGFR1c/KLB in lower species; therefore, no toxicology studies have been conducted in other species.

In nonclinical studies, there were no notable effects of MK-3655 on CV, respiratory, or neurobehavioral parameters in NHPs. In a 9-week repeat-dose study, MK-3655 was generally well tolerated in NHPs with no remarkable treatment-related changes in clinical observations or clinical pathology parameters up to the highest dose tested (15 mg/kg; Q2W). Body weight loss with associated microscopic changes in adipose tissue (reduced adipocyte size and fat content) were observed at all MK-3655 doses.

In a 28-week repeat-dose study, there were no effects noted in electrocardiography, ophthalmology, testicular volume, semen analysis, clinical pathology, or T-cell dependent antibody responses. Noteworthy findings related to MK-3655 treatment were generalized or widespread alopecia without corresponding microscopic changes in most animals, decreased food consumption, remarkable body weight loss, decreased fat mass (DXA), decreased bone mineral content, amenorrhea (1 animal) with microscopic alterations in female reproductive organs, prolonged menstrual cycles, and microscopic changes in adipose tissue (reduced adipocyte size and fat content). Alopecia, bone mineral content decreases, and menstrual cycle changes were considered likely secondary to body weight loss and adipose tissue changes. The amenorrhea and reproductive tract atrophy, both observed in a single female NHP, may be due entirely to weight loss and therefore not likely to be relevant to humans.

A subsequent 4-month menstrual cyclicity study in NHP with a 6-month recovery (control and 5 mg/kg Q4W groups; n=12 normally cycling females/group) was conducted to provide a definitive assessment of menstrual cycle changes in MK-3655 treated animals. In this study, NHP (n=12 with a total of 108 menstrual cycles) with demonstrated continuous MK-3655 exposure for up to 4 months and pharmacologically-mediated body weight loss (-10% to -34% of their prestudy weight) did not have test article-related menstrual cycle changes. The NOEL for menstrual cycle changes was 5 mg/kg Q4W (18,000 µg/mL*hour; 2 times the clinical exposure at 300 mg Q4W). Based on these data, the menstrual cycle changes observed in the 28-week repeat-dose toxicity study are attributed to normal variability in length of menstrual cycles in NHP, changes in social housing conditions, and/or stress/poor body condition resulting from body weight loss (see IB).

2.2.2.2 MK-3655 Clinical Overview

In clinical data available as of 06-DEC-2020, at least one dose of MK-3655 has been administered to 208 participants and at least one dose of placebo or comparator drug has been administered to 68 participants across 5 Phase 1 studies (4 completed and 1 ongoing) (MSD data on file). Safety data are summarized below.

In the MK-3655 P004 study (completed), healthy overweight and obese adult participants received single doses of MK-3655 3 mg to 360 mg (n=63) or placebo (n=20) and 53 healthy overweight and obese adult participants were randomized to receive MK-3655 10 mg to 240 mg or placebo (n=15) dosed Q4W for 3 months.

In the MK-3655 P005 study (completed), nondiabetic participants with increased LFC were randomized to receive either a single dose of MK-3655 240 mg (n=17) or pioglitazone 45 mg (n=8) orally daily for 35 days.

In the MK-3655 P002 study (completed), overweight and obese participants with increased LFC received 8 weekly doses of MK-3655 (n=15; 300 mg on Week 1 and 150 mg on Weeks 2 through 8) or placebo (n=5).

In the MK-3655 P003 study (completed), healthy Japanese male participants received single doses of MK-3655 60 mg to 360 mg (n=18) or placebo (n=6) and healthy Japanese male participants received 8 weekly doses of MK-3655 (n=6, 300 mg on Week 1 and 150 mg on Weeks 2 through 8) or placebo (n=2).

In the MK-3655 P006 study (ongoing), healthy Chinese male participants received single doses of MK-3655 60 mg to 360 mg (n=27) or placebo (n=9) and healthy Chinese male participants received 8 weekly doses of MK-3655 (n=9, 300 mg on Week 1 and 150 mg on Weeks 2 through 8) or placebo (n=3). Study P006 remains ongoing and blinded to treatment at the participant-level.

MK-3655 exposure versus time profiles and PK data suggest MK-3655 displays nonlinear kinetics at lower doses, which is anticipated for a mAb that displays target-mediated clearance. Based on the 120 mg, 240 mg, and 360 mg SAD dose cohorts in P004, the mean half-life ($t_{1/2}$) increased from approximately 9 days to 14 days with increasing dose level.

PK data from the P002 study indicate that the geometric mean $AUC_{D29\text{-}57}$ (989 day*µg/mL), representative of the highest exposures anticipated to be achieved over any 28-day interval in that study, was approximately 2.5-fold greater than the 28-day AUC reported following a single dose of 360 mg in Study P004 and approximately 3.3-fold greater than the 28-day AUC following 240 mg Q4W for 3 months. In the multiple-dose panel of Study P003, the 28-day AUC following the eighth weekly dose was 1065.80 day*µg/mL.

The ADA results from the completed clinical studies (P002, P003, P004, P005) suggest that the incidence of treatment-boosted and treatment-emergent positive participants was <10%. The ADA titer values in these studies were near the limit of detection. In addition, the

presence of ADA did not appear to affect the PK profiles in these subjects relative to other subjects in the same dose group who were negative for ADA.

PD data from the Phase 1 studies demonstrated that MK-3655 appears to be pharmacologically active for at least 4 weeks as evidenced by increased adiponectin, increased insulin sensitivity, and improved fasting lipid profiles including marked reductions in TG, more modest increases in HDL-C, and decreases in LDL-C. Effects on adiponectin and fasting lipids are sustained during multiple dosing with MK-3655 in overweight/obese participants. Improvement in insulin sensitivity has been most clearly demonstrated in Study P005 using hyper-insulinemic-euglycemic clamp following a single dose of MK-3655 in overweight/obese, insulin-resistant participants with elevated LFC. In other Phase 1 studies, among overweight/obese individuals who were not specifically selected for baseline insulin resistance, insulin sensitivity as estimated by HOMA-IR remained similar to baseline or trended toward greater insulin sensitivity following multiple doses of MK-3655. Furthermore, data from Study P005 showed that over 3 to 5 weeks after a single 240 mg dose of MK-3655, LFC measured by MRI-PDFF was substantially reduced.

Single and multiple doses of MK-3655 were generally well tolerated in the clinical program. No deaths have occurred. No drug-related SAEs have been reported. No anaphylactic or immune-mediated AEs have been reported. The majority of AEs have been mild or moderate.

The AE of increased appetite has occurred only in participants randomized to MK-3655 and has appeared to be more common at higher doses. Of participants randomized to MK-3655; 9.5% who received a single dose in the SAD portion and 37.7% who received multiple doses in the MAD portion in Study P004, 11.8% who received a single dose in Study P005, and 66.7% who received multiple doses in Study P002 reported AEs of increased appetite. None of the participants randomized to placebo or comparator drug in the Phase 1 studies have reported increased appetite. Notably, no participants in Study P003 reported increased appetite even though this study assessed single doses of MK-3655 tested in Study P004 and the multiple-dose regimen of MK-3655 tested in Study P002. No other AEs appeared to be potentially dose-related. The reason for the difference in occurrence of increased appetite AEs in Study P003 and other Phase 1 studies is unknown.

In contrast to the weight loss observed in NHPs, weight gain has been observed with MK-3655 treatment in humans. Body weight increased following single and multiple doses of MK-3655. Weight gain generally continued beyond the final dose, likely due to the long $t_{1/2}$ and biological activity of MK-3655. Throughout dosing and follow-up periods, body weight gain occurred in the context of unchanged or improved metabolic parameters relative to baseline including reduced hepatic fat, greater insulin sensitivity, reduced TG, and increased HDL-C.

In the MAD portion of Study P004, weight continued to increase over time in the MK-3655 groups. Following 3 monthly doses of MK-3655 in healthy overweight participants, statistically significant mean weight gain was observed at Day 85 in the 120 mg (3.90 kg ± 3.84 kg, p=0.007) and 240 mg (3.30 kg ± 2.90 kg, p<0.001) dosing groups. Weight gain in the placebo group was not significant (1.03 kg ± 3.36 kg, p=0.313). At the end of the follow-

up period on Day 141, nominal mean weight gain from baseline was observed in the 60 mg (3.78 kg ± 8.09 kg), 120 mg (4.67 kg ± 3.61 kg), and 240 mg (5.27 kg ± 3.48 kg) dosing groups. Lesser nominal weight gain from baseline was observed in the placebo group at Day 141 (0.63 kg ± 5.57 kg). No statistics were performed for weight change at Day 141.

Weight gain was also observed among participants randomized to multiple doses of MK-3655 in Study P002 and Study P003. In these studies, the final dose of MK-3655 was administered on Day 50 and weight gain continued for several weeks after the final dose up to a maximum placebo adjusted increase of 5% to 6% from baseline. The trajectory and magnitude following 150 mg Q1W dosing was similar to that following 120 mg Q4W or 240 mg Q4W dosing, suggesting that dosing regimens ≥120 mg Q4W do not result in greater weight gain. Clinical assessments, including physical examination and laboratory values, do not support fluid retention as a major contributor to weight gain. Exploratory analyses in the MAD module of Study P004, in Study P002 and in Study P003 using DXA measurements suggest the observed increase in body weight is due to increased accumulation of adipose tissue.

In both the P002 study and P003 study, greater increases in mean pulse and ventricular rate change from baseline were seen in the MK-3655 group than in the placebo group, but the between-group differences were typically small in magnitude and of uncertain clinical significance. Additionally, no meaningful differences in systolic or diastolic blood pressure were observed between the MK-3655 group and the placebo in either study.

Based on the clinical program to date, which has explored exposures above those planned for this study, no signals have been identified that would preclude further clinical development.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

In clinical studies to date, MK-3655 was found to be well tolerated with a favorable safety profile. Importantly, MK-3655 demonstrates a robust and clinically meaningful reduction in LFC as well as other beneficial metabolic effects including insulin sensitization, increased HDL-C, and decreased TG and LDL-C.

Each participant will have up to 2 liver biopsies. A liver biopsy is the gold standard for the assessment of fibrosis stage and disease progression in NASH patients and will be performed in this study. Although pain and bruising at the biopsy or incision site are the most common complications after a liver biopsy, infection and injury to another organ or prolonged bleeding from the biopsy or incision site may also occur.

Given the lack of available treatment options for patients with pre-cirrhotic NASH, the serious potential health risks of progressive fibrosis and cirrhosis, and the available preclinical and clinical data summarized above and in the IB that indicate MK-3655 may be

an effective and treatment for NASH, the benefit-to-risk assessment for conducting this study well tolerated is considered to be favorable.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In males and females aged 18 to 80 years (in Japan and Taiwan, aged 20 to 80 years [Appendix 7]) with pre-cirrhotic NASH:

Objectives	Endpoints
Primary	
To evaluate the effect of each dose of MK-3655 versus placebo on the proportion of individuals with NASH resolution without worsening of fibrosis after 52 weeks. Hypothesis (H1): At least 1 dose of MK-3655 is superior to placebo with respect to the proportion of individuals with NASH resolution without worsening of fibrosis after 52 weeks.	• NASH resolution (defined as a score of 0-1 for inflammation, 0 for ballooning, and any grade of steatosis) without worsening of fibrosis assessed with the NASH CRN scoring system (evaluated by BICR)
To evaluate the safety and tolerability of MK-3655 compared with placebo.	• AEs • Discontinuation of study intervention due to AEs
Secondary	
To evaluate the effect of each dose of MK-3655 versus placebo on mean percent relative reduction from baseline in LFC after 24 weeks.	• LFC (%) measured by MRI-PDFF (evaluated by BICR)
To evaluate the effect of each dose of MK-3655 versus placebo on the proportion of individuals with ≥1 stage improvement in fibrosis without worsening of steatohepatitis after 52 weeks.	• ≥1 stage improvement in fibrosis without worsening of steatohepatitis (defined as no increase in the ballooning, inflammation, or steatosis scores) assessed with the NASH CRN scoring system (evaluated by BICR)

Objectives	Endpoints
To evaluate the effect of each dose of MK-3655 versus placebo on the proportion of individuals with ≥2 point improvement in the NAS without worsening of fibrosis after 52 weeks.	• ≥2 point improvement in the NAS with ≥1 point improvement in inflammation or ballooning without worsening of fibrosis assessed with the NASH CRN scoring system (evaluated by BICR)
Tertiary/Exploratory	
To evaluate the effect of each dose of MK-3655 versus placebo on change from baseline in glycemic responses after 52 weeks.	• A1C (glycated hemoglobin) • FPG
To evaluate the effect of each dose of MK-3655 versus placebo on change from baseline in lipid levels after 52 weeks.	• Lipid profile: cholesterol (total, non-HDL-C, HDL-C, LDL-C) and TG • apoA1 and apoB
To evaluate the effect of each dose of MK-3655 versus placebo on change from baseline in NASH-specific quality of life, health state, and global severity of symptoms after 52 weeks.	• Total score and domain scores as measured by CLDQ NAFLD-NASH • Rating of global severity of symptoms measured by PGI-S • Health state description and evaluation by EQ-5D-5L
To evaluate the PK of each dose of MK-3655 at Weeks 0, 4, 8, 12, 24, 52, and 56.	• MK-3655 (serum PK): Trough concentration
To evaluate ADA to each dose of MK-3655 at Weeks 0, 4, 12, 24, 52, and 56.	• ADA to MK-3655: Incidence and magnitude (titer)
To evaluate the effect of each dose of MK-3655 versus placebo on change from baseline on PD parameters through Week 52.	• Adiponectin • Fasting insulin • HOMA-IR • FFA • Body composition assessed by DXA • Biomarkers/panels reflecting liver inflammation and fibrosis including routine liver tests (ALT, AST), FIB-4, NFS, APRI, and Pro-C3

Objectives	Endpoints
To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, PD activity, and/or the mechanism of action of MK-3655.	• Molecular (genomic, metabolic, and/or proteomic) determinants using blood and/or tissue and association to response
To explore the relationship between genetic variation, including but not limited to PNPLA3, TM6SF2, MBOAT7, GCKR, HSD17B13, PPP1R3B, and LYPLAL1 and response to the intervention(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	• Germline genetic variation and association to response

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2b, multi-site, randomized, placebo-controlled, parallel-group, double-blind, study of MK-3655 in participants with pre-cirrhotic NASH. This study will be conducted in conformance with GCP.

The duration of the study will be approximately 72 weeks (with up to 16 clinic visits) for each participant. This will include a 6-week (±28 days) screening period (Visit 1 through Visit 3); a 2-week single-blind placebo run-in period (Visit 4 up to Visit 5); a 52-week double-blind, placebo-controlled treatment period (Visit 5 through Visit 15/Week 52); a post-treatment follow-up visit (Visit 16) at 4 weeks after Visit 15; and post-treatment follow-up telephone contacts at Weeks 60 and 64.

Approximately 328 males and females aged 18 to 80 years (in Japan and Taiwan, aged 20 to 80 years [Appendix 7]) with histological confirmation of NASH, NAS ≥4 with a score ≥1 point in each component (steatosis, ballooning, and lobular inflammation) and a fibrosis score of Stage 2 or 3, will be randomized in this study to evaluate the efficacy and safety of MK-3655 compared with placebo.

Management of Participants Before Randomization

During the 6-week (±28 days) screening period (Visit 1 through Visit 3), participants will be evaluated for study eligibility using the staged process detailed below; Visit 1/Screening, Visit 2/MRI-PDFF, and Visit 3/Liver Biopsy. Eligibility for continued study participation will be assessed at Visits 1, 4, and 5 based on the criteria detailed in Section 5.

At Visit 1/Screening, consented participants will complete all Visit 1 procedures as detailed in the SoA, as well as be assessed for the availability of historical liver biopsy samples. Liver biopsies conducted within 6 months of Visit 1/Screening, for which slides can be obtained and submitted to the central laboratory vendor for BICR, are considered adequate for study entry as long as the tissue sample is considered adequate for evaluation by the central reader(s) and all criteria specified in Sections 5.1 and 5.2 are met.

Screening management after Visit 1/Screening and before Visit 4/Placebo Run-in will occur as follows:

- Participants with a historical liver biopsy performed within 6 months before Visit 1/Screening:
    - Safety laboratory tests (ie, liver function, renal function, and hematological parameters) must meet study eligibility criteria assessed at Visit 1/Screening before proceeding to Visit 2/MRI-PDFF. Other pending Visit 1/Screening laboratory assessment results are not required to proceed to Visit 2/MRI-PDFF.
        - **Note**: Participants will be screen failed for any exclusion criteria identified during Screening.
    - Biopsy samples will be submitted to the central laboratory vendor for processing and BICR if safety laboratory tests (ie, liver function, renal function, and hematological parameters) meet study eligibility criteria assessed at Visit 1/Screening.
    - Visit 2/MRI-PDFF may be scheduled/performed before receipt of the liver biopsy report from the central laboratory vendor.
    - If LFC by MRI-PDFF is ≥8% as determined by BICR at the iCRO, histology from the liver biopsy meets study entry criteria, and all other eligibility criteria are met, the participant will proceed to Visit 4/Placebo Run-in.
        - If LFC by MRI-PDFF or liver histology does not meet study eligibility criteria, the participant will be screen failed.

      Note: If the historical liver biopsy cannot be assessed for any reason (including sample quality), the participant, if agreeable, will proceed through screening procedures consistent with the process below for participants who do not have a historical liver biopsy within 6 months of Visit 1/Screening.

Participants without a liver biopsy performed within 6 months before Visit 1/Screening:

- Safety laboratory tests (ie, liver function, renal function, and hematological parameters) must meet study eligibility criteria assessed at Visit 1/Screening before proceeding to Visit 2/MRI-PDFF.
    - **Note**: Other pending Visit 1/Screening laboratory assessment results are not required to proceed to Visit 2/MRI-PDFF. Participants will be screen failed for any exclusion criteria identified during Screening.

- If LFC by MRI-PDFF is ≥8% as determined by BICR at the iCRO and all other Visit 1/Screening eligibility criteria are met, the participant will progress to Visit 3/Liver Biopsy.
- If liver histology meets study eligibility criteria at Visit 3 and all other eligibility criteria are met, the participant will proceed to Visit 4/Placebo Run-in.
- If a participant does not meet study eligibility criteria for LFC (Visit 2) or liver histology (Visit 3), they will be screen failed following that visit.

Placebo Run-in

Eligible participants will enter the 2-week, single-blind, placebo run-in period at Visit 4/Week -2 and will:

- Receive training/instructions on the preparation and self-administration of the investigational product and be witnessed in the administration of two 1.5 mL subcutaneous injections of single-blind investigational product.

  Note: Participants will be re-instructed on appropriate injection technique as needed based on observed injection experience.

- Receive a diary that will be used throughout the study to record experience with self-injection and immediate/delayed injection reactions.

- Receive dietary and activity counseling. Note, at subsequent study visits as specified in the SoA, the participant will review the diet and activity guidance sheets. Counseling will be provided.

- Be assessed for suicidal ideation and behavior using the C-SSRS and depression severity using the PHQ-9.

- Have DXA imaging performed to assess baseline body composition and BMD. If the DXA image is unusable due to failing quality control requirements, it will not be repeated.

Participants meeting study entry eligibility criteria at Visit 4/Placebo Run-in as detailed in Sections 5.1 and 5.2, will proceed to Visit 5/Randomization.

Management of Randomized Participants

At Visit 5/Day 1, participants who meet eligibility criteria will enter the 52-week double-blind treatment period. Participants (82 per group) will be randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups: (1) MK-3655 50 mg Q4W, (2) MK-3655 100 mg Q4W, (3) MK-3655 300 mg Q4W, and (4) matching placebo. Participants will administer 2 subcutaneous injections at a volume of 1.5 mL each once every 4 weeks.

Randomization will be stratified according to: (1) concurrent diagnosis of T2DM at the time of randomization, (2) fibrosis score (Stage 2 or 3), and (3) region (Japan, East Asia excluding

Japan, or Other). If either proportion of participants, those with T2DM or those without T2DM, exceeds approximately 60% of the total targeted sample size, the remaining participants enrolled will be restricted to the other stratum within this stratification factor. **Note**: In Japan, enrollment will not be restricted by this cap, and sites will be able to continue to enroll participants with or without T2DM (see Appendix 7).

After completing the 52-week double-blind, placebo-controlled treatment period, participants will enter the post-treatment period and complete a follow-up visit 4 weeks after Visit 15/Week 52. Post-treatment follow-up telephone contacts will be performed for all participants at Weeks 60 and 64.

AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE, Version 5.0 (see Section 10.14). Regular safety assessments will be performed during the study (see Section 8.3).

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

There will be a non-binding IA performed once ≥25 participants per group have been randomized and have completed an MRI-PDFF at the 24-week post-randomization assessment. The IA will include a review of MRI-PDFF and safety data. Results of the IA will be reviewed by an eDMC, who will make a recommendation to continue, modify, or end the study according to the plan to be described in detail in the eDMC charter.

4.2 Scientific Rationale for Study Design

The goals of this Phase 2b study design are to provide evidence of efficacy on histological endpoints (including NASH resolution and improvement in fibrosis), to obtain adequate dose response information to support dose selection for the Phase 3 program, and to assess safety and tolerability over 52 weeks in the intended treatment population.

The MK-3655 dose range of 50 mg to 300 mg Q4W evaluated in this study is expected to enable the identification of the optimal dose and treatment frequency for Phase 3 while balancing efficacy, safety, and convenience.

The study treatment period of 52 weeks is based on the timeframe in which a histological response with MK-3655 treatment is expected; informed by the experience of other NASH programs and for consistency with agency recommendations [European Medicines Agency 2018] [Neuschwander-Tetri, B. A., et al 2015] [Food and Drug Administration 2018] [Ratziu, V., et al 2016]. The study design will enable characterization of the treatment effect size and variability around the histological endpoints to support planning of statistical analyses and powering for Phase 3 studies.

The incorporation of an IA will allow for review of interim efficacy and safety data to inform administrative decisions regarding other aspects of the MK-3655 program, and to support

potential termination of the study for futility based on poor LFC (MRI-PDFF) response and/or safety/tolerability issues.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

One of the key goals of this study is to demonstrate the efficacy of MK-3655 in the treatment of individuals with pre-cirrhotic NASH. The primary efficacy endpoint is NASH resolution (defined as a score of 0-1 for lobular inflammation, 0 for ballooning, and any grade of steatosis) without worsening of fibrosis after 52 weeks of treatment. The primary efficacy endpoint is a histological assessment of paired liver biopsies (baseline and end of 52 weeks of treatment) performed centrally and blinded to time point, participant, and clinical information. The key features of NASH (ie, lobular inflammation, ballooning, and steatosis) and changes in fibrosis will be evaluated according to the NASH CRN scoring system (see Section 8.2.2 and Appendix 12), which is a validated, semi-quantitative tool used to assess treatment response and provides a reliable way to define and quantify the severity of ongoing liver injury as assessed by a liver biopsy. The NASH CRN scoring system assesses NASH activity and fibrosis stage based on the following scoring scales: lobular inflammation score (0-3); hepatocyte ballooning score (0-2); steatosis score (0-3); and fibrosis score (0-4). The NAS is calculated as the unweighted sum of the scores for inflammation, ballooning, and steatosis and ranges from 0-8 (highest activity).

The main secondary efficacy endpoint is the mean percent relative reduction from baseline in LFC measured by MRI-PDFF after 24 weeks of treatment with the data analysis performed by a central reading center. MRI-PDFF is a highly accurate noninvasive measure of the proportion of fat content of a tissue. This technique separates the water and fat signals in the image using the difference in magnetic resonance frequencies of protons in water and fat. It represents the percentage ratio of fat signal over the sum of fat and water signal. MRI-PDFF can be used for measuring LFC over the entire liver and is usually reported as a single value averaged over the whole liver. MRI-PDFF is an established methodology for quantitative assessment of LFC that has been assessed as a primary or secondary endpoint in some Phase 2 clinical development programs for NASH [Madrigal Pharmaceuticals, Inc. 2017] [Bautz, D. 2018] [Harrison, S. A., et al 2018].

The other secondary efficacy endpoints are histological assessments to support the primary efficacy endpoint and include: (1) at least 1 stage improvement in fibrosis without worsening of steatohepatitis (defined as no increase in the NAS for ballooning, inflammation, or steatosis) after 52 weeks and (2) at least a 2 point improvement in the NAS including at least 1 point improvement in inflammation or ballooning, without worsening of fibrosis after 52 weeks.

Exploratory efficacy endpoints that will be assessed include glycemic and lipid metabolism. Glycemic efficacy endpoints will include the changes from baseline after 52 weeks of treatment in A1C and FPG. A1C reflects average glucose concentrations over the past 3 to 4 months and, therefore, provides a useful index of the glycemic control of MK-3655 over that period. The measurement of FPG will provide insight into the effects of MK-3655 on

this endpoint and characterize the earlier time course of glucose control in this study. Lipid metabolism endpoints will include changes in baseline after 52 weeks of treatment in cholesterol (total, non-HDL-C, HDL-C, LDL-C), TG, apoA1, and apoB. These parameters provide insight into the effects of MK-3655 on this endpoint and characterize the time course of lipid metabolism in this study.

4.2.1.2 Patient-Reported Outcomes

An evaluation of PROs at Week 0 and Week 52 of treatment will be conducted using the CLDQ NAFLD-NASH, PGI-S, and EQ-5D-5L. An assessment of disease impact and treatment experience from the participant's perspective can provide important information in evaluation of benefits and risks of a developing medical product. These questionnaires will be used to supplement information obtained from the primary and secondary endpoints.

CLDQ NAFLD-NASH

The CLDQ NAFLD-NASH, a NASH-specific version of the CLDQ, measures disease-specific health-related quality of life. The CLDQ NAFLD-NASH consists of 36 questions divided into 6 domains: abdominal symptoms, activity, emotional, fatigue, systemic symptoms, and worry. The CLDQ NAFLD-NASH has a 7-point Likert-type response scale ranging from 1 (all the time) to 7 (none of the time) with "1" indicating most impairment and "7" indicating least impairment. The recall period is "during the last 2 weeks". The CLDQ NAFLD-NASH was first validated in patients with NAFLD, and later validated in NASH populations, in 2 separate studies [Younossi, Z. M., et al 2017] [Younossi, Z. M., et al 2019].

PGI-S

To help interpret the data from the CLDQ NAFLD-NASH, a PGI-S question will be included in this study and responses will be used as an anchor for characterizing clinically meaningful changes. The PGI-S is a single-item question for assessing the severity of overall symptoms associated with fatty liver disease. The response options of the PGI-S include: no symptoms, mild, moderate, severe, and very severe. Consistent with CLDQ NAFLD-NASH, the recall period is "past 2 weeks". Information from anchor-based analysis using data from this study will provide the basis for a CLDQ NAFLD-NASH total score characterization which will be useful to interpret PRO data collected within future confirmatory studies. The anchor-based approach is proposed in accordance with the 2009 FDA Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims [U.S. Food and Drug Administration 2009].

EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels and the participant will be asked to indicate their health state using a 5-level rating scale. The EQ visual analog scale records the participant's self-rated health on a

vertical visual analog scale where the endpoints are labeled “best imaginable health state” and “worst imaginable health state”. This information can be used as a quantitative measure of health outcome as judged by the individual participant.

4.2.1.3 Safety Endpoints

The safety data for MK-3655 to date has been described in detail in Section 2.2.2 and in the IB.

In support of the safety objective to evaluate the safety and tolerability profile of MK-3655, the safety and tolerability endpoints will be assessed by clinical evaluation of AEs (including adjudication of malignancies and CV events) and inspection of other study parameters including vital signs (ie, heart rate, blood pressure, temperature), body weight, physical examination, standard laboratory safety tests, 12-lead ECGs, ketone levels, BMD by DXA, and evaluation of biomarkers of bone formation (P1NP) and resorption (CTX) will be performed. Additional class-related hypothalamic-pituitary function safety endpoints will be assessed including bedtime salivary cortisol, ACTH, TSH, FT4, and IGF-1.

All procedures will be conducted at the time points specified in the SoA. AEs will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE, Version 5.0 (see Section 10.14). **Note**: For AEs that are an exception to the NCI CTCAE grading, see Section 7.1.

4.2.1.4 Pharmacokinetic Endpoint

The PK endpoint for MK-3655 is C_{trough} taken before dose administration. PK samples will be collected from all participants on each visit as described in the SoA (Section 1.3) and in Table 5. These samples will be used to evaluate not only PK concentrations, but also PK/PD and PK/AE relationships of MK-3655 via modeling exercises, as appropriate.

4.2.1.5 Immunogenicity Endpoints

Immunogenicity to MK-3655 will be described as the results of the ADA assay from samples taken during the double-blind treatment period (Visits 5, 6, 8, 11, and 15) and during the post-treatment period (Visit 16). ADA samples will be collected before the administration of study intervention (if applicable) and from all participants. The incidence and magnitude (titer) of ADA positive participants and potential effects of ADA on PK, PD, and safety will be reported, as appropriate.

4.2.1.6 Pharmacodynamic Endpoints

PD endpoints that will be assessed include changes from baseline through Week 52 in adiponectin, HOMA-IR, fasting insulin, fasting FFAs, body composition assessed by DXA, and biomarkers reflecting liver inflammation and fibrosis.

Adiponectin is a protein produced by adipocytes and an established marker for FGFR1c/KLB target engagement at adipose tissue that may potentially mediate some of the beneficial

therapeutic effects of MK-3655 on the liver. Adiponectin has been demonstrated preclinically to have an anti-fibrotic action in the liver and epidemiological studies have shown that low adiponectin levels are associated with NASH independent of insulin resistance and BMI [Fitzpatrick, E. 2014] [Targher, G., et al 2004].

HOMA-IR (fasting glucose [mmol/L] multiplied by fasting insulin [µU/L], then divided by the constant 22.5) has been widely used for the estimation of insulin resistance [Matthews, D. R., et al 1985]. The anti-steatotic effect of MK-3655 is expected to be due, in part, to improved adipose insulin sensitivity resulting in decreased trafficking of FFA from adipose to the liver. Therefore, fasting FFA will be assessed to inform on the therapeutic mechanism of MK-3655. Body composition will be assessed by DXA; a validated, fast, reproducible, noninvasive method of assessing body composition.

Since fibrosis stage is a major predictor of liver-related mortality, the evaluation of liver inflammation and fibrosis are critical in the management of patients with NAFLD. The following biomarkers or composite scores will be assessed as potential metrics for estimation of baseline severity of liver inflammation and fibrosis and/or response to treatment: routine liver tests (ALT, AST), FIB-4, NFS, APRI, and Pro-C3. These noninvasive biomarkers or composite scores will be used to supplement information obtained from the primary and secondary efficacy endpoints (see Section 8.8.2).

4.2.1.7 Planned Exploratory Biomarker Research

MK-3655 is intended to deliver therapeutic benefit through targeting a mechanism of action (FGFR1c/KLB agonism) that has demonstrated promising pharmacology regarding liver fat, insulin sensitivity, and lipid profiles in MK-3655 studies and in studies of FGF21 and FGF19 analogs. However, the mechanisms through which these effects are achieved are not completely understood. Therefore, much remains to be learned regarding how MK-3655 works and how it may be best used to treat patients with NASH. To aid future patients, it is important to investigate, in our clinical studies, the determinants of therapeutic response to MK-3655 as well as any safety/tolerability issues associated with MK-3655. Additionally, there is a critical need in the NASH field for the development of noninvasive approaches to the diagnosis, risk stratification, and treatment response monitoring for patients with NASH. Therefore, it is also important to investigate potential strategies to address these gaps.

To aid in these efforts, exploratory assessments of known and/or unknown biomarkers may be performed. Specifically, blood samples will be collected to enable exploratory analyses of circulating molecules (eg, protein, DNA, RNA, metabolites). In addition, exploratory assessments of liver biopsy tissue (eg, alternative methods for quantifying fibrosis, immunohistochemical analyses to assess specific cell populations, gene expression analyses) maybe also performed. Such exploratory histologic analyses will not require collection of liver tissue beyond that collected to address the specified study objectives.

4.2.1.7.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants

that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

In addition to studying variation across the human genome, genes previously associated with NASH will specifically be investigated to assess their relationship to treatment response including: PNPLA3, TM6SF2, MBOAT7, GCKR, HSD17B13, PPP1R3B, and LYPLAL1.

4.2.1.8 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

A placebo group is included in this study to maintain the study blind; allowing for an unbiased assessment of efficacy and safety. Additionally, placebo-controlled studies are considered the most rigorous design to determine the risks and benefits of a new treatment.

4.2.3 Rationale for Suicidal Ideation and Behavior Monitoring

Prospective assessment of suicidal ideation and behavior will be performed in this study using the C-SSRS. This assessment is being conducted in compliance with the 2012 FDA guidance requiring prospective assessment in clinical studies conducted under IND

applications and studies that are intended for submission in a NDA or BLA to the Neurology or Psychiatry Divisions of the FDA, as well as assessment in studies that fall within the guidance for other reasons (eg, CNS active/penetrant compounds, and known mechanisms or indications for which suicidal ideation/behavior has been previously identified as a potential concern).

Published human gene expression profiling data indicate that KLB and FGFR1c may be co-expressed in the CNS [Talukdar, S., et al 2016]. Though penetrance into the CNS for a mAb, such as MK-3655, is typically low, it is unknown whether CNS concentrations of MK-3655 are high enough to exert a pharmacologic effect. Though there are no specific psychiatric concerns for the KLB/FGFR1c target, it has not been well-studied and there may be biological plausibility for psychiatric effects. Additionally, there is a high prevalence of obesity in the NASH population and there is an association of obesity with depression. Therefore, this study will use the C-SSRS for prospective assessment of suicidal ideation and behavior and the PHQ-9 for depression severity during the study.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

Participants will be on a fixed dose regimen of MK-3655 (50 mg Q4W, 100 mg Q4W, or 300 mg Q4W) or matching placebo for the duration of the study.

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose for participants will be 300 mg Q4W. Participants will be exposed to MK-3655 for approximately 52 weeks. For more information, see Section 6.1 and Section 8.1.9.

4.3.3 Rationale for Dose Interval and Study Design

In Phase 1 single and multiple ascending dose testing, MK-3655 demonstrated good safety and tolerability, a PK profile potentially consistent with monthly dosing by subcutaneous administration, and biomarker confirmation of robust on-target pharmacology. To identify optimal doses and regimens for further development we will use three Q4W dose groups in this study design.

The dose range for this study was selected based on several different PK/PD analyses assessed from Phase 1 data, which reflect target engagement and/or presumed target-mediated pharmacology including adiponectin, TG, HDL-C, HOMA-IR, and MRI-PDFF-assessed LFC. Currently, the relationship between changes in these biomarkers and the histologic efficacy is unknown. Based on these analyses, the low dose of 50 mg Q4W is predicted to achieve discernable, but sub-maximal LFC reduction and improvements in other PD biomarkers assessed, while 300 mg Q4W is predicted to deliver near-maximal or maximal responses in those same measurements.

Steady state exposures at the 300 mg Q4W dose level in Phase 2b is currently predicted to exceed those of the chronic toxicology NOAEL (AUC_{D0-28}: 146 day*µg/mL) by 3.2-fold, though remain well below the highest exposures assessed in the chronic toxicology study (AUC_{D0-28}: 5875 day*µg/mL). As noted in Section 2.2.2.2, single and multiple doses of MK-3655 were generally well tolerated in the clinical program, including the 150 mg Q1W dose regimen of MK-3655 has been generally well tolerated in the multiple-dose Phase 1 study P002 and the multiple-dose portion of the Phase 1 study in Japanese participants P003. Exposures in P002 and P003, over the last 4 weeks of dosing were approximately 6.8-fold and 8.2-fold, respectively, greater than those at the chronic toxicology NOAEL and approximately 2.1-fold and 2.6-fold, respectively, greater than those predicted for the 300 mg Q4W dose arm in this study.

Exceeding the NOAEL in this study is considered appropriate given the nature of the toxicities and the mitigations incorporated in the protocol. The dose-limiting weight loss observed in NHPs does not appear to translate to humans given the modest weight gain observed in Phase 1 and would be easily detected through the frequent body weight assessments in this study.

Published nonclinical data suggest potential for a weight-independent, mechanism-based effect of FGF21 on bone [Wei, W., et al 2012] [Owen, B. M., et al 2015]. Administration of one FGF21 analog in humans resulted in bone biomarker changes consistent with net bone loss, though there was potentially confounding concurrent weight loss [Talukdar, S., et al 2016]. Notably, there was no evident impact of MK-3655 on biomarkers of bone formation (P1NP) or resorption (CTX) or on DXA-assessed BMD over 12 weeks of dosing in the MAD part of MK-3655 P004 study (NGM 15-0201). There was also no evident impact of MK-3655 on P1NP or CTX over 8 weeks of dosing in MK-3655 P002 in which exposures over the last 4 weeks of dosing (AUC_{D29-57}: 989 day*µg/mL) were approximately 2-fold greater than those predicted for the top (300 mg Q4W) dose arm in this study and approached the exposures at which decreased bone mineral content was observed in female NHPs ($\geq AUC_{D0-28}$: 971 day*µg/mL). The observed trend to reversibility of the bone mineral content effect in chronic toxicology provides additional reassurance regarding safety for study participants.

Menstrual cycle prolongation, which was previously observed in the chronic toxicity study, was not recapitulated at comparable MK-3655 exposures in a 4-month repeat-dose study dedicated to assessing menstrual cyclicity in cynomolgus monkeys. MK-3655 treatment resulted in substantial body weight loss but did not cause menstrual cycle changes in a large cohort of regularly cycling NHP evaluated in this study. At the NOEL of the NHP menstrual cyclicity study, MK-3655 exposure was 2-fold higher than the projected clinical exposure at 300 mg Q4W. Based on these data, menstrual cycle changes in the chronic toxicity study are attributed to normal variability in length of menstrual cycles in NHP, changes in social housing conditions, and/or stress/poor body condition resulting from body weight loss. Therefore, the totality of the MK-3655 nonclinical data indicate that MK-3655 does not cause menstrual cycle changes in cynomolgus monkeys. Further, based on the totality of the nonclinical data, there is no evidence that MK-3655 will impact fertility in female or male participants (see IB).

This study population will include premenopausal and postmenopausal women and will follow CTFG guidance for investigational products with demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy [Heads of Medicines Agencies 2020]. Concerns related to the potential for developmental toxicity are based on nonclinical FGF21 data that suggest that KLB/FGFR1c agonism may affect fetal growth, bone development/growth, and adipose tissue development. All WOCBP included in this study will be required to use a contraceptive method that is highly effective (with low user dependency) throughout the treatment period and through the post-treatment follow-up period. Additionally, WOCBP must have a negative highly sensitive pregnancy test within 24 hours before the first dose of study intervention and a pregnancy test conducted at monthly intervals during the treatment and post-treatment follow-up periods (see Sections 5.1, 8.3.10, and 10.5.2). As preclinical developmental toxicity studies have not been conducted with MK-3655, no specific exposure threshold for developmental risk has been identified. Contraception and pregnancy testing for WOCBP will continue for 16 weeks after the last dose of MK-3655 (ie, Week 48), by which time complete or near-complete washout of MK-3655 will have been achieved and drug concentrations will have declined to sub-pharmacologic levels. The post-treatment follow-up for all participants will extend through Week 64.

The accrued bone biomarker and DXA data summarized above suggest low risk for MK-3655 to have deleterious bone effects. To expand this characterization, bone biomarkers (P1NP and CTX) and BMD (DXA) will be assessed in this study. To minimize the potential for confounding these assessments, participants will be excluded from study participation if at Visit 1/Screening they have a known history of osteoporosis or other indication for treatment with specified bone-active agents (see Section 5.2). Participants **will not** be excluded if an indication for treatment with the bone-active pharmacological classes of agents listed in Section 5.2 is identified after Visit 1/Screening. This includes any participant diagnosed with osteoporosis by DXA imaging performed during the placebo run-in. The number of such participants is expected to be small, and unlikely to undermine the study-wide characterization of bone biomarker and bone density responses. Such participants will be referred to their personal physician for management of osteoporosis.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent.

The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area, the local start of the study in the European Economic Area is defined as First Site Ready in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

This study may be terminated early by the eDMC for safety concerns or futility based on the results of the IA (see Section 9.7).

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age, race, ethnicity, and sex. The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Males and females with pre-cirrhotic NASH aged 18 to 80 years (in Japan and Taiwan, aged 20 to 80 years [Appendix 7]) will be randomized in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Has histological confirmation of NASH based on a liver biopsy obtained ≤6 months before Visit 1/Screening. If no acceptable biopsy performed ≤6 months before Visit 1/Screening is available, a liver biopsy will be performed at Visit 3/Liver Biopsy. Histological criteria for study entry include:

    - NAS ≥4 with a score ≥1 point in each component (steatosis, ballooning, and lobular inflammation),

        AND

    - NASH CRN fibrosis score of Stage 2 or 3.

2. Has an MRI-PDFF ≥8% as assessed at Visit 2/MRI-PDFF.

    Note: Prior MRI-PDFF imaging of the liver performed ≤2 months before Visit 1/Screening, obtained from the same study-qualified imaging center(s), and imaged per the Site Imaging Manual for this study may be acceptable to determine LFC % as part of eligibility.

3. Has a baseline MELD-Na score ≤12 at Visit 1/Screening.

Demographics

4. Is a male or female aged 18 years to 80 years (in Japan and Taiwan, aged 20 to 80 years [Appendix 7]), at the time of signing the ICF.

5. Has a BMI ≥25 kg/m^2 and ≤50 kg/m^2 at the time of Visit 1/Screening.

6. Has stable weight (based on self-reporting) defined as ≤5% gain or loss of body weight for at least 3 months before Visit 1/Screening.

   Note: For participants whose baseline liver biopsy was obtained before Visit 1/Screening, weight must have been stable for at least 3 months before the date of the historical liver biopsy and through Visit 1/Screening.

7. Meets one of the following criteria:

   - Has no history of T2DM.

     OR

   - Has a history of T2DM with an A1C ≤9.5% at Visit 1/Screening and controlled by diet or stable doses of AHAs.

     Note: See Section 5.2 (Exclusion Criteria) and Table 1 for allowable AHAs and their associated stability definitions.

8. Has a systolic blood pressure of ≤160 mm Hg and a diastolic blood pressure ≤90 mm Hg (after at least a 10-minute seated rest) based on the mean of 3 measurements at Visit 1/Screening **OR** blood pressure is considered likely to be below these limits by Visit 5/Randomization (Day 1) with initiation or adjustment of antihypertensive medication.

   Note: Investigators are encouraged to maximize blood pressure control according to current guidelines before Visit 5/Randomization.

   - The participant may have blood pressure medication initiated or adjusted and be enrolled if repeat blood pressure measurements meet the inclusion criterion at Visit 5/Randomization.

   - Randomization may be rescheduled once by 1 week in an attempt to meet the Visit 5/Randomization blood pressure requirement. If at the rescheduled visit a participant still does not meet the Visit 5/Randomization blood pressure inclusion requirement, they will be screen failed.

   - All participants must meet the blood pressure inclusion requirement at Visit 5/Randomization.

9. Be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and/or other study procedures.

Male Participants

10. Contraceptive use by male participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

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

- Is not a WOCBP

  OR

- Is a WOCBP and:
  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 16 weeks after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

  - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.10.

  - Abstains from breastfeeding during the study intervention period and for at least 16 weeks after the last dose of study intervention.

  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

12. The participant (or legally acceptable representative, if applicable) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the main study without participating in FBR.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has presence of cirrhosis on liver biopsy.
2. Has Type 1 diabetes.
3. Has a history of malignancy, unless cancer free ≥5 years, or is under evaluation for active or suspected malignancy before signing the ICF except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
4. Has a history of bariatric surgery (Roux-en-Y gastric bypass, sleeve gastrectomy, gastric band) ≤5 years before Visit 1/Screening.

   Note: For participants whose baseline liver biopsy was obtained before Visit 1/Screening, there must be no history of bariatric surgery ≤5 years before the liver biopsy and through Visit 1/Screening.
5. Has undergone a major surgical procedure ≤3 months before signing the ICF or has major surgery planned during the study.

   Note: A participant who has undergone minor surgery ≤3 months before Visit 1/Screening and is fully recovered or a participant who has planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving local anesthesia.
6. Has a history or evidence of:

   - Chronic liver disease other than NASH
   - Hepatitis B as defined by the presence of HBsAg
   - Hepatitis C as defined by the presence of HCV RNA or positive Hepatitis C antibody (anti-HCV); participants with a history of HCV infection may be included if HCV PCR is negative ≥3 years

     Note: For participants whose baseline liver biopsy was obtained before Visit 1/Screening, HCV PCR must be negative ≥3 years before the liver biopsy and through Visit 1/Screening.
   - Drug-induced liver disease
   - Ongoing autoimmune liver disease
   - Decompensated liver disease (ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, or other signs or symptoms of advanced liver disease)

- HIV
- Primary biliary cirrhosis (cholangitis)
- Primary sclerosing cholangitis
- Reye Syndrome
- Splenomegaly
- Wilson's disease
- Documented Cushing disease, Cushing syndrome, or any condition associated with hypercortisolism (ie, high amounts of circulating cortisol that may be a pathological or non-pathological condition [eg, functional adrenal adenoma, micronodular and macronodular hyperplasia])
- Hyperthyroidism, and is currently being treated.
- Hypothyroidism, and is on thyroid hormone replacement therapy that has not been at a stable dose for at least 12 weeks prior to Visit 1/Screening.

  Note: Participants who meet this exclusion criterion may be rescreened after being on a stable dose of thyroid hormone replacement therapy for at least 12 weeks.
- Alpha-1-antitrypsin deficiency
- Hemochromatosis or iron overload
- Spontaneous bacterial peritonitis
- Known bile duct obstruction
- Hepatocellular carcinoma
- Untreated obstructive sleep apnea
- Hemostasis disorder (eg, Von Willebrand disease, hemophilia, Factor V Leiden thrombophilia, sickle-cell disease, polycythemia, leukemia)
- Hematological disorder (eg, aplastic anemia, myeloproliferative or myelodysplastic syndromes, thrombocytopenia)

7. Has significant systemic or major illnesses other than liver disease, including recent events (≤6 months before Visit 1/Screening) of congestive heart failure (NYHA functional class III to IV of the American Heart Association), unstable coronary artery disease, arterial revascularization, pulmonary disease, renal failure, stroke, transient ischemic attack, or organ transplantation.

8. Has a known hypersensitivity to any of the ingredients or excipients of the IMP.

9. Has experienced any bone trauma, fracture, or bone surgery ≤2 months before Visit 1/Screening.

10. Has a history of osteoporosis or an indication that requires treatment with a bone-active pharmacological agent in the classes listed in exclusion criterion #18 at Visit 1/Screening.

    Note: Participants **will not** be excluded from study participation if an indication requires treatment with a bone-active pharmacological agent in the classes listed in exclusion criterion #18 that is identified after completion of Visit 1/Screening. This includes any participant diagnosed with osteoporosis by DXA imaging performed during placebo run-in (see Section 4.3.3).

11. Has current or history of significant alcohol consumption for a period of more than 3 consecutive months ≤24 months before Visit 1/Screening. Significant alcohol consumption is defined as approximately 7 standard drinks per week in females and approximately 14 standard drinks per week in males, on average. One standard drink is defined as any beverage containing 14 g of pure alcohol or as defined by local guidelines.

    Note: For participants whose baseline liver biopsy was obtained before Visit 1/Screening, there must be no history of significant alcohol consumption, as defined above, for a period of more than 3 consecutive months ≤24 months before the date of the liver biopsy and through Visit 1/Screening.

12. Has an inability to reliably quantify alcohol consumption.

13. Has a recent history of drug abuse (defined as ≤3 years) or is a current user of recreational or illicit drugs at the time of Visit 1/Screening.

14. Has a known psychiatric or any other cognitive disorder per the opinion of the investigator, that would interfere with the participant's ability to cooperate with the requirements of the study.

15. Is at imminent risk of self-harm, based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive response to item 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the past 2 months or suicidal behavior in the past 6 months. See Section 8.3.11.1.1 for further details.

16. Has a total score >12 on the PHQ-9 (see Section 8.3.11.1.2).

    Note: If a participant's score on Question #9 of the PHQ-9 is ≥1 (see Appendix 11), but the participant answered "No" to all the questions on the C-SSRS, the investigator must reconcile the discrepancy to determine a participant's study eligibility.

Prior/Concomitant Therapy

17. Is on treatment with or has been treated with the following agents:

- Within ≤12 months before Visit 1/Screening:
  - Thiazolidinediones (ie, pioglitazone, rosiglitazone)
  - Investigational agents:
    - Investigational PPAR-gamma activators (eg, lanifibranor)
    - FXR agonists (eg, obeticholic acid, cilofexor [GS-9674], tropifexor [LJN452])
    - FGF21 analogs (eg, pegbelfermin [BMS-986036], efruxifermin [AKR-001], BIO89-100)
    - Aldafermin (NGM282)
    - BFKB8488A (KLB/FGFR1c-activating antibody)

  Note: For participants whose baseline liver biopsy was obtained before Visit 1/Screening, the use of these agents is prohibited ≤12 months before the date of the liver biopsy and through Visit 1/Screening.

- Within ≤6 months before Visit 1/Screening:
  - L-ornithine L-aspartate
  - Investigational agents:
    - Thyroid hormone receptor beta-agonists including resmetirom (MGL-3196) and VK2809
    - DGAT2 inhibitors including PF-06865571 and ION224
    - ACC inhibitors including firsocostat (GS-0976) and PF-05221304

  Note: For participants whose baseline liver biopsy was obtained before Visit 1/Screening, the use of these agents is prohibited ≤6 months before the date of the liver biopsy and through Visit 1/Screening.

18. Is on treatment with or has used bone-active agents in the classes listed below ≤24 months before Visit 1/Screening:

    - Bisphosphonates
    - Calcitonin
    - Selective estrogen receptor modulator (estrogen receptor agonist/antagonist)
    - PTH and PTH analogs
    - RANK ligand inhibitor
    - Anti-sclerostin antibody
    - Aromatase inhibitors
    - GnRH agonists

    Note: Participants **will not** be excluded from study participation if agents from these classes are initiated based on an indication identified after completion of the Visit 1/Screening. This includes any participant diagnosed with osteoporosis by DXA imaging performed during the placebo run-in (see Section 4.3.3).

19. Is on treatment with or has used drugs associated with NAFLD ≤6 months before Visit 1/Screening:

    - Amiodarone
    - Anabolic steroids
    - Chemotherapeutic agents (ie, 5-fluorouracil, tamoxifen, irinotecan, cisplatin, and asparaginase)
    - Cocaine
    - Dronedarone
    - Estrogens at doses greater than those used for hormone replacement or contraception
    - Methotrexate
    - Nucleoside reverse transcriptase inhibitors
    - Tetracycline (intravenous administration at high doses)
    - Valproic acid

- Other known hepatotoxins

Notes:

- Drugs known to be hepatotoxic (ie, drugs with a warning of hepatotoxicity in the package insert) should be avoided during the administration of study intervention.
- The maximum allowable dose of acetaminophen is 4000 mg/day.
- For participants whose baseline liver biopsy was obtained before Visit 1/Screening, the use of these agents is prohibited ≤6 months before the date of the liver biopsy and through Visit 1/Screening.

20. Is on treatment or likely to require treatment for ≥14 consecutive days or repeated courses of pharmacologic doses of corticosteroids (eg, prednisone 5 mg or equivalent doses of other glucocorticoids).

    Note: Inhaled, nasal, ophthalmic, and topical corticosteroids, and physiological replacement doses of adrenal steroids are permitted.

21. Is on treatment with anticoagulants (eg, warfarin, heparin).

22. Is on treatment with an AHA or other medications listed in Table 1, and is not on a stable dose according to Table 1.

Table 1 Stability Definitions for Medications and Other Substances

Medications: Antihyperglycemic Agents	Stability Definition
• Insulin	Stable dose (defined as ≤20% variance in total daily dose) required for ≥3 months: (1) before Visit 1/Screening or (2) from the date of historical liver biopsy.
• Alpha glucosidase inhibitors • DPP-4 inhibitors • Meglitinides • Metformin • Sulfonylureas	Stable dose required for ≥3 months: (1) before Visit 1/Screening or (2) from the date of historical liver biopsy.
• GLP-1 agonists[a] • SGLT2 inhibitors[a]	Stable dose required for ≥6 months: (1) before Visit 1/Screening or (2) from the date of historical liver biopsy.
Medications: Other	**Stability Definition**
• Weight loss medication (eg, orlistat, phentermine, topiramate, lorcaserin, naltrexone/bupropion, GLP-1 agonists) • Medications associated with weight changes (eg, anti-psychotic medications [eg, olanzapine, risperidone, quetiapine fumarate])	Stable dose required for ≥6 months: (1) before Visit 1/Screening or (2) from the date of historical liver biopsy.
• Lipid lowering agents (eg, statins, ezetimibe, fibric acid derivatives [fibrates], icosapent ethyl)	Stable dose required for ≥3 months: (1) before Visit 1/Screening or (2) from the date of historical liver biopsy.
• Doses of vitamin E >100 IU/day	Stable dose required for ≥6 months: (1) before Visit 1/Screening or (2) from the date of historical liver biopsy.
• Chronic prescription pharmacotherapy initiated and/or a recent change in prescription medication, dose, or frequency of medication which in the opinion of the investigator may potentially interfere with the study.	Stable dose required for ≥1 month before Visit 5/Randomization.

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; IU=international units; SGLT2=sodium-glucose cotransporter-2.
[a] If a participant should require additional medications for control of diabetes, the initiation of SGLT2 inhibitors and GLP-1 agonists are prohibited.

Prior/Concurrent Clinical Study Experience

23. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device ≤3 months before participating in this current study. Participants enrolled in observational studies may be included and will be reviewed on a case-by-case basis for approval by the Sponsor. **Note**: See Appendix 7 for Korea-specific study requirements.

Diagnostic Assessments

24. Has exclusionary laboratory values as listed in Table 2.

    Note: If any of the laboratory exclusion criteria in Table 2 are met, the site may have the abnormal value retested one time.

Table 2 Laboratory Exclusion Criteria

Parameter[a]	Population (if applicable)	Study Limit for Exclusion
ALP	-	>2 × ULN
ALT	-	>5 × ULN
AST	-	>5 × ULN
eGFR[b]	-	<45 mL/min/1.73 m^2
FT4	-	Outside the central laboratory normal range
Hemoglobin	Male Female	<11 g/dL (110 g/L) <10 g/dL (100 g/L)
IGF-1	-	Above the central laboratory age-appropriate normal range
INR	-	≥1.3
Bedtime salivary cortisol[c]	-	>1.5 × ULN
Platelet count	-	<140 × 10^9/L
Serum albumin	-	<3.5 g/dL
Total bilirubin[d]	-	≥1.3 mg/dL
TSH	-	Outside the central laboratory normal range

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; eGFR=estimated glomerular filtration rate; FT4=free thyroxine; IGF-1=insulin-like growth factor-1; INR=international normalized ratio; MDRD=Modification of Diet in Renal Disease; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

[a] Participants with an exclusionary laboratory value may have one repeat determination performed if the investigator considers the Visit 1/Screening result to be inconsistent with prior determinations. Only the laboratory test not meeting entry criterion should be repeated (not the entire panel). The last laboratory draw/result should be used to assess the exclusion criterion.

[b] Calculated by the central laboratory using the 4-variable MDRD Equation. For the calculation of eGFR for participants in Japan, the Japanese 3-variable Equation 4 will be used (Appendix 7) [Matsuo, S., et al 2009]. See Appendix 13 for eGFR equations.

[c] Bedtime salivary cortisol samples should be collected between 9 PM and midnight.

[d] Participants with an elevated total bilirubin but with a direct bilirubin within normal limits are eligible.

25. Has poor venous access that precludes routine peripheral blood sampling required for this study.

26. Has received blood products ≤2 months before Visit 1/Screening and/or donated blood products ≤1 month before Visit 1/Screening.

    Note: Participants are not to donate blood products throughout the duration of the study.

27. Has a clinically significant ECG abnormality that requires further diagnostic evaluation or intervention (eg, new, clinically significant arrhythmia, or a conduction disturbance).

28. Has claustrophobia to a degree that prevents tolerance of MRI scanning procedure. Sedation is permitted at the discretion of the investigator.

29. Has a metallic implant of any sort that prevents MRI examination including, but not limited to, aneurysm clips, metallic foreign body, vascular grafts or cardiac implants, neural stimulator, metallic contraceptive device, metallic tattoo, body piercing that cannot be removed, cochlear implant, or any other contraindication to MRI examination.

Other Exclusions

30. In the opinion of the investigator, the participant has any other condition which would impede competence or compliance or possibly hinder completion of the study.

31. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Diet and Activity Counseling

Participants will receive dietary and activity counseling at Visit 4/Placebo Run-in. At subsequent visits as detailed in Section 1.3 (SoA), the site staff will review the diet and activity guidance sheets with the participant. Detailed dietary and activity information will not be captured.

All participants will receive counseling on diet uniformly across the sites. Participants will also be counseled to maintain a medically appropriate, routine exercise program and consistent physical activity level during the study. Participants should not engage in strenuous exercise (ie, weightlifting, running, bicycling, etc.) for 48 hours before each blood collection for clinical laboratory tests for the duration of the study.

Additional registered nutritionist/dietician (or equivalent outside the US) referrals may be provided during the study and for up to an additional 3-month (optional) period after study completion if participants meet certain criteria as described in Section 8.3.3.

5.3.2 Alcohol Restrictions

Participants will be counseled to limit alcohol use to ≤1 standard drink per day or less than approximately 7 standard drinks per week in females, and ≤2 standard drinks per day or less than approximately 14 standard drinks per week in males, on average. One standard drink is defined as any beverage containing 14 g of pure alcohol or as defined by local guidelines.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

Any participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies (study interventions provided by the Sponsor) will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strengths	Dosage Level(s)	Route of Admin	Treatment Period	Use	IMP or NIMP/AxMP	Sourcing
Group 1 (Run-in Period)	Experimental	MK-3655 Matching Placebo	Drug	Vial	0 mg	2 x 1.5 mL injections once	SC	V4 up to V5 (Run-in Period)	Placebo	IMP	Provided centrally by the Sponsor
Group 1	Experimental	MK-3655 33.3 mg/mL	Drug	Vial	50 mg	1 x 1.5 mL injection Q4W	SC	V5 to V15 (Double-Blind Treatment Period)	Test Product	IMP	Provided centrally by the Sponsor
Group 1	Experimental	MK-3655 Matching Placebo	Drug	Vial	0 mg	1 x 1.5 mL injection Q4W	SC	V5 to V15 (Double-Blind Treatment Period)	Placebo	IMP	Provided centrally by the Sponsor
Group 2 (Run-in Period)	Experimental	MK-3655 Matching Placebo	Drug	Vial	0 mg	2 x 1.5 mL injections once	SC	V4 up to V5 (Run-in Period)	Placebo	IMP	Provided centrally by the Sponsor
Group 2	Experimental	MK-3655 33.3 mg/mL	Drug	Vial	100 mg	2 x 1.5 mL injections Q4W	SC	V5 to V15 (Double-Blind Treatment Period)	Test Product	IMP	Provided centrally by the Sponsor
Group 3 (Run-in Period)	Experimental	MK-3655 Matching Placebo	Drug	Vial	0 mg	2 x 1.5 mL injections once	SC	V4 up to V5 (Run-in Period)	Placebo	IMP	Provided centrally by the Sponsor
Group 3	Experimental	MK-3655 100 mg/mL	Drug	Vial	300 mg	2 x 1.5 mL injections Q4W	SC	V5 to V15 (Double-Blind Treatment Period)	Test Product	IMP	Provided centrally by the Sponsor
Group 4 (Run-in Period)	Placebo Comparator	MK-3655 Matching Placebo	Drug	Vial	0 mg	2 x 1.5 mL injections once	SC	V4 up to V5 (Run-in Period)	Placebo	IMP	Provided centrally by the Sponsor
Group 4	Placebo Comparator	MK-3655 Matching Placebo	Drug	Vial	0 mg	2 x 1.5 mL injections Q4W	SC	V5 to V15 (Double-Blind Treatment Period)	Placebo	IMP	Provided centrally by the Sponsor

Admin=administration; EEA=European Economic Area; IMP=Investigational Medicinal Product; NIMP/AxMP=Non-Investigational Medicinal Product/Auxiliary Medicinal Product; Q4W=once every 4 weeks; SC=subcutaneous; V=visit.

Notes:

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

In Japan, administration of study intervention will not be allowed by a caregiver. See Section 8.1.8.3 and Appendix 7.

All supplies indicated in Table 3 will be provided per the "Sourcing" column depending upon local country operational requirements.

Refer to Section 8.1.9 for details regarding administration of the study intervention.

All placebos were created by the Sponsor to match the active product.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 4 study intervention arms. Participants will be assigned randomly in a 1:1:1:1 ratio to 1 of 3 doses of MK-3655 study intervention (50 mg Q4W, 100 mg Q4W, or 300 mg Q4W) or a matching placebo study intervention Q4W, respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Concurrent diagnosis of T2DM at the time of randomization (Yes or No)

2. Fibrosis score (Stage 2 or Stage 3)

3. Region (Japan, East Asia excluding Japan, or Other)

    - Japan and East Asia excluding Japan were each added as a separate stratum in region stratification to ensure that randomization of the Japan population and overall East-Asian population (ie, Japan and East Asia excluding Japan) are balanced between-treatment groups. This stratification will allow for an optimal assessment of the Japan subpopulation as required by the regulatory agency, as well as the overall East-Asian population.

If either proportion of participants, those with T2DM or those without T2DM, exceeds approximately 60% of the total targeted sample size, the remaining participants enrolled will be restricted to the other stratum within this stratification factor. **Note**: In Japan, enrollment will not be restricted by this cap, and sites will be able to continue to enroll participants with or without T2DM (see Appendix 7).

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. All MK-3655 doses and matching placebo will have the same dose volume and be packaged identically so that the blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants will be unaware of the intervention assignments.

See Section 8.1.11 for a description of the method of unblinding a participant during the study should such action be warranted.

6.4 Study Intervention Compliance

When participants self-administer study intervention at the site, compliance with study intervention will be assessed by site personnel observation. The date and time of each dose administered in the clinic will be recorded in the source documents, the CRF, and the

participant diary. At all protocol-specified site visits, the investigator or qualified designee is to record whether treatment had been taken per protocol. If not, the date(s) and reason for each dosing noncompliance must be recorded.

When participants self-administer study intervention at home, compliance with study intervention will be assessed at the next site visit. Compliance will be assessed using participant diaries. A visual inspection of the vials returned (used and unused) will also be performed (when available). Deviation(s) from the prescribed dosage regimen will be recorded in the CRF.

A record of the number of vials dispensed to and returned by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

Note: In Japan, administration of study intervention will not be allowed by a caregiver. See Section 8.1.8.3 and Appendix 7.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the study (see Section 5.2). If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. Medications required to be stable upon study entry (see Table 1) that require adjustment during the trial may result in discontinuation. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor or appropriate designee should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified to be used in this study. Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

6.6 Dose Modification

Participants will be randomized to a fixed dose regimen of MK-3655 (50 mg Q4W, 100 mg Q4W, or 300 mg Q4W) or matching placebo for the duration of the study. Dose modifications (ie, delays in the administration of study intervention) are permitted if clinically warranted (eg, due to AEs).

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.11). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.6.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the

investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.10 and Section 8.11.6.

A participant must be discontinued from study intervention but should continue to be monitored in the study for any of the following reasons:

1. The participant or participant's legally acceptable representative requests to discontinue study intervention.

2. The participant has a medical condition or personal circumstance, which in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

3. The participant has a positive urine pregnancy test and confirmed by positive serum pregnancy test.

Clinical Events

4. The participant has a CTCAE Grade 3 clinical AE that is considered drug-related by the investigator.

5. The participant has any CTCAE Grade 4 clinical AE, unless the investigator and Sponsor concur that the AE is ***clearly not*** causally related to study intervention and that continuation/resumption of study intervention does not place the participant at unnecessary risk.

The following AEs are exceptions to #4 and #5. For these events, CTCAE severity grading will not be used as a basis for a participant to be discontinued from study intervention. The requirements for a participant to be discontinued from study intervention are listed for each AE.

- **Weight gain**: Participants will be discontinued from study intervention if body weight measured at the study site has increased ≥15% from baseline (Visit 5/Randomization) at any time during the study.

- **Obesity**: The CTCAE grading for obesity is not applicable to this study as participants with a BMI of 25.0 kg/m^2 to 50.0 kg/m^2 are eligible for study participation (see Section 5.1, inclusion criterion #5). Instead, discontinuation of study intervention will be based on weight gain as described above.

- **Hypoglycemia in participants with T2DM**: A participant with T2DM will be discontinued from study intervention if the participant has repeated (2 or more episodes since the prior visit) FPG or fingerstick glucose <50 mg/dL (<2.8 mmol/L) with or without symptoms of hypoglycemia or ≤70 mg/dL (≤3.9 mmol/L) with symptoms of hypoglycemia, and without a reasonable explanation (such as increased physical activity or skipped meal).

If a participant is taking any concomitant medications known to cause hypoglycemia (ie, insulins, sulfonylureas, and meglitinides), discontinuation of study intervention should occur only if hypoglycemia persists after down-titration and discontinuation of those medications.

Note: The investigator should ensure that the participant's glucose meter is functioning accurately and that the test procedure is being correctly performed by the participant before discontinuation of study intervention.

- Participants known to have hypertension or with a baseline blood pressure >120 mm Hg (systolic) or >80 mm Hg (diastolic) before randomization: Participants known to have hypertension or with a baseline blood pressure >120 mm Hg (systolic) or >80 mm Hg (diastolic) before randomization will be discontinued from study intervention for a persistent increase from baseline of ≥20 mm Hg (systolic blood pressure) and/or ≥10 mm Hg (diastolic blood pressure) despite continuation of any antihypertensive regimen being used at baseline AND initiation and/or dose increase of >2 anti-hypertensive agents are required for management. Note: Multiple changes made to a single medication (eg, initiation at lower dose followed by dose increase) counts as only one adjustment.

  Note: NCI CTCAE, Version 5.0 will not be used for grading AE severity for participants known to have hypertension or with a baseline blood pressure >120 mm Hg (systolic) or >80 mm Hg (diastolic) before randomization. Instead, the investigator will assess AE intensity according to the following modified CTCAE grading:

  – Grade 1: Persistent increase from baseline of 10 mm Hg to 19 mm Hg (systolic blood pressure) and/or 5 mm Hg to 9 mm Hg (diastolic blood pressure) despite continuation of any anti-hypertensive regimen being used at baseline.

  – Grade 2: Persistent increase from baseline of ≥20 mm Hg (systolic blood pressure) and/or ≥10 mm Hg (diastolic blood pressure) despite continuation of any anti-hypertensive regimen being used at baseline **AND** initiation and/or dose increase of ≤2 anti-hypertensive agents required for management.*

  – Grade 3: Persistent increase from baseline of ≥20 mm Hg (systolic blood pressure) and/or ≥10 mm Hg (diastolic blood pressure) despite continuation of any anti-hypertensive regimen being used at baseline **AND** initiation and/or dose increase of >2 anti-hypertensive agents required for management.*

  – Grade 4: Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated.

  – Grade 5: Death related to AE.

  ***Note**: Multiple changes made to a single medication (eg, initiation at lower dose followed by dose increase) counts as only one adjustment.

Laboratory Abnormalities

6. The participant has a CTCAE Grade 3 laboratory abnormality considered drug-related by the investigator, if clinically significant medical intervention is required to treat the event ***and/or*** the abnormality leads to hospitalization.

7. The participant has any CTCAE Grade 4 laboratory abnormality that requires clinically significant medical intervention to treat the event ***and/or*** the abnormality leads to hospitalization. Continuation/resumption of study medication may be considered if the investigator and Sponsor concur that the abnormality is ***clearly not*** causally related to study medication and that this does not place the participant at unnecessary risk.

The following laboratory abnormalities are exceptions to #6 and #7. For these events, CTCAE severity grading will not be used as a basis for a participant to be discontinued from study intervention. The requirements for a participant to be discontinued from study intervention are listed for each laboratory abnormality.

- **Abnormalities of ALT and/or AST**: If the participant has abnormal ALT and/or AST meeting criteria specified in Appendix 10 and no other cause for the combination of laboratory abnormalities is immediately apparent (eg, prolonged INR with warfarin use), study intervention will be discontinued.

  Note: See Appendix 10 for additional details on management of blinded study intervention for participants with elevated liver enzymes.

- **Reduction of renal function**: If the participant has an eGFR that is persistently <30 mL/min/1.73 m^2 as calculated by the MDRD formula, study intervention will be discontinued. For participants in Japan, eGFR will be calculated with the Japanese 3-variable Equation 4 (Appendix 7) [Matsuo, S., et al 2009]. See Appendix 13 for the eGFR equations.

  Note: A persistent eGFR value is defined as a repeat measurement, performed within 2 weeks after notification from the central laboratory, that remains <30 mL/min/1.73 m^2, despite correction of potential causative factors (eg, correction of volume depletion, discontinuation of NSAIDs). If the eGFR value continues to meet the discontinuation criterion but demonstrates stability or improvement relative to the prior result, an additional repeat measurement may be performed within 7 days.

- **Salivary cortisol**: If the participant has a bedtime salivary cortisol test value >1.5 × ULN **AND** >50% above baseline during the study, a repeat bedtime salivary cortisol will be obtained. If the second test value is also >1.5 × ULN **AND** >50% above baseline, a 24-hour urinary cortisol test will be performed. If the 24-hour urinary cortisol value is elevated >1 × ULN, study intervention will be discontinued (see Section 8.3.9.1).

  Note: The baseline assessment for the salivary cortisol test value is considered the one closest to but before dosing (Visit 5/Randomization [Day 1]). However, if no sample is collected before the Visit 5/Randomization, the Visit 1/Screening test value should be used for the baseline assessment.

- **TSH, FT4**: If the participant has TSH and/or FT4 values outside the normal range of the assay and any signs or symptoms of hyperthyroidism or hypothyroidism accompany the changes in thyroid function tests, study intervention will be discontinued (see Section 8.3.9.2).
- **IGF-1**: If the participant has 2 sequential IGF-1 values above the age-appropriate ULN of the assay **AND** >30% above baseline during the study, study intervention will be discontinued (see Section 8.3.9.3).

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 500 mL (Appendix 9). **Note**: See Appendix 7 for China-specific blood volume collection requirements.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant or their legally acceptable representative before participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority

requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the trial protocol number, trial protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated ICF should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant (or the participant's legally acceptable representative), answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician (or a qualified designee), to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention

randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified requirements (see Section 5.2 and Table 1), and record prior medication taken by the participant before Visit 1/Screening.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study on the appropriate eCRF.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.11.3.1.

After all required screening procedures have been completed and a participant's eligibility has been confirmed, the study randomization visit will be registered in IRT.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Compliance (Intervention/Diet/Activity/Other)

8.1.8.1 Diet and Activity Counseling/Monitoring

Participants will receive diet and activity guidance sheets (see Section 5.3.1). At each site visit, site staff will reinforce the information on the diet and activity guidance sheets.

8.1.8.2 Assessment of Alcohol Consumption

Participants will report the average number of drinks consumed per week since the last visit.

Participants who consume more than the recommended amount of alcoholic drinks per week (ie, more than approximately 7 standard drinks per week in females or more than approximately 14 standard drinks per week in males; see Section 5.3.2) must be counseled by the site. If a participant is non-compliant with the alcohol use restrictions for 3 or more visits over the course of the study, consultation between the investigator and Sponsor is required for a collaborative decision on participant management.

8.1.8.3 Self-injection Training (Participant and/or Caregiver)

Participants/caregivers will be trained by site staff on the proper method for self-injection.

At Visit 4/Week -2

1. Participants/caregivers will receive training from the site staff and will review written instructions for self-injection.

2. Participants/caregivers will be expected to administer the single-blind study intervention (MK-3655 matching placebo) under the guidance of the site staff.

3. Participants/caregivers will take home the written instructions and will be instructed to review these materials at home, before Visit 5/Week 0.

If a participant/caregiver is unable to administer study intervention, the site staff may administer the doses of study intervention to the participant.

Note: In Japan, administration of study intervention can only be performed by a medically qualified person (eg, physician, supporting nurse); self-administration by the participant him/herself is the only exception. Therefore, administration of study intervention by a caregiver will not be allowed in Japan (see Appendix 7).

8.1.8.4 Witnessed Dosing

Administration of study intervention will be witnessed by the investigator and/or qualified study staff at **ALL** scheduled study visits during the placebo run-in and the double-blind treatment period. Dosing should occur after completion of all study procedures including the collection of all fasting blood samples.

During the double-blind treatment period:

1. Participants/caregivers will administer the double-blind study intervention (MK-3655/matching placebo) in the presence of the site staff except at Weeks 28, 36, and 44.

    - Telephone contacts will be made at Weeks 28, 36, and 44 (see SoA [Section 1.3]) to assess for compliance with study intervention administration at home by participants/caregivers, and to record AEs, body weight, and concomitant medications. See Section 8.1.8.8 for further details.

2. Retraining will be provided and documented by site staff as appropriate.

3. Participants/caregivers should be instructed to refer to the written instructions when administering injections of the double-blind study intervention at home.

Notes:

- No coaching by site staff will be provided unless deemed necessary.

- If a participant/caregiver is unable to administer study intervention, the site staff may administer the doses of study intervention to the participant.

- In Japan, administration of study intervention will not be allowed by a caregiver. See Section 8.1.8.3 and Appendix 7.

8.1.8.5 Dispense Single-Blind and Double-Blind Study Intervention

Participants will be dispensed single-blind study intervention (MK-3655 matching placebo) at Visit 4/Week -2.

Participants will be dispensed double-blind study intervention (MK-3655/matching placebo) at all scheduled study visits from Visit 5/Week 0 (Day 1) through Visit 14/Week 48.

At Visit 11/Week 24, Visit 12/Week 32, and Visit 13/Week 40, study intervention kits will be dispensed to participants to self-administer study intervention at home on Week 28, Week 36, and Week 44, respectively.

Refer to Section 8.1.9 for further details.

8.1.8.6 Dispense/Review Participant Dosing Diary

Participants will receive dosing diaries as specified in the SoA (see Section 1.3) to document their experience with self-injection; specifically, to collect the date, time, and who is administering the injection, as well as any comments related to the injection experience. Participants should bring their completed diary to all study visits and be reminded to do so (eg, by phone or text) before each visit. Site personnel should review the diaries at each study visit to monitor compliance and review for any potential AEs from the comments entered.

8.1.8.7 Investigational Product Accountability

When participants self-administer study intervention at home (ie, Weeks 28, 36, and 44) accountability for the administration of study intervention will be assessed at the next site visit. Compliance will be assessed using participant diaries. A visual inspection of the vials returned (used and unused) will also be performed (when available) to ensure accurate drug accountability.

Consultation between the investigator and Sponsor is required if a participant misses 2 consecutive doses of study intervention during the double-blind treatment period.

Refer to Section 6.4 for further details on study intervention compliance.

8.1.8.8 Telephone Contact

During the 6-week (±28 days) screening period, telephone contact by the investigator/qualified designee will be made within the 3 days before Visit 2/MRI-PDFF and Visit 3/Liver Biopsy to assess for concomitant medications and AEs.

At Week 2 post-randomization, telephone contact by the investigator/qualified designee will be made to perform a C-SSRS assessment (see Section 8.3.11.1.1).

During the double-blind treatment period, telephone contact by the investigator/qualified designee will be made at the midpoint between study visits from Visit 11 through Visit 14 (ie, Weeks 28, 36, and 44) to assess weight, concomitant medications, AEs, pregnancy status (if applicable), and compliance with study intervention administration (see Section 1.3). Unscheduled visit(s) may be performed as needed if the participant requires retraining on study intervention administration.

If the participant reports a weight at the time of telephone contact that is greater than or equal to a 10% weight gain from baseline (Visit 5/Randomization), an unscheduled site visit will be required to confirm the participant's body weight and to assess the potential need for additional dietary intervention (see Section 8.3.3).

During the post-treatment period, telephone contact by the investigator/qualified designee will be made at Weeks 60 and 64 to record AEs and assess pregnancy status, if applicable (see Section 1.3).

If a participant reports a pregnancy at the time of telephone contact, an unscheduled site visit will be required to confirm the participant's pregnancy status with a serum pregnancy test (see Section 8.3.10).

Section 6.4 summarizes the approach to assessment of compliance as well as addressing noncompliance when necessary.

8.1.9 Study Intervention Administration

Administration of study intervention will be witnessed by the investigator and/or study staff at **ALL** scheduled study visits (see Section 1.3). Beginning at Week 0, participants will be instructed to administer two 1.5 mL subcutaneous injections of MK-3655/matching placebo once every 4 weeks. Refer to Section 8.1.9.1 for further details.

Note: In Japan, administration of study intervention will not be allowed by a caregiver. See Section 8.1.8.3 and Appendix 7.

8.1.9.1 Timing of Dose Administration

After it is confirmed that a participant meets study eligibility criteria, study intervention (MK-3655/matching placebo) will be administered subcutaneously once every 4 weeks after the completion of predose procedures for the duration of the 52-week double-blind treatment period.

Week 0 through Week 24 of the double-blind treatment period:

- Study intervention will be administered by participants/caregivers as a witnessed dose at the study site.
- A study intervention kit will be provided by the site to each participant on Week 24 to self-administer study intervention at home on Week 28.

After Week 24 through Week 48 of the double-blind treatment period:

- On Weeks 28, 36, and 44, study intervention will be administered at home, 4-weeks after the previous dose of study intervention by participants/caregivers.
- Telephone contact by the investigator/qualified designee will be made on Weeks 28, 36, and 44 to assess weight, concomitant medications, AEs, and compliance with study intervention administration.
- On Weeks 32, 40, and 48, study intervention will be administered by participants/caregivers as a witnessed dose at the study site.
- Study intervention kits will be provided by the site to participants at the Week 32 and Week 40 visits to self-administer study intervention at home on Weeks 36 and 44, respectively.

If necessary, administration of study intervention by site personnel is acceptable. Participants will be re-instructed on appropriate injection technique as needed based on observed injection experience.

Note: In Japan, administration of study intervention will not be allowed by a caregiver. See Section 8.1.8.3 and Appendix 7.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the double-blind treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA (Section 1.3) and Section 8.11.6.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the DC visit at the time of withdrawal. Section 8.11.6 outlines specific instructions for collection of the end of study MRI-PDFF, DXA imaging, and liver biopsy for participants who withdraw from the study. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@msd.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.11 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, they will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant’s intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc., in

the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

For participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or non-study treating physician, discontinuation from study intervention is only required if deemed medically necessary. Participants who are discontinued from study intervention should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

Critical equipment for this study includes a digital body weight scale. The study site is responsible for conducting accuracy checks at least monthly to ensure the scale to measure body weight is working correctly. Additional details are provided in the operations manual.

8.2 Efficacy Assessments

8.2.1 Liver Fat Content by MRI-Estimated Proton Density Fat Fraction

LFC will be assessed by MRI-PDFF during screening (Visit 2/MRI-PDFF) and at Visit 11/Week 24. The process for image collection and transmission to the iCRO is in the Site Imaging Manual. The same imaging technique and MRI scanner should be used for a participant throughout the study to minimize variability.

The screening MRI-PDFF must be performed at Visit 2. All participants must have safety laboratory tests (ie, liver function, renal function, and hematological parameters) that meet Visit 1/Screening eligibility criteria before imaging can be performed.

> **Note**: Other pending Visit 1/Screening laboratory results are not required to proceed to Visit 2/MRI-PDFF. Participants will be screen failed for any exclusion criteria identified during Screening.

For participants who discontinue study intervention before Visit 11/Week 24, an MRI-PDFF should be performed at the time of study intervention discontinuation if at least 4 weeks have passed since the first dose of double-blind study intervention (see Section 8.11.6).

All scheduled MRI-PDFF images/data for all participants will be submitted to the iCRO for LFC assessment by BICR (see Section 8.11.3.2). The iCRO will communicate to the site whether a participant has met the MRI-PDFF entry criterion (ie, LFC ≥8%). A specific LFC score will not be communicated to the sites or participants during the study.

Clinically significant findings in the local interpretation of the MRI-PDFF images at baseline and during the double-blind treatment period that are reported by the site investigator should be recorded appropriately.

For further information see Section 8.11.3.2.

8.2.2 Liver Biopsy (Histology) and Assessment of Disease

Full instructions concerning the number and type of samples to be collected at each visit, the sample collection methods, sample processing, labeling, and shipping will be provided in the laboratory manual.

All liver biopsy assessments, including determination of study eligibility based on NASH diagnosis, NAS, and fibrosis staging during the 6-week (±28 days) screening period, will be performed centrally by independent pathologists. Participants should be fasted for at least 8 hours before liver biopsy collection. Biopsy tissue is recommended to be of adequate size (≥2.0 cm in length; obtained with at least a 16-gauge instrument) and of adequate quality for interpretation. For study eligibility, the central pathologists must confirm at baseline, the histological presence of NASH based on a NAS score ≥4 with a score of at least one in each component (steatosis, ballooning, and lobular inflammation) and a fibrosis score of Stage 2 or 3. NAS and fibrosis staging will be graded in accordance with the NASH CRN criteria for scoring [Kleiner, D. E., et al 2005] and as summarized in Appendix 12.

For participants who discontinue study intervention before Visit 15/Week 52, a liver biopsy should be performed at the time of study intervention discontinuation if at least 12 weeks have passed since the first dose of double-blind study intervention (see Section 8.11.6).

For further information see Section 8.11.3.3.

8.2.3 Glycemic and Lipid Metabolism

The laboratory efficacy endpoints for glycemic metabolism (A1C and FPG) and lipid metabolism (cholesterol [total, HDL-C, LDL-C], TG, apoA1, and apoB) should be collected as specified in the SoA (see Section 1.3). Participants should be fasted for at least 8 hours before collection and should take their non-AHA medications as prescribed (see Section 8.11.1).

Sample collection, storage, and shipment instructions for samples will be provided in the laboratory manual.

8.2.4 Patient-Reported Outcomes

The CLDQ NAFLD-NASH, PGI-S, and EQ-5D-5L questionnaires will be administered by trained site personnel and completed by participants at Visit 5/Week 0 and Visit 15/Week 52 in the following order: CLDQ NAFLD-NASH first, followed by PGI-S, then EQ-5D-5L. The questionnaires should be administered before administration of study intervention and according to the SoA (see Section 1.3).

It is best practice and strongly recommended that PROs are administered to randomized participants before study intervention administration, AE evaluation, and disease status notification.

If a participant discontinues early from study intervention but agrees to be followed for the remaining study visits, the participant will be asked to complete the PROs at the DC Visit.

For further information see Section 4.2.1.2.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood volumes per period, can be found in Appendix 9. **Note**: See Appendix 7 for China-specific blood volume collection requirements.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

Complete and directed physical examinations will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard and as outlined in the SoA (see Section 1.3). The complete physical examinations will at minimum include assessments of general appearance, skin, lymphatic system, eyes, ears, nose, throat, CV system, respiratory system, abdomen/gastrointestinal system, urological system, musculoskeletal system, and neurological system. Unless the study investigator feels there is a specific need, genitourinary, rectal, and breast examination should be omitted from the full physical examination.

The directed physical examinations will at a minimum include assessment of the heart, lungs, abdomen, skin, and extremities. Other body systems may be evaluated with either type of examination. Abnormalities considered clinically significant should be reported as AEs.

A physical examination (complete or directed) may be performed at any unscheduled visit if deemed necessary by the investigator or medically qualified designee.

8.3.2 Height

Height will be measured without shoes using a calibrated stadiometer at Visit 1/Screening. Document height in meters to the nearest 0.01 meter (0.01 meter = 1 cm).

8.3.3 Body Weight Assessment and Monitoring

Body weight (kg) will be measured in duplicate using a standardized, digital scale as outlined in the SoA (Section 1.3). Detailed information regarding the collection of body weight can be found in the operations manual.

At Visit 11/Week 24, all participants will be dispensed a digital weight scale (provided by the Sponsor) to measure body weight at home on Weeks 28, 36, and 44. Telephone contact by the investigator/qualified designee will be made at Weeks 28, 36, and 44 to record the weight reported by the participant. Participants should weigh themselves on the day of the scheduled telephone contact wearing underwear and socks, first thing in the morning, and after voiding (ie, emptying their bladder). If the participant reports a weight at the time of telephone contact that is greater than or equal to a 10% weight gain from baseline (Visit 5/Randomization), an unscheduled site visit will be required to confirm the participant's body weight and potential need for intervention as described below.

Interventions Triggered by Weight Gain

If at any time during the study, a participant has weight gain ≥10% from the Visit 5/Randomization baseline measured at the study site using the methodology described above, the following will occur:

- Local site diet and activity counseling will continue to be provided at each site visit.
- A referral to a registered nutritionist/dietician (or equivalent outside the US) will be provided, and the investigator must promptly notify the Sponsor. The nutritional/dietary consult is recommended to occur within approximately 2 weeks of the initial referral. The Sponsor recommends that the registered nutritionist/dietician (or equivalent outside the US) encourages the participant to achieve a 0.5 to 0.9 kg (1 to 2 lb) weight loss per week.

If a participant has a weight gain ≥15% from baseline (Visit 5/Randomization) at any time during the study:

- Study intervention will be discontinued.
- Local site diet and activity counseling will continue to be provided at each site visit.
- A referral to a registered nutritionist/dietician (or equivalent outside the US) will be provided (if not provided already) for the remainder of the study, and the investigator must promptly notify the Sponsor.

Poststudy, participants should work with their primary care physician/equivalent physician for further weight management, as appropriate. Any participant who has been referred to a registered nutritionist/dietician (or equivalent outside the US) at any point during the study

for having weight gain ≥10% from randomization will be eligible to continue with their nutritional/dietary consult for up to an additional 3 months following completion of the study. Specific information regarding this additional nutritional/dietary consultation following study completion will be provided in a separate procedure manual.

8.3.4 Body Mass Index

BMI will be calculated (weight/height^2 in kg/m^2) by the investigator or qualified designee based on participant's height and weight at Visit 1/Screening to ensure the participant meets study inclusion criteria (see Section 5.1). Document BMI to the nearest 0.1 kg/m^2.

8.3.5 Model for End-Stage Liver Disease-Sodium Score

MELD-Na score will be calculated by the laboratory vendor based on the participant's bilirubin, INR, creatinine, and sodium levels at Visit 1/Screening and communicated to the site to ensure the participant meets study inclusion criteria (see Section 5.1).

Note: Should the laboratory vendor be unable to perform the MELD-Na score calculation, consult the operations manual.

8.3.6 12-Lead Electrocardiogram

A standard supine 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) according to the SoA (see Section 1.3). Clinically significant abnormal findings during the 6-week (±28 days) screening period should be recorded as medical history. Assessments may be repeated during the study, as clinically indicated.

- Participants should avoid the ingestion of caffeine and nicotine-containing products for at least 30 minutes before the scheduled ECGs.
- ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position and before the assessment of blood pressure and heart rate as well as before blood collection.

All ECGs performed should be reviewed at the investigative site for participant safety monitoring. The investigator is responsible for retaining all copies of the ECG reports.

8.3.7 Vital Signs

Vital signs will be measured at all scheduled site visits, except Visit 2/MRI-PDFF and Visit 3/Liver Biopsy (see Section 1.3 [SoA]). Oral temperature (in centigrade) will only be measured at Visit 5/Randomization. At all scheduled visits, blood pressure and heart rate should be measured under the following conditions:

- Triplicate assessment of sitting systolic and diastolic blood pressure (mm Hg) and heart rate (beats per minute) will be collected at approximate 2-minute intervals using

automated devices. The time, positioning, and arm used should be recorded for each measurement.

- Measurements must be conducted after a 10-minute resting period with the participant comfortably seated in a chair with the legs uncrossed and the back and arm supported. Measurements should not be made while the participant is on an examination table. The participant should be instructed to relax as much as possible and to not talk during the measurement procedure.

- Site personnel should ensure that the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum).

- The participant should be asked to remove all clothing that covers the location of cuff placement.

- Site personnel should use the same blood pressure measuring device (ie, automated device) and under the same external conditions throughout the study for each participant.

- Other procedures should not be performed during the time of the blood pressure and heart rate measurements.

Detailed information regarding blood pressure and heart rate monitoring is contained in the operations manual. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.8 Dual-Energy X-ray Absorptiometry

DXA images to monitor whole body composition and BMD should be collected from all participants/sites willing and able to have the test performed and according to country law. These participants will undergo DXA of the total body, lumbar spine, and hip for BMD as well as body composition. All scheduled DXA images will be submitted to the iCRO.

Participants will not be excluded from participation in the study if unable to have DXA imaging performed.

Only participants who are confirmed eligible at Visit 1/Screening will undergo DXA imaging during the Visit 4/Placebo Run-in period (baseline). If iCRO DXA quality control should fail, no repeat DXA imaging will be performed. Only participants with valid baseline DXA images should have DXA imaging performed at Visit 15 (Week 52 ±5 days). For participants who discontinue study intervention after Visit 11/Week 24, DXA imaging should be performed at the time of study intervention discontinuation (DC visit). Refer to Section 8.11.6 for end of study DXA collection recommendations.

All scheduled DXA images will be evaluated by BICR. The BICR will not be performed in real-time and analysis results will not be provided to the site/participant. For clinical management of the participant, the DXA images should be reviewed and interpreted by a

qualified individual. Clinically significant findings noted in the local interpretation of the DXA images at baseline and during the double-blind treatment period should be recorded appropriately.

For each participant, the same imaging equipment should be used throughout the study to optimize assessment. Details on DXA acquisition and quality assurance will be included in the iCRO manual for DXA.

8.3.9 Clinical Laboratory Assessments (Hematology, Chemistry, Urinalysis, and Other)

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (see Section 1.3).

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

- Participants will be counseled to fast (ie, no food, double-blind study intervention, or drink except water and non-AHA medications as prescribed) for at least 8 hours before study visits requiring fasted blood collections or procedures (see Section 8.11.1).

- Serum hCG testing will be performed in female participants where a pregnancy is suspected.

8.3.9.1 Bedtime Salivary Cortisol

Salivary cortisol testing kits will be provided to the participant as described in the SoA (see Section 1.3).

- At Visit 1/Screening:
    - Participants will be provided with the salivary cortisol testing kit on the day of the visit (unless provided in advance if the informed consent is obtained before the visit).
    - Participants should be instructed to collect the sample at bedtime between 9 PM and midnight that evening and return the sample to the site the next day if possible but no later than 72 hours from the time of collection.
- All visits after Visit 1/Screening:
    - Participants will be provided with the salivary cortisol testing kit at the visit prior to the next required sample collection timepoint.
    - Participants should be instructed to collect the sample at bedtime between 9 PM and midnight the evening prior to the visit and return the sample to the site the next day but no later than 72 hours from the time of collection.

If the bedtime salivary cortisol test value is >1.5 × ULN **AND** >50% above baseline during the study, a repeat bedtime salivary cortisol test should be performed within 1 week to confirm the value. If the second test value is also >1.5 × ULN **AND** >50% above baseline, a 24-hour urinary cortisol test will be performed. If the 24-hour urinary cortisol value is elevated >1 × ULN, study intervention will be discontinued and the participant should be referred to an endocrinologist, or an appropriate medical provider when an endocrinologist is not available.

Sample collection, storage, and shipment instructions for samples will be provided in the laboratory manual.

8.3.9.2 TSH and FT4

TSH and FT4 will be measured as detailed in the SoA (see Section 1.3). If a participant develops TSH and/or FT4 values outside the normal range of the assay during the study, repeat testing and further evaluation by an endocrinologist, or an appropriate medical provider when an endocrinologist is not available, are warranted. Study intervention should be discontinued if any treatment-emergent signs or symptoms of hyperthyroidism or hypothyroidism accompany the changes in thyroid function tests.

Sample collection, storage, and shipment instructions for samples will be provided in the laboratory manual.

8.3.9.3 IGF-1

IGF-1 will be measured as detailed in the SoA (see Section 1.3). If a participant develops IGF-1 values during the study that are both above the age-appropriate ULN of the assay **AND** >30% above baseline, a repeat IGF-1 test should be performed. If both test values are above the age-appropriate ULN **AND** >30% above baseline, study intervention will be discontinued and the participant should be referred to an endocrinologist, or an appropriate medical provider when an endocrinologist is not available.

Sample collection, storage, and shipment instructions for samples will be provided in the laboratory manual.

8.3.10 Pregnancy Testing

- Pregnancy testing for WOCBP:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine and/or serum) should be conducted at monthly intervals during intervention.
    - At all scheduled site visits (except Visits 2 and 3) a urine pregnancy test will be performed (see Section 1.3).
    - At Visit 11/Week 24, Visit 12/Week 32, and Visit 13/Week 40, the site will also dispense a urine pregnancy test kit for use at home on Weeks 28, 36, and 44.
    - At Visit 16/Week 56, the site will dispense urine pregnancy test kits for use at home on Weeks 60 and 64.
    - Telephone contact by the investigator/qualified designee will be made at the midpoint between study visits from Visit 11 through Visit 14 (ie, Weeks 28, 36, and 44) and Weeks 60 and 64 to assess AEs and pregnancy status (see Section 8.1.8.8). If the participant reports a pregnancy at the time of telephone contact, an unscheduled site visit will be required to confirm the participant's pregnancy status with a serum pregnancy test.
  - Pregnancy testing (urine and/or serum) should be conducted as per the SoA for the time required to eliminate systemic exposure after the last dose of study intervention and should correspond with the time frame for participant's contraception as noted in Section 5.1. The length of time required to continue pregnancy testing for study intervention is 16 weeks after the last dose of study intervention.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.11 Suicidal Ideation and Behavior Monitoring

8.3.11.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring

8.3.11.1.1 Columbia-Suicide Severity Rating Scale

Suicidal ideation and behavior will be prospectively assessed during this study using the C-SSRS. The C-SSRS should be administered by trained raters at specified time points, as indicated in the SoA, as well as at unscheduled visits as clinically indicated. Site staff should review the contents of the C-SSRS for completeness.

If the C-SSRS is administered by someone other than the investigator, the completed C-SSRS should be provided to the investigator for review before their assessment of the participant to further inform their evaluation.

During the Visit 1/Screening visit, the participant's suicidal symptoms and actions over the past 6 months should be evaluated with the C-SSRS. The C-SSRS is not explicit about whether the participant specifically has suicidal ideation at the time of Visit 1/Screening. If a participant reports a prior history of suicidal ideation/behavior, the assessor should also inquire and document if this is also present at the time of Visit 1/Screening. For all other assessments, the participant's suicidal symptoms and actions since the last assessment should be evaluated.

Participants must be excluded if they report suicidal ideation meeting the description of C-SSRS items 4 or 5 (ie, suicidal ideation with intent with or without a plan) within the past 2 months or suicidal behavior within the past 6 months at Visit 1/Screening. Additionally, participants must be excluded at Visit 4/Placebo Run-in or Visit 5/Randomization if they report suicidal ideation of items 4 or 5 or suicidal behavior, as measured by the C-SSRS since the last assessment. Excluded participants who meet the description of C-SSRS items 4 or 5 or suicidal behavior will be immediately referred to a qualified mental health professional and must be evaluated that day.

Participants who, at any time during this study (ie, pre- or post-randomization), report suicidal ideation or behavior that is considered to be an AE, either between visits or during visit interviews, must be assessed by the investigator. Participants who report suicidal ideation with intent, with or without a plan or method (ie, a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or ***ANY*** suicidal behavior must be evaluated **that day** by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker, or mental health nurse practitioner (or comparable professional qualification in countries outside the US). Participants whose suicidal ideation is considered to be passive, and who expressly deny any intent to act, and who, after evaluation by a psychiatrist or mental health professional, are not judged to be at serious risk for self-harm during the course of the study may continue on study intervention; others must be interrupted from study intervention and receive appropriate clinical follow-up care to ensure their safety. If after appropriate follow-up care, the investigator judges that the participant can safely resume study intervention, re-dosing can be considered with Sponsor approval. If

after appropriate follow-up care, the investigator judges it is not appropriate for a participant to resume dosing, the participant should be discontinued from study intervention.

All AEs of suicidal ideation or behavior must be recorded as an ECI (see Section 8.4.7). Even if suicidal ideation is present at Visit 1/Screening and has not changed or worsened by Visit 4/Placebo Run-in, the site should still report the suicidal ideation as an ECI. Sites are to designate which health care professionals are to be responsible for acute care on-site and to specify referral center(s) to be used for further evaluation.

Notes:

- The Sponsor Clinical Director or appropriate qualified designee should be contacted at any time during the study if a participant reports a positive response to items 1, 2, or 3 in the assessment of suicidal ideation on the C-SSRS.

- Unscheduled assessments can be conducted for individual participants as considered appropriate by study investigators and, if warranted by emerging data during the conduct of the study, more frequent assessments can be implemented.

8.3.11.1.2 Patient Health Questionnaire – 9

The PHQ-9 is a 9-item self-reported depression screening tool which takes approximately 10 minutes to complete and will be used as a clinical assessment and monitoring tool.

Before Randomization

The investigator must assess the PHQ-9 score at Visit 1/Screening, Visit 4/Placebo-Run-in, and Visit 5/Randomization:

- Actions:
    - Participants with a total score >12 should be excluded from participating in the study.
    - Participants with a total score ≥15 will be referred to a mental health professional.
    - Investigator is expected to exercise good clinical judgment to ensure participant's safety.

Notes:

- The PHQ-9 should be scored and evaluated before all other assessments/procedures.

- If a participant's score on Question #9 of the PHQ-9 is ≥1 (see Appendix 11), but the participant answered "No" to all the questions on the C-SSRS, the investigator must reconcile the discrepancy to determine a participant's study eligibility.

After Randomization

The PHQ-9 will be administered at **ALL** clinic visits to take appropriate action based on score.

- Actions While on Study Intervention:
    - Participants will be referred to a mental health professional if they have a total score ≥15 on the PHQ-9. The investigator will be expected to comply with local/state clinical practice mandates if in the opinion of the investigator the event is deemed an emergency.
    - The Sponsor Clinical Director should be contacted for any score ≥15 on the PHQ-9.

Note: The PHQ-9 should be scored and evaluated before all other assessments/procedures.

8.3.12 Adverse Event Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the SoA (Section 1.3) and more frequently if clinically indicated. AEs will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE, Version 5.0 (see Section 10.14). **Note**: For AEs that are an exception to the NCI CTCAE grading, see Section 7.1.

The criteria for the discontinuation of study intervention for individual participants are described in Section 7.1.

Please refer to Section 8.4 for detailed information regarding assessing and reporting AEs, SAEs, and other reportable safety events.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events 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 as well as other reportable events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent but before intervention randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

For all participants, all AEs, SAEs, and other reportable safety events must be reported by the investigator from the time of intervention randomization through Week 64.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events 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 the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor. This includes any cardiovascular SAE or any malignancy an investigator learns about in a participant who has been discharged from the study through the last participant's last treatment visit in the study must be promptly reported to the Sponsor for adjudication regardless of whether the event is considered related to the study intervention.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 4.

Table 4 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs - ECIs not requiring regulatory reporting - Suicidal ideation, suicidal behaviors	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Certain patient reported outcomes, observer reported outcomes and/or surveys designed for patient respondents that are included in the study require review for SAE identification and

reporting by the investigator or a qualified designee. The assessment of these SAEs should follow the requirements outlined in Section 8.4. The specific patient reported outcomes, observer reported outcomes and /or surveys designed for patient respondents that need to be reviewed for SAE identification, assessment and reporting are listed below:

1. CLDQ NAFLD-NASH
2. PGI-S
3. EQ-5D-5L
4. PHQ-9

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

There are no disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. For participants with ALT and AST **≤ULN at baseline** who meet **ANY** of the following criteria*:

    - ALT or AST >3 × ULN
    - Total bilirubin >2 × ULN (if direct bilirubin is elevated)
    - Alkaline phosphatase >3 × ULN
    - INR >1.5 × ULN**
    - Clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant discomfort, fever, nausea, vomiting, jaundice, rash, or eosinophilia >5%)

2. For participants with ALT and/or AST **>ULN at baseline** who meet **ANY** of the following criteria*:

    - ALT and/or AST >2 × baseline***
    - Total bilirubin >1.5 × baseline AND >ULN (if direct bilirubin is elevated)
    - Alkaline phosphatase >3 × ULN
    - INR >1.5 × ULN**

- Clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant discomfort, fever, nausea, vomiting, jaundice, rash, or eosinophilia >5%).

*Note: The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent). During a period of close observation for DILI, study intervention can be continued, if desired, at the discretion of investigator in consultation with the Sponsor Clinical Director.

**Note: For participants who initiate anticoagulant therapy after study initiation, the INR threshold does not apply.

***Note: If only one of the analytes (ie, ALT or AST) was >ULN at baseline, this criterion (ie, >2 × baseline) would only apply to the analyte that is >ULN at baseline while the criterion noted under #1 above (ie, >3 × ULN) would apply to the analyte that was ≤ULN at baseline.

3. Suicidal ideation, suicidal behaviors

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than the prescribed dose of MK-3655 or matching placebo as defined in the protocol.

No specific information is available on the treatment of overdose of MK-3655. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

8.6 Pharmacokinetics

The decision as to which serum samples collected will be assayed for evaluation of PK will be collaboratively determined by the Sponsor. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for additional PD markers.

8.6.1 Blood Collection for Serum MK-3655

Sample collection, storage, and shipment instructions for serum samples will be provided in the laboratory manual.

PK samples will be collected from all randomized participants according to the PK sampling scheme shown in Table 5 and as outlined in the SoA (Section 1.3). A total of 7 PK samples will be taken from each participant. At all study visits during the double-blind treatment

period where a PK sample will be collected, the participant must withhold their MK-3655/matching placebo dose until after PK sample collection. During the double-blind treatment period, the date and time of the last dose of MK-3655/matching placebo will be recorded. Throughout the study, the date and time of each PK sample will also be recorded.

All PK samples will be used to evaluate not only PK exposures, but also to assess the PK/PD and PK/AE relationships of MK-3655, as appropriate.

Note: In Japan, administration of study intervention will not be allowed by a caregiver. See Section 8.1.8.3 and Appendix 7.

Table 5 Pharmacokinetic Sampling Time Points

Visit Number	Week/Study Day
Visit 5	Week 0/Day 1
Visit 6	Week 4/Day 28
Visit 7	Week 8/Day 56
Visit 8	Week 12/Day 84
Visit 11	Week 24/Day 168
Visit 15	Week 52/Day 364
Visit 16	Week 56/Day 392

ADA=anti-drug antibodies; eCRF=electronic case report form; PK=pharmacokinetic.

Notes:

- Approximately 2 mL of blood will be collected for the PK only timepoint at Visit 7 (Week 8/Day 56). At all other prespecified timepoints, approximately 4 mL of blood will be collected for assessment of ADA and PK.
- The date and time of the PK sample collection for all MK-3655 PK samples must be recorded in the eCRF.
- At the time of PK sample collection, participants will be asked to provide information regarding the time/date of the last dose of MK-3655/matching placebo before the PK sample collection.

8.7 Immunogenicity

ADA samples will be collected from all randomized participants according to the ADA sampling scheme outlined in the SoA (Section 1.3). A total of 6 ADA samples will be taken from each participant. At all study visits during the double-blind treatment period where an ADA sample will be collected, the participant must withhold their MK-3655/matching placebo dose until after ADA sample collection. During the double-blind treatment period, the date and time of the last dose of MK-3655/matching placebo will be recorded. Throughout the study, the date and time of each ADA sample will be recorded.

Sample collection, storage, and shipment instructions for serum samples will be provided in the laboratory manual.

8.8 Pharmacodynamics

PD assessments will be conducted as outlined in the SoA (Section 1.3).

8.8.1 Plasma and Serum Pharmacodynamic Samples

Plasma or serum samples will be used for measurement of the following PD assessments:

- Adiponectin
- Fasting insulin
- HOMA-IR (calculated from fasting glucose and fasting insulin)
- Fasting FFA

Sample collection, storage, and shipment instructions for PD samples will be provided in the laboratory manual.

8.8.2 Biomarkers/Panels Reflecting Liver Inflammation and Fibrosis

The following biomarkers/composite scores will be used to assess liver inflammation and fibrosis:

- The FIB-4 is an index with high clinical utility as it can be calculated by using the patient's age and 3 indirect markers: ALT, AST, and PLT levels. The FIB-4 formula is (((age expressed in years) × (AST [U/L])) / ((PLT [109/L]) × (square root of ALT [U/L]))) [Shah, A. G., et al 2011].
- The NFS is a validated serum-based model used for identifying patients with advanced fibrosis. The NFS uses 6 variables: age, BMI, IFG/diabetes, AST/ALT ratio, PLT, and albumin. The algorithm for NFS = −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × PLT (× 109/L) – 0.66 × albumin (g/dL) [Angulo, P., et al 2007].
- The APRI is an algorithm that uses serum biomarkers for staging fibrosis risk and is calculated using the following equation ([AST level/AST ULN]/PLT count) × 100 [Fallatah, H. I. 2014].
- Pro-C3 levels in serum have been demonstrated to increase with worsening of fibrosis and decrease with fibrosis improvement/regression; suggesting that Pro-C3 may be a potentially useful biomarker in identifying patients with advanced fibrosis and active fibrogenesis, as well as in assessing changes in fibrosis over time. Pro-C3 may also be used to monitor disease progression and therapeutic response [Nielsen, M. J., et al 2015].

Sample collection, storage, and shipment instructions for serum samples will be provided in the laboratory manual. Composite scores will be calculated during data analysis and will not be calculated by the study site.

8.9 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Blood for genetic analysis
- Blood for serum biomarkers
- Blood for plasma biomarkers
- Liver Biopsy

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the laboratory manual.

8.9.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample will be drawn for PNPLA3, TM6SF2, MBOAT7, GCKR, HSD17B13, PPP1R3B, and LYPLAL1 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to PNPLA3, TM6SF2, MBOAT7, GCKR, HSD17B13, PPP1R3B, and LYPLAL1. If the participant provides documented informed consent for FBR, the leftover extracted DNA will be stored for FBR.

Genetic analysis samples will only be collected from randomized participants. If a sample for genetic analysis is not collected at Visit 5/Randomization, it can be collected at a subsequent visit.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the laboratory manual.

8.10 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover DNA for future research

- Leftover main study serum biomarkers for future research
- Leftover main study plasma biomarkers for future research
- Leftover main study liver biopsy for future research

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Fasting Before Scheduled Visits

Participants should be counseled to fast (ie, no food or drink except water) for at least 8 hours before study visits requiring fasted blood collections or procedures (see Section 1.3). Participants who have not fasted for the Visit 1/Screening should have all blood collections rescheduled and completed before the Visit 2/MRI-PDFF. After randomization (Visit 5/Week 0), participants who do not fast before a scheduled visit will be required to return fasted for a study visit within 3 days.

Note: Participants should take their non-AHA medications as prescribed before study visits requiring fasted blood collections or procedures (see Section 1.3).

8.11.2 Scheduling Visits

At Visit 1/Screening, the Visit 2/MRI-PDFF, Visit 3/Liver Biopsy, and Visit 4/Placebo Run-in (including DXA imaging), will be scheduled in advance.

At the end of each study visit from the placebo run-in through the double-blind treatment period, the next study visit should be scheduled. Every effort should be made to adhere to the visit schedule (see Section 1.3). Visit 5/Week 0 (Day 1) should be scheduled 2 weeks ±3 days after Visit 4/Placebo Run-in. Visits during the double-blind treatment period should be scheduled within ±3 days (Visit 5/Week 0 [Day 1] through Visit 11/Week 24) and ±5 days (Visit 12/Week 32 through Visit 15/Week 52). If unavoidable and after consultation with the Sponsor, a visit may be scheduled at a time outside this recommended range. After Visit 5/Week 0 (Day 1), the schedule for subsequent visits must be adjusted so that the total duration of the double-blind treatment period is as close as possible to 52 weeks. Visits during the double-blind treatment period should be scheduled relative to the date of Visit 5/Week 0 (Day 1). If a visit is scheduled at a time other than the protocol designated time, careful consideration must be given to the amount of investigational product the participant has available.

Study sites should contact IVRS at the timepoints outlined in the SoA (see Section 1.3) for purposes of enrollment tracking.

8.11.2.1 Visit Reminders

Before each study visit, participants should be called and be reminded of:

- The date and time of next appointment.
- The requirement:
  - To not engage in physically strenuous exercise (ie, weightlifting, running, bicycling, etc.) within 48 hours before their study visit.
  - To fast for at least 8 hours before all study visits requiring fasting laboratory collections.
  - To not take AHA medications at home the morning of the study visit. Non-study medications that are not AHA medications should be taken as directed by the prescribing physician.
  - To bring blinded study intervention (used and unused vials) on Weeks 32, 40, and 48.
  - To bring participant dosing diaries to each site visit.
  - That administration of study intervention will be witnessed by the investigator and/or study staff at the study visit.

8.11.3 Screening

The interval from Visit 1 through Visit 3 will constitute a screening period of approximately 6 weeks (±28 days). The screening period may be extended under special circumstances (eg, scheduling issues, delays in obtaining MRI-PDFF or liver biopsy results) with the explicit approval of the Sponsor Clinical Director.

8.11.3.1 Visit 1/Screening

Determination of eligibility will be based mostly on medical history of standard of care tests and procedures that were completed before Visit 1/Screening. Potential participants will be evaluated at Visit 1/Screening to determine if they fulfill the entry requirements as described in Sections 5.1 and 5.2. For participants assessed as eligible to participate in the study, blood and urine samples will be obtained according to the SoA (see Section 1.3). Participants who have not fasted for the Visit 1/Screening should have all blood collections rescheduled and completed before Visit 2/MRI-PDFF.

Note: All participants at study sites in Argentina must be tested for Hepatitis B, Hepatitis C, and HIV at Visit 1/Screening (see Appendix 7).

If any participant fails to meet the study entry criteria, Visit 1/Screening procedures may be repeated based on investigator judgment after initial screening, and after consultation with the Sponsor. Participants may only be rescreened once.

See Section 8.11.3.3.1 for managing participants with a historical liver biopsy.

8.11.3.2 Visit 2/MRI-PDFF

LFC will be measured by MRI-PDFF in consented participants whose safety laboratory tests (ie, liver function, renal function, and hematological parameters) meet study eligibility criteria assessed at Visit 1/Screening. Other pending Visit 1/Screening laboratory assessment results are not required to proceed to Visit 2/MRI-PDFF. Participants will be screen failed for any exclusion criteria identified during Screening.

All MRI-PDFF scans will be evaluated by BICR. The appointed iCRO will review all baseline scans and confirm participants meet the MRI-PDFF entry criteria (see Section 5.1) before Visit 3/Liver Biopsy.

Note: A second MRI-PDFF will be performed at 24 weeks after Visit 5/Randomization.

8.11.3.3 Visit 3/Liver Biopsy

8.11.3.3.1 Participants With Historical Liver Biopsies

For consented participants who have had a historical liver biopsy performed within 6 months of Visit 1/Screening and whose safety laboratory tests (ie, liver function, renal function, and hematological parameters) satisfy Visit 1/Screening entry criteria, biopsy samples will be submitted to the central laboratory vendor for processing and BICR to confirm study eligibility.

Notes:

- Other pending Visit 1/Screening laboratory assessment results are not required for submission of biopsy samples to the central laboratory vendor. Participants will be screen failed for any exclusion criteria identified during Screening.
- An MRI-PDFF can be performed in consented participants with pending historical liver biopsy assessments.
- If the historical liver biopsy does not meet study eligibility criteria, the participant will be screen failed.
- If the historical liver biopsy cannot be assessed for any reason (including sample quality), the participant, if agreeable, may have a liver biopsy performed at Visit 3/Liver Biopsy; however, all Visit 1/Screening assessments/procedures and LFC by MRI-PDFF must meet study eligibility criteria before performing the liver biopsy.

8.11.3.3.2 Participants Who Require an In-Study Liver Biopsy

Participants who have not had a liver biopsy within 6 months of Visit 1/Screening, or whose previous liver biopsy is not available for review by the central pathology vendor, or whose previous liver biopsy is of inadequate quality, must have a liver biopsy completed at

Visit 3/Liver Biopsy to be eligible to participate in this study. The biopsy should be performed once the participant has been found to be eligible with respect to all other inclusion and exclusion criteria (see Sections 5.1 and 5.2).

Participants should be fasted (ie, no food or drink except water) for at least 8 hours before the liver biopsy procedure. Biopsy tissue should be of adequate size and of adequate quality for interpretation (see Section 8.2.2). All biopsies will be read by BICR by the central pathology vendor.

Note: A second liver biopsy sample will be collected at Visit 15/Week 52.

8.11.4 Placebo Run-in Period

At Visit 4/Week -2, participants who meet all enrollment criteria as described in Sections 5.1 and 5.2 will be eligible to enter the 2-week, single-blind, placebo run-in period.

After completion of all other study procedures as specified in the SoA (see Section 1.3), eligible participants will be provided instruction and be witnessed in the administration of 2 subcutaneous injections of single-blind investigational product at a volume of 1.5 mL each.

Note: Participants will be re-instructed on appropriate injection technique as needed based on observed injection experience. See Section 8.1.8.3 for further details.

Participants will have a baseline DXA scan performed. If quality control fails and a repeat DXA is required, one will not be performed. The data point will be recorded as a missing value.

8.11.5 Double-Blind Treatment Period

At Visit 5/Randomization (Day 1), participants who meet all study entry criteria will enter the double-blind treatment period of approximately 52 weeks. Participants will be randomized in a 1:1:1:1 ratio to MK-3655 50 mg Q4W, MK-3655 100 mg Q4W, MK-3655 300 mg Q4W, or MK-3655 matching placebo Q4W and assigned a unique treatment/randomization number.

On Day 1 (Visit 5/Randomization) participants will have all study procedures, including the collection of fasting blood samples, performed as described in the SoA (see Section 1.3) **before** the administration of the double-blind study intervention. Study intervention will be administered by participants/caregivers as a witnessed dose at the study site.

At **all scheduled site visits** from Visit 6/Week 4 through Visit 14/Week 48, study intervention will be dispensed, and participants will administer study intervention as a witnessed dose at the study site after all study procedures have been performed as described in the SoA (see Section 1.3).

After Visit 11/Week 24, once administration of study intervention at home applies, participants will be expected to self-administer study intervention as specified in the SoA (ie, Weeks 28, 36, and 44). Therefore, at Visit 11/Week 24, Visit 12/Week 32, and

Visit 13/Week 40, the site will also dispense (supported by IRT) a study intervention kit for administration at home.

On Weeks 28, 36, and 44, participants will record in their diary the date, time, and who administered the injection as well as any comments related to the injection experience. Participants will return their diary, used and unused medication, and the study intervention kit packaging at their next scheduled site visit.

Participants will return to the study site approximately 4 weeks after the last dose of double-blind study intervention (MK-3655/matching placebo) for Visit 15/Week 52.

See Section 8.1.9.1 for timing of dosing study intervention on the day of study visits.

8.11.6 Participants Discontinued From Study Intervention but Continuing to Be Monitored in the Study

It is intended that all randomized participants should be followed through completion of the study, regardless of premature discontinuation of treatment, unless the participant withdraws consent from any study follow-up. Thus, participants who discontinue from study intervention before completion of the study should continue to be monitored after the DC visit procedures are completed to obtain relevant information through the end of the study.

If a participant is discontinued from the study intervention early:

- A DC visit should be completed as specified in the SoA (see Section 1.3) except as noted below:
  - For participants who have completed at least 24 weeks of treatment, DXA imaging should be encouraged as part of the DC visit procedures. For participants who withdraw from the study before completing 24 weeks of treatment, end of study DXA imaging should not be performed at the time of withdrawal.
  - For participants who have completed at least 12 weeks of treatment, completion of the end of study liver biopsy should be encouraged as part of the DC visit procedures. For participants who withdraw from the study before completing 12 weeks of treatment, an end of study liver biopsy should not be performed at the time of withdrawal.
  - For participants where at least 4 weeks have passed since the first dose of double-blind study intervention, the end of study MRI-PDFF should be encouraged as part of the DC Visit procedures. Note, MRI-PDFF assessed in these participants will potentially be used for further evaluation of the kinetics of LFC reduction from the onset of treatment. For participants where less than 4 weeks have passed since the first dose of study intervention, an end of study MRI-PDFF should not be performed at the time of withdrawal.

- Study site visits/telephone contacts should continue to be performed for all participants as outlined in the SoA through Week 64.

- For WOCBP pregnancy testing should continue to be performed monthly until 16 weeks have passed since the last dose of study intervention.

For those participants who have discontinued study intervention early and who miss the remaining study visits, sites will be instructed to make diligent efforts to continue to contact them. To enable sites to reach participants, the participants should provide primary and secondary contact information (eg, home telephone, work telephone, mobile telephone). Sites must document the outcome of the telephone contact(s) to demonstrate diligent efforts have been made.

Additionally, the ICF will explain the importance of continued data collection from participants, including the use of continued contact by telephone.

8.11.7 Post-Treatment Visit and Telephone Contacts

The final scheduled site visit (Visit 16) will occur approximately 4 weeks after Visit 15.

Post-treatment follow-up telephone contacts will be performed at Weeks 60 and 64.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study that are considered principal in nature. If changes are made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses after the study has begun but before any unblinding, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to the analysis of PK data and FBR) will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized here. The comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 2b Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-3655 in Individuals With Pre-cirrhotic Nonalcoholic Steatohepatitis
Treatment Assignment	Participants (82 per group) will be randomized in a 1:1:1:1 ratio among 4 treatment groups: (1) MK-3655 50 mg Q4W, (2) MK-3655 100 mg Q4W, (3) MK-3655 300 mg Q4W, and (4) matching placebo.
Primary Analysis Populations	Efficacy: FAS Safety: APaT
Primary Endpoint	• NASH resolution without worsening in fibrosis by histology (evaluated by BICR) after 52 weeks
Key Secondary Endpoints	• Percent relative reduction in LFC based on MRI-PDFF (evaluated by BICR) after 24 weeks • ≥1 stage improvement in fibrosis without worsening of steatohepatitis by histology (evaluated by BICR) after 52 weeks • ≥2 point reduction in NAS with ≥1 point reduction in inflammation or ballooning without worsening of fibrosis by histology (evaluated by BICR) after 52 weeks
Statistical Methods for Key Efficacy Analyses	Primary: • The differences in proportions and the associated 95% CI and p-values will be provided (MK-3655 minus placebo; 3 pair-wise comparisons) based on the stratified M&N method [Mehrotra, D. V. 2000]. Key Secondary: • For LFC, the differences in means and the associated 95% CIs and p-values will be provided (MK-3655 minus placebo; 3 pair-wise comparisons) based on a cLDA model. • Other key secondary endpoints will follow methods for the primary efficacy endpoint.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences (MK-3655 minus placebo) in the percentage of participants with events, these analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985].

Interim Analyses	A single IA is planned for administrative purposes and to assess futility. The IA is planned to be performed once ≥25 participants per group have completed an MRI-PDFF at the Week 24 post-randomization assessment. Results will be reviewed by an eDMC. Key endpoints to be evaluated include LFC (efficacy), body weight, AEs, and PDLC in laboratory parameters. The study may stop for futility if the posterior probability is <5% that the true mean difference (MK-3655 minus placebo) in percent reduction from baseline in LFC is ≥40% for all active treatment groups.
Multiplicity	There are 3 pair-wise treatment group comparisons that may be tested to address the primary hypothesis. Testing will be performed in order of descending dose and will stop with the first comparison that has a one-sided *p*-value >0.025.
Sample Size and Power	The sample size was chosen based on the proportion of participants with NASH resolution without worsening in fibrosis after 52 weeks. Assuming the proportion with this endpoint based on a non-completer = failure approach is 30% for each MK-3655 dose/modality versus 10% for placebo, a sample size of 82 participants per group provides 90% power for each of the 3 pair-wise treatment comparisons using a one-sided alpha = 0.025.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

The Sponsor will generate the randomized allocation schedule for study intervention assignment for this protocol, and the randomization will be implemented in IVRS.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

Blinding procedures related to the planned IA are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary Efficacy Endpoint

- Proportion of individuals with NASH resolution (defined as a score of 0-1 for lobular inflammation, 0 for ballooning, and any grade of steatosis) without worsening of fibrosis by histology (evaluated by BICR) after 52 weeks

Secondary Efficacy Endpoints

- Mean percent relative reduction from baseline in LFC measured by MRI-PDFF (evaluated by BICR) after 24 weeks

- Proportion of individuals with ≥1 stage improvement in fibrosis without worsening of steatohepatitis (defined as no increase in the NAS for ballooning, inflammation, or steatosis) by histology (evaluated by BICR) after 52 weeks

- Proportion of individuals with ≥2 point improvement in NAS with ≥1 point improvement in inflammation or ballooning without worsening of fibrosis by histology (evaluated by BICR) after 52 weeks

Efficacy endpoints are further described in Section 4.2.1.1.

9.4.2 Patient-Reported Outcome Endpoints

PRO endpoints (eg, score change from baseline over time) include CLDQ NAFLD-NASH, a participant's specific quality of life total and domain scores; PGI-S, a participant's rating of global severity of symptoms; and EQ-5D-5L, health state description and evaluation. Week 52 is the primary timepoint of interest. The PRO endpoints are described in Section 4.2.1.2 and Section 8.2.4.

9.4.3 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory safety tests, vital signs, and body weight.

Safety parameters are described in Section 4.2.1.3.

9.4.4 Pharmacokinetic Endpoint

The key exploratory PK endpoint for MK-3655 is C_{trough}.

Additional details are in Section 4.2.1.4.

9.4.5 Immunogenicity Endpoints

The exploratory immunogenicity endpoints are the incidence and magnitude (titer) of ADA to MK-3655.

Additional details are in Section 4.2.1.5.

9.4.6 Pharmacodynamic Endpoints

The exploratory PD endpoints are adiponectin, fasting insulin, HOMA-IR, FFA, body composition assessed by DXA, and biomarkers/composite scores reflecting liver inflammation and fibrosis (ie, ALT, AST, FIB-4, NFS, APRI, and Pro-C3).

Additional details are in Section 4.2.1.6.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The FAS population will serve as the primary population for all efficacy analyses. All randomized participants who have at least one injection (including only partial) of study intervention and have at least one assessment will be included in this population. Participants will be included in the treatment group to which they are randomized.

9.5.2 Patient-Reported Outcome Analysis Population

The primary PRO population will be based on the FAS population. This population consists of all randomized participants who had at least one dose of study intervention and had completed at least one baseline or post-baseline PRO assessment. The FAS population definition is applied separately to each questionnaire. Participants will be included in the treatment group to which they are randomized.

9.5.3 Safety Analysis Population

Analyses of safety will be performed in the APaT population, consisting of all randomized participants who received at least one injection (including only partial) of study intervention. Participants will be included in the treatment group corresponding to the study intervention they received for the analysis of safety data. This will be the randomized treatment group for all participants except for those who take incorrect study intervention for the entire treatment period. Such participants will be included in the treatment group corresponding to the study intervention actually received. Any participant who receives both correct and incorrect study intervention injections will be analyzed according to the randomized treatment group and a narrative will be provided for any events that occur during the injection period for which the participant was incorrectly dosed.

At least one laboratory or vital sign measurement obtained after at least one dose of study intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.5.4 Pharmacokinetic Analysis Population

The population for PK data analysis is defined as all participants with at least one measurable PK sample.

9.5.5 Immunogenicity Analysis Population

The population for immunogenicity analysis includes all participants with at least one ADA assay result following treatment with MK-3655.

9.5.6 Pharmacodynamic Analysis Population

The primary analysis approach for the PD endpoints will be the FAS population. All randomized participants who have at least one injection (including only partial) of study intervention and have at least one assessment for those analyses for which this is required will be included in this population. Participants will be included in the treatment group to which they are randomized.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the exploratory objectives will be described in the sSAP.

P-values for the key secondary efficacy endpoints may be provided as an assessment of strength of evidence without intent to make inferential claims.

For analysis purposes, the baseline assessment is considered the one closest to but before or on the day of randomization (Day 1).

For stratified analyses, the stratification factors used for randomization (Section 6.3.2) will be applied to the analysis. Small strata will be combined in a way specified by a blinded statistician before the analysis, if needed. The stratification for region (Japan, East Asia excluding Japan, or Other) will be used for randomization to ensure balance in all treatment groups, but it is not considered prognostic and will not be adjusted for in statistical analyses.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and key secondary objectives related to the efficacy endpoints.

The primary efficacy estimand used for this study follows the guidance in ICH E9 (R1) [European Medicines Agency 2020] and has the following 5 attributes:

1. The **treatment** condition of interest and, as appropriate, the alternative treatment condition to which comparison will be made: intervention with MK-3655 or placebo.

2. The **population** of patients targeted by the clinical question: individuals with pre-cirrhotic NASH.

3. The **variable** (or endpoint) to be obtained for each patient that is required to address the clinical question: NASH resolution without worsening of fibrosis.

4. The specification of how to account for **other intercurrent events** to reflect the scientific question of interest: the outcome regardless of intercurrent events is of primary interest.

5. The **population-level summary** for the endpoint which provides the basis for a comparison between-treatment conditions: difference (MK-3655 minus placebo) in the proportion with the primary endpoint at 52 weeks in the effect of being randomized regardless of treatment adherence.

9.6.1.1 Primary Efficacy Endpoint

The primary approach for addressing the primary hypothesis will use the stratified M&N method with minimum risk weights [Mehrotra, D. V. 2000]. The proportion of participants achieving NASH resolution without worsening in fibrosis will be summarized by treatment group. The difference in proportion, 95% CI, and *p*-values will be provided to address the primary objective and associated hypothesis (MK-3655 minus placebo; 3 pair-wise comparisons).

Participants with missing histology data at Week 52 will be considered as not achieving the primary efficacy endpoint.

A *p*-value for the comparison of MK-3655 versus placebo ≤0.025 (one-sided) will be considered statistically significant contingent on the multiplicity strategy (Section 9.8).

Some participants may discontinue before their Week 52 assessment and have a histologic assessment post-randomization (Day 1). For the analysis at the Week 52 timepoint, the Week 52 assessment used in the analysis will be the assessment that is closest to the Week 52 nominal visit (Day 364) that is on or after relative Day 84.

Endpoint response assessment will be based on a centrally-read assessment of both baseline and end of study specimens, blinded to time, and performed when the end of study specimen is available. This post-randomization assessment of the baseline specimen will be considered as the primary histologic baseline assessment for assessing treatment response, though it will not impact on the inclusion of participants in the primary approach to analysis of the primary efficacy endpoint.

9.6.1.2 Secondary Efficacy Endpoints

Liver Fat Content

The primary approach for addressing the change in percent relative reduction from baseline in LFC will use a cLDA method proposed by Liang and Zeger [Liang, K-Y. and Zeger, S. L. 2000]. This model assumes a common baseline mean across treatment groups within stratum and a different mean for each treatment group at the Week 24 post-baseline time point. In

this model, the response vector consists of the baseline value and the value observed at the Week 24 post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will also adjust for treatment, time, stratification (Section 6.3.2), and time by stratification interaction. The treatment difference for each of the 3 pair-wise comparisons of MK-3655 versus placebo in terms of mean change in percent relative reduction from baseline in LFC after 24 weeks will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

Although the baseline measurement is included in the response vector, it is independent of treatment, and hence, the baseline means are constrained to be the same for different treatment groups within each stratum. Of note, in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal ANCOVA model which uses the baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and CIs for individual treatment effects. Moreover, this model allows the inclusion of participants who are missing either the baseline or the Week 24 post-baseline measurement, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation code will be provided in the sSAP.

The cLDA method assumes that the mechanism for missing data is MAR. Sensitivity analyses that will assess the robustness of the MAR-based analysis to deviations from this assumption will be described in the sSAP.

The model-based least squares mean and empirical mean change (with 95% CIs) from baseline for each treatment group and difference between-treatment groups at the Week 24 post-baseline time point will be summarized.

Some participants may discontinue before their Week 24 assessment and have an LFC by MRI-PDFF assessed post-randomization. For the primary analysis at the Week 24 timepoint, the Week 24 assessment used in the analysis will be the assessment that is closest to the Week 24 nominal visit (Day 168) that is on or after relative Day 84.

Histologic

The proportion of participants achieving each of the following secondary histologic efficacy endpoints will be summarized in a similar manner as the primary efficacy endpoint:

- ≥1 stage improvement in fibrosis without worsening of steatohepatitis
- ≥2 point reduction in NAS with ≥1 point reduction in inflammation or ballooning without worsening of fibrosis

Table 6 summarizes the key analysis strategies of the primary and secondary efficacy endpoints.

Table 6 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint			
NASH resolution without worsening in fibrosis after 52 weeks	M&N	FAS	Missing=Failure
Key Secondary Endpoints			
Percent relative reduction from Baseline in LFC after 24 weeks	cLDA	FAS	Model-based
≥1 stage improvement in fibrosis without worsening of steatohepatitis after 52 weeks	M&N	FAS	Missing=Failure
≥2 point reduction in NAS score with ≥1 point reduction in inflammation or ballooning without worsening of fibrosis after 52 weeks	M&N	FAS	Missing=Failure

cLDA=constrained longitudinal data analysis method; FAS=full analysis set; LFC=liver fat content; M&N=Miettinen and Nurminen method; NAS=nonalcoholic fatty liver disease activity score; NASH=nonalcoholic steatohepatitis.

9.6.2 Analysis Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, body weight, and vital signs.

Adverse Events

AEs will be coded using the standard MedDRA and grouped according to SOC.

The analysis of safety results will follow a tiered approach (Table 7). The tiers differ with respect to the analyses that will be performed.

Tier 1 Events

The safety profile of MK-3655 is not understood sufficiently to prespecify any Tier 1 events.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-treatment differences in the proportion of participants with events.

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event; all other AEs and PDLCs will belong to Tier 3. The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when the treatment groups each have fewer than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful

descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and PDLCs.

In addition, summary measures of AEs consisting of the percentage of participants with any AE, with a drug-related AE, with an SAE, with an AE which is both drug-related and serious, who discontinued due to an AE, and who died will be considered Tier 2 endpoints.

The 95% CIs will be provided for between-treatment differences in the percentage of participants with each Tier 2 event; these analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985].

Weight change from baseline will also be considered a Tier 2 endpoint. This analysis will be performed using a cLDA model as described for LFC in Section 9.6.1.2.

Tier 3 Events

Safety endpoints that are not Tier 2 events will be considered Tier 3 events. Only point estimates by treatment group will be provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory and vital signs parameters, summary statistics for baseline, on treatment, and change from baseline values will be provided by treatment group.

Adjudicated Adverse Experiences

For AEs prespecified for adjudication (CV and malignancy), results of adjudication will be summarized. Further details may be provided in the sSAP.

Safety Topics of Special Interest

Safety topics of special interest include suicidal ideation and behavior evaluated by C-SSRS, depression severity evaluated by PHQ-9, and AEs reflecting abuse potential. The AEs reflecting abuse potential will be analyzed as Tier 2 or Tier 3 analogously to AEs. Further details will be provided in the sSAP.

Table 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	*p*-Value for Treatment Comparison	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	-	X	X
	Any Serious AE	-	X	X
	Any Drug-related AE	-	X	X
	Any Serious and Drug-related AE	-	X	X
	Discontinuation Due to AE	-	X	X
	Death	-	X	X
	Specific AEs, SOCs, or PDLCs (Incidence ≥4 Participants in one of the Treatment Groups)	-	X	X
	Weight Change From Baseline	-	X	X
	AEs Reflecting Abuse Potential (Incidence ≥4 Participants in one of the Treatment Groups)	-	X	X
Tier 3	Specific AEs, SOCs, or PDLCs (Incidence <4 Participants in all the Treatment Groups)	-	-	X
	Change From Baseline Results (Laboratory Tests, ECGs, Vital Signs)	-	-	X
	ADA	-	-	X
	Adjudicated Events (CV and malignancy)	-	-	X
	AEs Reflecting Abuse Potential (Incidence <4 Participants in one of the Treatment Groups)	-	-	X
	C-SSRS and PHQ-9	-	-	X

ADA=anti-drug antibodies; AE=adverse event; CI=confidence interval; C-SSRS=Columbia-Suicide Severity Rating Scale; CV=cardiovascular; ECG=electrocardiogram; PDLC=predefined limit of change; PHQ-9=Patient Health Questionnaire – 9; SOC=system organ class; X=results will be provided.

9.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed using tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

A single IA is planned for both administrative purposes and to assess futility. The IA is planned to be performed once ≥25 participants per group have had LFC measured at the Week 24 post-randomization assessment. Key endpoints to be evaluated include LFC (efficacy), body weight, AEs, and laboratory PDLC.

The IA will be conducted by limited Sponsor personnel not otherwise involved in study conduct, who will be unblinded to treatment information. Results of the IA will be reviewed by an eDMC with recommendations provided to an internal EOC.

The administrative purpose addressed by the IA is to enable the EOC to assess whether the interim results are favorable enough to merit initiation of additional programmatic activities. The EOC will review unblinded interim results on a recommendation by the eDMC. Criteria for this recommendation will be provided in the eDMC charter. If the EOC considers that interim data warrant administrative action regarding other aspects of the development program, the unblinded interim data may be reviewed by additional individuals with responsibility for programmatic oversight. Individuals directly involved in study conduct will not have access to unblinded interim results.

The study may stop for futility if the posterior probability is <5% that the true mean difference (MK-3655 minus placebo) in percent reduction from baseline in LFC is ≥40% for all MK-3655 treatment groups. If this non-binding futility criterion is met, the EOC, and possibly additional individuals with responsibility for programmatic oversight, will review unblinded interim results on a recommendation by the eDMC. The study will be stopped for futility if the EOC considers this to be warranted.

The study will neither stop nor be modified unless the futility criterion is met as defined for all MK-3655 groups. There is a 5.0% (<0.1%) chance of observing a posterior probability <5% for a given treatment group if the true mean difference is 40% (50%). There is 0.01% chance that all MK-3655 doses meet the futility criterion if the true mean difference (MK-3655 minus placebo) is 40% for all dose levels. There is a >99% chance that the criterion for stopping for futility will be met if MK-3655 doses are not different from placebo. The posterior probabilities that the true mean difference (MK-3655 minus placebo) in percent relative reduction from baseline in LFC is ≥40% for a range of observed differences in percent reduction from baseline in LFC are presented in Table 8. An observed mean difference <30% for any given MK-3655 dose level would have a posterior probability <5%. All calculations assume a common standard deviation of 20% as well as a normal distribution for the percent relative reduction in LFC.

Table 8 Posterior Probabilities for Observed Differences in % Relative Reduction in LFC

Observed Difference (MK-3655 Minus Placebo) in % Relative Reduction in LFC	**Posterior Probability[a]**
30%	4.2%
35%	19.1%
38%	36.3%
40%	50.0%

LFC=liver fat content.
[a] Posterior probability that the true mean difference (MK-3655 minus placebo) in percent relative reduction from baseline in LFC is ≥40%.

Study enrollment is likely to be ongoing at the time of the IA for futility. Blinding to intervention assignment will be maintained at all investigational sites. The results of the IA will not be shared with the investigators before the completion of the study. Participant-level

unblinding will be restricted to an internal unblinded statistician and scientific programmer performing the IA, who will have no other responsibilities associated with the study.

The eDMC charter will be referenced in the CSR. Before final study unblinding, individuals who have been unblinded at any level will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IA.

The eDMC will also perform rigorous reviews of safety information obtained during the clinical study. Details about the frequency and content of these reviews will be provided in the eDMC charter.

9.8 Multiplicity

There are 3 pair-wise treatment group comparisons that may be tested to address the primary hypothesis. Testing will start with the 300 mg MK-3655 Q4W, then proceed to the 100 mg MK-3655 Q4W dose, and then to the 50 mg MK-3655 Q4W dose, stopping after the first test with a *p*-value >0.025 (1-sided).

The multiplicity strategy strongly controls the Type I error at 2.5% (one-sided) to address the primary hypothesis.

9.9 Sample Size and Power Calculations

9.9.1 Efficacy

Through 24 weeks post-randomization, drop-out is expected to be approximately 10% in each treatment group. The drop-out through 52 weeks post-randomization is expected to be approximately 15% in each treatment group. However, based on the approach to missing data, all 82 randomized participants per group are expected to be included in the primary and key secondary analyses and are the basis for sample size and power calculations.

The sample size was chosen based on the proportion of participants with NASH resolution without worsening in fibrosis after 52 weeks. Assuming the true proportion with this endpoint is 35% for each MK-3655 dose versus 12% for placebo, the assumed proportion using a non-completer = failure approach would be 30% for each MK-3655 versus 10% for placebo. Under these assumed proportions, a sample size of 82 participants per group provides 90% power to demonstrate superiority for each of the 3 pair-wise treatment comparisons using a one-sided alpha = 0.025.

With respect to the secondary endpoint of percent relative reduction from baseline in LFC after 24 weeks, a sample size of 82 participants per group provides >99% power (standard deviation = 20% and assumed mean difference over placebo ≥40%) using a one-sided alpha = 0.025.

9.9.2 Safety

Given the sample size of 82 per group, Table 9 provides examples of minimum differences in proportions in AEs between each MK-3655 dose and placebo that would have a 95% CI that excludes zero based on the M&N method [Miettinen, O. and Nurminen, M. 1985].

Table 9 Examples of AE Incidences for Which the 95% CI for the Difference Would Exclude Zero

MK-3655 n/N (%)	**Placebo** n/N (%)
7/82 (9%)	1/82 (1%)
10/82 (12%)	3/82 (4%)
15/82 (18%)	6/82 (7%)
M&N=Miettinen and Nurminen method; n=sample size; N=population size. Based on the M&N method [Miettinen, O. and Nurminen, M. 1985].	

9.10 Subgroup Analyses

Primary and key secondary efficacy endpoints will be summarized for each of the following baseline defined subgroups:

- Concurrent diagnosis of T2DM at the time of randomization (Yes or No)
- Fibrosis score (Stage 2 or Stage 3)
- Region (Japan, East Asia excluding Japan, or Other)
- Age (≥65 years vs <65 years)
- BMI (>30 kg/m^2 vs ≤30 kg/m^2)
- Region (to be defined in the sSAP)
- LFC (>20% vs ≤20%)
- Sex (male vs female)

9.11 Compliance (Medication Adherence)

Compliance and accountability data for study intervention will be collected during the study. Any deviation from protocol-directed administration will be reported. The primary definition of compliance is defined as the proportion of participants who received the expected number of injections over the duration of time that they were in the study divided by the total number of participants receiving at least one injection. Further detail will be provided in the sSAP.

Drug accountability data for study treatment will be collected during the study. Compliance with study treatment administration will be measured by subjects: (1) receiving unscheduled study agent injections; (2) missing an injection. Numbers and percentages of subjects and

injection visits with any deviation in these measures will be reported for all randomized participants.

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in terms of number of injections. Dose interruption will be summarized. Summary statistics will be provided on extent of exposure for the APaT population. Further detail will be provided in the sSAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations, (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus

source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the eDMC regarding the study.

Additionally, on a recommendation by the eDMC, the EOC will perform an administrative look to assess whether the interim results are favorable enough to merit initiation of additional programmatic activities.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an eDMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the eDMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The eDMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the eDMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 Interim Analyses) and recommend to the EOC whether the study should continue in accordance with the protocol. Additionally, the eDMC will inform the EOC if interim results meet the criteria to initiate an administrative look (to be defined in the eDMC charter).

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of eDMC reports, minutes, and recommendations will be described in the eDMC charter that is reviewed and approved by all the eDMC members.

10.1.4.3 Clinical Adjudication Committee (CAC)

A CAC will evaluate the following events for the purposes of confirming them according to the criteria in the Adjudication Charter, as well as evaluating the presence of confounding factors.

Multiple CACs will evaluate the following events:

1. Malignancy: Thorough evaluation of malignancies is important in the development program of all investigational medications; therefore, detailed information will be collected for participants who develop a malignancy.

2. Serious CV Events: Patients with NASH often have associated metabolic comorbidities that include obesity, dyslipidemia, T2DM, and MetS. Since CV disease is a major cause of mortality for individuals with these conditions, serious CV events will be adjudicated in this study (including events from participants who continue to be followed after discontinuation of double-blinded study intervention).

All personnel involved in the adjudication process will remain blinded to study intervention allocation throughout the study.

Specific details regarding endpoint definitions can be found in the Adjudication Charter.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10 will be performed by the central laboratory.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2 of the protocol.

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10 Protocol-Required Laboratory Assessments

Laboratory Assessments			
Hematology	**Chemistry**	**Other Tests**	**Routine Urinalysis[a]**
• Hemoglobin • Hematocrit • RBC count • RBC morphology • Mean corpuscular volume • Platelet count • WBC count • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	BUN Serum creatinine • eGFR calculation[b] Glucose Sodium Potassium Chloride • Total carbon dioxide (bicarbonate) AST (SGOT) ALT (SGPT) ALP Albumin Total bilirubin • Direct (conjugated) bilirubin • Indirect (unconjugated) bilirubin	• Hepatitis B (HBsAg) and Hepatitis C (anti-HCV) serology[c] • HIV[c] • FSH • hCG pregnancy test (urine and/or serum)[d] • INR • TSH • FT4 • Cortisol (bedtime salivary) • ACTH[e] • IGF-1 • Hemoglobin A1C • FPG • Insulin • Lipid profile (Total Cholesterol, non-HDL-C, HDL-C, LDL-C, and TG) • apoA1 and apoB[f] • Ketones (serum)[g] • Adiponectin • FFA • Bone biomarkers (CTX and P1NP) • Pro-C3 • Immunogenicity assay (ADA) • Prothrombin time	• Blood • Glucose • Protein • Leukocyte esterase • Nitrates • Specific gravity • pH • Microscopic examination (if abnormal results are noted)

A1C=glycated hemoglobin; ACTH=adrenocorticotropic hormone; ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; apoA1=apolipoprotein A1; apoB=apolipoprotein B; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CTX=collagen type 1 cross-linked telopeptide; eGFR=estimated glomerular filtration rate; FFA=free fatty acid; FPG=fasting plasma glucose; FSH=follicle stimulating hormone; FT4=free thyroxine; HBsAg=Hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=Hepatitis C virus; HDL-C=high density lipoprotein-cholesterol; HIV=human immunodeficiency virus; IGF-1=insulin-like growth factor-1; INR=international normalized ratio; LDL-C=low density lipoprotein-cholesterol; MDRD=Modification of Diet in Renal Disease; P1NP=procollagen type 1 N terminal propeptide; pH=potential of hydrogen; Pro-C3=propeptide of type III collagen; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; RBC=red blood cell; TG=triglycerides; TSH=thyroid-stimulating hormone; WBC=white blood cell.

[a] Dipstick to be performed at the study site.
[b] eGFR calculated using the MDRD formula. For participants in Japan, eGFR will be calculated using the Japanese Equation 4 (Appendix 7) [Matsuo, S., et al 2009]. See Appendix 13 for the eGFR equations.
[c] For participants in Argentina, Hepatitis B, Hepatitis C, and HIV tests are required at Visit 1/Screening (see Appendix 7).
[d] A serum pregnancy test should only be performed if the local urine pregnancy test is positive or inconclusive, or if a serum pregnancy test is required per local guidelines.
[e] ACTH samples should be collected between 7 AM and 10 AM.
[f] apoB and apoA1 will not be collected at Visit 1/Screening.
[g] Includes acetoacetic acid and beta-hydroxybutyrate.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Note: Congenital disorders (eg, present from birth) not detected or diagnosed prior to study intervention administration do not qualify for reporting as AE

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to 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.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE). A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, Version 5.0. Any AE that changes CTCAE Grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

- Grade 4: Life-threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- The following components are to be used to assess the relationship between the **Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

- If no, this is a negative dechallenge.

- (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

  - If yes, did the AE recur or worsen?

  - If yes, this is a positive rechallenge.

  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- Consistency with study intervention profile: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

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

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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 no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:

- Highly Effective Contraceptive Methods That Have Low User Dependency
  Failure rate of <1% per year when used consistently and correctly.
  - Progestogen-only subdermal contraceptive implant[b]
  - IUS[c]
  - Non-hormonal IUD
  - Bilateral tubal occlusion
  - Azoospermic partner (vasectomized or secondary to medical cause)
    This 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. A spermatogenesis cycle is approximately 90 days.

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

- 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 intervention. 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.

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

[b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.

[c] IUS is a progestin releasing IUD.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.10 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@msd.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@msd.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 China-specific Requirements

Section 8 Study Assessments and Procedures

The information in this appendix is added to the main protocol to describe the blood volume collection for participants in China.

Parameters Collected per Participant	Screening Period	Double-Blind Treatment Period	Post-Treatment Follow-up	Total Collections	mL per Collection	Total (mL)/ Test
		V5 to V15	V16			
FPG	1	7	-	8	2	16
Fasting FFA and P1NP	-	3	-	3	2.5	7.5
PT and INR	1	-	-	1	1.8	1.8
Hepatitis screen (HBsAg, anti-HCV, and HCV [RNA])	1	-	-	1	8.5	8.5
Hematology laboratory tests and when applicable A1C	1	6	-	7	2	14
Chemistry laboratory tests, fasting lipid profile[a], and when applicable apoA1, apoB, and hCG	1	4	-	5	3.5	17.5
Chemistry laboratory tests	-	2	-	2	2.5	5
TSH, FT4, and when applicable FSH	1	5	-	6	2.5	15
Acetoacetic acid and beta-hydroxybutyrate	-	6	-	6	5	30
IGF-1	1	5	-	6	2.5	15
ACTH	-	8	-	8	2	16
CTX	-	3	-	3	2.5	7.5
Fasting insulin	-	3	-	3	2	6
Adiponectin	-	3	-	3	2.5	7.5
Blood for serum MK-3655 PK assay (for PK only timepoint)	-	1	-	1	2	2
Blood for serum MK-3655 PK assay and immunogenicity assay (ADA)	-	5	1	6	4	24
					Total Blood Volume per Participant[b]	193.3 mL

A1C=glycated hemoglobin; ACTH=adrenocorticotropic hormone; ADA=anti-drug antibodies; apoA1=apolipoprotein A1; apoB=apolipoprotein B; CTX=collagen type 1 cross-linked telopeptide; EOT=end of treatment; FFA=free fatty acid; FPG=fasting plasma glucose; FT4=free thyroxine; FSH=follicle stimulating hormone; HBsAg=Hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=Hepatitis C virus; HDL-C=high density lipoprotein-cholesterol; IGF-1=insulin-like growth factor-1; INR=international normalized ratio; LDL-C=low density lipoprotein-cholesterol; P1NP=procollagen type 1 N-terminal propeptide; PK=pharmacokinetic; PT=prothrombin time; RNA=ribonucleic acid; TG=triglycerides; TSH=thyroid-stimulating hormone; V=visit.

[a] Includes total cholesterol, non-HDL-C, HDL-C, LDL-C, and TG.

[b] If additional pharmacokinetic/pharmacodynamic and/or safety analyses are necessary, additional blood (up to 50 mL) may be obtained.

10.7.2 Argentina-specific Requirements

Section 1.3 Schedule of Activities (SoA), Section 8.11.3.1 Visit 1/Screening and Section 10.2 Appendix 2: Clinical Laboratory Tests

All participants at study sites in Argentina must be tested for Hepatitis B, Hepatitis C, and HIV at Visit 1/Screening before randomization.

10.7.3 Taiwan-specific Requirements

Section 1.1 Synopsis, Section 1.2 Schema, Section 3 Hypotheses, Objectives, and Endpoints, Section 4.1 Overall Design, Section 5 Study Population and Section 5.1 Inclusion Criteria

All participants at study sites in Taiwan must be a male or female aged 20 years to 80 years with capacity of will, at the time of signing the ICF.

10.7.4 Japan-specific Requirements

Section 1.1 Synopsis, Section 1.2 Schema, Section 3 Hypotheses, Objectives, and Endpoints, Section 4.1 Overall Design, Section 5 Study Population, and Section 5.1 Inclusion Criteria

All participants at study sites in Japan must be a male or female aged 20 years to 80 years, at the time of signing the ICF.

Section 1.3 Schedule of Activities (SoA), Section 6.1 Study Intervention(s) Administered, Section 6.4 Study Intervention Compliance, Section 8.1.8.3 Self-injection Training (Participant and/or Caregiver), Section 8.1.8.4 Witnessed Dosing, Section 8.1.9 Study Intervention Administration, Section 8.1.9.1 Timing of Dose Administration, and Section 8.6.1 Blood Collection for Serum MK-3655

In Japan, administration of study intervention can only be performed by a medically qualified person (eg, physician, supporting nurse); self-administration by the participant him/herself is the only exception. Therefore, administration of study intervention by a caregiver will not be allowed in Japan.

Section 4.1 Overall Design and 6.3.2 Stratification

If either proportion of participants, those with T2DM or those without T2DM, exceeds approximately 60% of the total targeted sample size, the remaining participants enrolled will be restricted to the other stratum within this stratification factor. In Japan, enrollment will not be restricted by this cap, and sites will be able to continue to enroll participants with or without T2DM.

Section 5.2 Exclusion Criteria, Section 7.1 Discontinuation of Study Intervention, Section 10.2 Appendix 2: Clinical Laboratory Tests, and Section 10.13 Appendix 13: eGFR Equations

For the calculation of eGFR for participants in Japan, the Japanese 3-variable Equation 4 will be used (see Appendix 13) [Matsuo, S., et al 2009].

10.7.5 Korea-specific Requirements

Section 5.2 Exclusion Criteria

Prior/Concurrent Clinical Study Experience

23. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device ≤3 months **or ≤5 half-lives (whichever is longer)** before participating in this current study. Participants enrolled in observational studies may be included and will be reviewed on a case-by-case basis for approval by the Sponsor.

10.8 Appendix 8: Other Medical Device: Complaints Including Product Quality Complaint, Malfunction, Serious Injury, Death, Fetal Distress/Fetal Death and Congenital Anomaly: Definitions and Reporting

Not applicable.

10.9 Appendix 9: Approximate Blood Volume Table

Parameters Collected per Participant	Screening Period	Double-Blind Treatment Period	Post-Treatment Follow-up	Total Collections	mL per Collection	Total (mL)/Test
		V5 to V15	V16			
FPG	1	7	-	8	2	16
Fasting FFA and P1NP	-	3	-	3	2.5	7.5
PT and INR	1	-	-	1	1.8	1.8
Hepatitis screen (HBsAg, anti-HCV, and HCV [RNA])	1	-	-	1	8.5	8.5
Hematology laboratory tests and when applicable A1C	1	6	-	7	2	14
Chemistry laboratory tests, fasting lipid profile[a], and when applicable apoA1, apoB, and hCG	1	4	-	5	3.5	17.5
Chemistry laboratory tests	-	2	-	2	2.5	5
TSH, FT4, and when applicable FSH	1	5	-	6	2.5	15
Acetoacetic Acid	-	6	-	6	6	36
Beta-hydroxybutyrate	-	1	-	1	2.5	2.5
Beta-hydroxybutyrate and IGF-1	-	5	-	5	2.5	12.5
IGF-1	1	-	-	1	2.5	2.5
ACTH	-	8	-	8	2	16
CTX	-	3	-	3	2.5	7.5
Adiponectin	-	3	-	3	2.5	7.5
Fasting insulin	-	3	-	3	2	6
Pro-C3	-	3	-	3	2.5	7.5
Blood for serum biomarkers	1	5	-	6	4	24
Blood for plasma biomarkers	1	5	-	6	6	36
Blood for serum MK-3655 PK assay (for PK only timepoint)	-	1	-	1	2	2
Blood for serum MK-3655 PK assay and immunogenicity assay (ADA)	-	5	1	6	4	24
Blood for planned genetic analysis	-	1	-	1	8.5	8.5
					Total Blood Volume per Participant[b]	277.8 mL

A1C=glycated hemoglobin; ACTH=adrenocorticotropic hormone; ADA=anti-drug antibodies; apoA1=apolipoprotein A1; apoB=apolipoprotein B; CTX=collagen type 1 cross-linked telopeptide; EOT=end of treatment; FFA=free fatty acid; FPG=fasting plasma glucose; FT4=free thyroxine; FSH=follicle stimulating hormone; HBsAg=Hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=Hepatitis C virus; HDL-C=high density lipoprotein-cholesterol; IGF-1=insulin-like growth factor-1; INR=international normalized ratio; LDL-C=low density lipoprotein-cholesterol; P1NP=procollagen type 1 N-terminal propeptide; PK=pharmacokinetic; Pro-C3=propeptide of type III collagen; PT=prothrombin time; RNA=ribonucleic acid; TG=triglycerides; TSH=thyroid-stimulating hormone; V=visit.

[a] Includes total cholesterol, non-HDL-C, HDL-C, LDL-C, and TG.

[b] If additional pharmacokinetic/pharmacodynamic and/or safety analyses are necessary, additional blood (up to 50 mL) may be obtained.

10.10 Appendix 10: Management of Participants With Elevated Liver Enzymes

Although participants enrolled in this study will have baseline liver disease, their hepatic function should not be significantly impaired. However, at baseline, some may have liver biochemistry levels above the ULN.

The central laboratory report will alert the investigator if a participant meets the thresholds outlined in Section 8.4.7. The investigator should initiate close observation and discontinue the participant from blinded study intervention if a prespecified criterion for discontinuation is met.

Close Observation for DILI Guidelines:

- Repeating liver biochemistries (ALT, AST, ALP, total bilirubin, INR) within 48 hours
- Obtaining a more detailed history of symptoms and prior or concurrent disease
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtaining a history of exposure to environmental chemical agents
- Ruling out other causes of liver disease as needed (obtain viral hepatitis panel, imaging for evaluation of biliary tract disease, etc. if required in the opinion of the primary investigator)
- Continuing to monitor liver biochemistries twice weekly. Frequency can decrease to once a week or less if abnormalities stabilize or study intervention has been discontinued and participant is asymptomatic
- Reviewing ***Discontinuation of Study Intervention for Elevated Liver Enzymes*** (see below) to see if a participant meets a given criterion
- Considering a gastroenterology or hepatology consultation
- Considering a liver biopsy

Discontinuation of Study Intervention for Elevated Liver Enzymes

However, for all participants, study intervention should be discontinued if any of the specified criteria below are met and no other cause for the combination of laboratory abnormalities is immediately apparent:

For participants with ALT and AST **≤ULN at baseline** who meet **ANY** of the following criteria:

- ALT or AST >3 × ULN **AND** either total bilirubin >2 × ULN or INR >1.5*
- ALT or AST >3 × ULN **AND** the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN **AND** participant is unwilling or unable to undergo repeat ALT and AST testing at the frequency defined above in the ***Close Observation for DILI Guidelines***
- ALT or AST >8 × ULN (confirmed by repeat testing)

For participants with ALT and/or AST **>ULN at baseline**[**] who meet **ANY** of the following criteria:

- ALT and/or AST >2 × baseline **AND** total bilirubin >2 × ULN or INR >1.5[*] (confirmed by repeat testing)
- ALT and/or AST >2 × baseline **AND** the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) (confirmed by repeat testing)
- ALT and/or AST >5 × baseline for more than 2 weeks
- ALT and/or AST >3 × baseline **AND** participant is unwilling or unable to undergo repeat ALT and AST testing at the frequency defined above in the ***Close Observation for DILI Guidelines***
- ALT and/or AST ≥500 U/L (confirmed by repeat testing)

[*]**Note**: For participants who initiate anticoagulant therapy after study initiation, the INR threshold does not apply.

[**]**Note**: If only one of the analytes (ie, ALT or AST) was >ULN at baseline, each criterion below would only apply to the analyte that was >ULN at baseline.

10.11 Appendix 11: Patient Health Questionnaire - 9

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____
=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

10.12 Appendix 12: NASH Clinical Research Network (CRN) Scoring System for Determining Eligibility and Assessing Secondary Histological Endpoints

NAFLD Activity Score (NAS)		**Fibrosis Staging**	
Parameter	Scoring Criteria	Parameter	Staging Criteria
Steatosis	0 = <5% 1 = 5% to 33% 2 = >33% to 66% 3 = >66%	Stage 0	No Fibrosis
Lobular Inflammation	0 = No Foci 1 = <2 Foci per 200 × field 2 = 2 to 4 Foci per 200 × field 3 = >4 Foci per 200 × field	Stage 1 Stage 1a Stage 1b Stage 1c	Perisinusoidal or Periportal Mild, Zone 3, Perisinusoidal Moderate, Zone 3, Perisinusoidal Portal / Periportal
Ballooning	0 = None 1 = Few Balloon Cells 2 = Many Cells / Prominent Ballooning	Stage 2	Perisinusoidal and Portal / Periportal
		Stage 3	Bridging Fibrosis
		Stage 4	Cirrhosis

Source ID: [Kleiner, D. E., et al 2005]

10.13 Appendix 13: eGFR Equations

MDRD Equation:

- eGFR = 175 × Serum Creatinine-1.154 × Age-0.203 × 1.212 (if participant is black) × 0.742 (if female)

Equation 4 (for participants in Japan only [Appendix 7]):

- eGFR = 194 × Serum Creatinine-1.094 × Age-0.287 × 0.739 (if female).

10.14 Appendix 14: Common Terminology Criteria for Adverse Events Version 5.0

The descriptions and grading scales found in the NCI CTCAE, Version 5.0 will be used for AE reporting (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf) except as noted in Section 7.1.

10.15 Appendix 15: Abbreviations

Abbreviation	Expanded Term
A1C	Glycated Hemoglobin
ACC	Acetyl-CoA Carboxylase
ACTH	Adrenocorticotropic Hormone
ADA	Anti-drug Antibodies
AE	Adverse Event
AHA	Antihyperglycemic Agent
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
APaT	All Participants as Treated
apoA1	Apolipoprotein A1
apoB	Apolipoprotein B
APRI	AST/Platelet Ratio Index
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AxMP	Auxiliary Medicinal Product
BICR	Blinded Independent Central Review
BLA	Biologics License Application
BMD	Bone Mineral Density
BMI	Body Mass Index
CAC	Clinical Adjudication Committee
CFR	Code of Federal Regulations
CI	Confidence Interval
cLDA	Constrained Longitudinal Data Analysis
CLDQ-NAFLD-NASH	Chronic Liver Disease Questionnaire for Nonalcoholic Fatty Liver Disease - NASH
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRN	Clinical Research Network
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
C_{trough}	Trough Concentration
CTX	Collagen Type 1 Cross-linked Telopeptide
CV	Cardiovascular
DC	Discontinuation
DGAT2	Diacylglycerol O-Acyltransferase 2
DILI	Drug-induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DXA	Dual-energy X-ray Absorptiometry
ECG	Electrocardiogram
ECI	Event of Clinical Interest
(e)CRF	(Electronic) Case Report Form
EDC	Electronic Data Collection
eDMC	External Data Monitoring Committee
eGFR	Estimated Glomerular Filtration Rate

Abbreviation	Expanded Term
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	End of Treatment
EU	European Union
EU CTR	European Union Clinical Trial Regulation
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FIB-4	Fibrosis-4
FFA	Free Fatty Acid
FGF19, -21	Fibroblast Growth Factor-19, -21
FGFR1c	Fibroblast Growth Factor Receptor-1c
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone
FT4	Free Thyroxine
FXR	Farnesoid X Receptor
GCKR	Glucokinase Regulatory Protein
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GnRH	Gonadotropin-Releasing Hormone
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDL-C	High Density Lipoprotein-Cholesterol
HIV	Human Immunodeficiency Virus
HOMA-IR	Homeostatic Model Assessment-Insulin Resistance
HRT	Hormone Replacement Therapy
HSD17B13	Hydroxysteroid 17-Beta Dehydrogenase 13
IA(s)	Interim Analysis(ses)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	Imaging Clinical Research Organization
IEC	Independent Ethics Committee
IFG	Impaired Fasting Glycemia
IGF-1	Insulin-like Growth Factor-1
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Progestin releasing IUD
IVRS	Interactive Voice Response System
KLB	β-klotho
LDL-C	Low Density Lipoprotein-Cholesterol
LFC	Liver Fat Content
LYPLAL1	Lysophospholipase-like Protein 1
M&N	Miettinen and Nurminen Method
mAb	Monoclonal Antibody

Abbreviation	Expanded Term
MAD	Multiple Ascending Dose
MAR	Missing at Random
MBOAT7	Membrane Bound O-Acyltransferase Domain-Containing 7
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MetS	Metabolic Syndrome
MRI	Magnetic Resonance Imaging
MRI-PDFF	MRI-Estimated Proton Density Fat Fraction
MTD	Maximum Tolerated Dose
Na	Sodium
NAFLD	Nonalcoholic Fatty Liver Disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic Steatohepatitis
NCI	National Cancer Institute
NDA	New Drug Application
NFS	NAFLD Fibrosis Score
NGM	NGM Biopharmaceuticals, Inc
NHP	Nonhuman Primate
NIMP	Non-Investigational Medicinal Product
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
P1NP	Procollagen Type 1 N-terminal propeptide
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PDLC	Predefined Limits of Change
PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire – 9
PK	Pharmacokinetic
PLT	Platelet
PNPLA3	Patatin-like Phospholipase Domain-Containing Protein 3
PPAR	Peroxisome Proliferator-activated Receptor
PPP1R3B	Protein Phosphatase 1 Regulatory Subunit 3B
PRO	Patient-Reported Outcome
Pro-C3	Propeptide of Type III Collagen
PTH	Parathyroid Hormone
Q1W/Q2W/Q4W	Once Every Week/Once Every 2 Weeks/Once Every 4 Weeks
RANK	Receptor Activator of Nuclear Factor Kappa-B
RNA	Ribonucleic Acid
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
siDMC	Standing Internal Data Monitoring Committee
SLAB	Supplemental Laboratory Test(s)
SoA	Schedule of Activities
SOC	System Organ Class
sSAP	Supplementary Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction

Abbreviation	Expanded Term
$t_{1/2}$	Half-Life
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
TM6SF2	Transmembrane 6 Superfamily Member 2
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
WOCBP	Woman/Women of Childbearing Potential

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