Clinical Study Protocol

NCT Number: NCT07052682

Title: A Multicenter, Single-arm, Open-label, Phase 1b Study to Explore the Mechanism of Action and Evaluate the Safety of Ontamalimab in Participants With Nonalcoholic Steatohepatitis With Fibrosis Stage 1 Through 4

Study Number: TAK-647-1001

Document Version and Date: Amendment no. 3, 18 Sep 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Multicenter, Single-arm, Open-label, Phase 1b Study to Explore the Mechanism of Action and Evaluate the Safety of Ontamalimab in Participants With Nonalcoholic Steatohepatitis With Fibrosis Stage 1 Through 4

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA
Study Number:	TAK-647-1001
Study Phase:	Phase 1b

IND Number:	163193	**EudraCT/CTIS Number:**	Not applicable
Investigational Product:	TAK-647 (ontamalimab)		
Date:	18 September 2023	**Version/Amendment Number:**	Amendment 3

Amendment History:

Date	Amendment Number	Region
02 November 2022	Initial version	Global
15 December 2022	Amendment 1	Global
25 April 2023	Amendment 2	Global
18 September 2023	Amendment 3	Global

APPROVALS

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP)
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations

SIGNATURE OF THE RESPONSIBLE TAKEDA MEDICAL OFFICER

[redacted], MD
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Translational Medicine & Biomarkers
Gastroenterology Drug Discovery Unit

[redacted]

19-Sep-2023 | 08:37:22 JST

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Summary of Change(s) Since the Last Version of the Approved Protocol	
Protocol Amendment 3	
Amendment Date: 18 September 2023	**Global/Region/Country/Site Specific:** Global
Overall Reason for the Amendment The overall reasons for this protocol amendment are to: • Revise inclusion and exclusion criteria to improve study feasibility. • Clarify the screening period eligibility and extension of its duration. • Clarify the acceptable conditions for including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-infected participants into the study and to allow adequate time for recovery of symptoms before screening.	

Description of Each Change and Rationale			**Section(s) Affected by Change**
#	**Description of change(s)**	**Rationale for change(s)**	**Section**
1.	Revised the title of the protocol from, "A Multicenter, Single-arm, Open-label, Phase 1b Study to Explore the Mechanism of Action and Evaluate the Safety of Ontamalimab in Participants With Nonalcoholic Steatohepatitis With Fibrosis Stages 2 Through 4" to "A Multicenter, Single-arm, Open-label, Phase 1b Study to Explore the Mechanism of Action and Evaluate the Safety of Ontamalimab in Participants With Nonalcoholic Steatohepatitis With Fibrosis Stage 1 Through 4"	Correction.	Section 1.1 Synopsis
2.	• Added the word "noncirrhotic (F1-F3)" to define the fibrosis stages F1-F3. • Replaced "evidence for nonalcoholic steatohepatitis (NASH)" or "biopsy-confirmed NASH" with "indication of/for NASH". • Revised the statement from, "Ontamalimab will be administered at Day 1 and Q4W thereafter for up to 24 weeks (last dose at Week 20)" to "Ontamalimab will be administered subcutaneously (SC) every 4 weeks (Q4W) starting on Day 1 and the last dose is administered at Week 20 (total treatment period is 24 weeks)". • Added the word "clinically significant" to provide clarification on	Clarification.	Section 1.1 Synopsis Figure 1 Study Schema Section 1.3.1 Schedule of Activities: Screening Period Section 1.3.2 Schedule of Activities: Treatment Period Section 4.1 Overall Design Section 4.4 End of Study/Study Completion Definition Section 5.1 Inclusion Criteria, Criteria #6 and #13 Section 5.2 Exclusion Criteria, Criteria #1, #2, #13, #21 Section 5.1.1 Justification of Inclusion Criteria Section 5.4 Screening

Description of Each Change and Rationale			**Section(s) Affected by Change**
#	**Description of change(s)**	**Rationale for change(s)**	**Section**
	"abnormal chest X-ray findings" in Exclusion criterion #13. • Revised Exclusion criteria #1, #2 and #21. • Screening Period: Added a few statements related to screening period. 1. "(Maximum allowed time between historical liver biopsy and first dose of study drug is 34 weeks for any participant, except for the participants who test positive for SARS-CoV-2 at screening)". 2. "Progression of screening is contingent on successful confirmation of eligibility along with the sponsor's approval". 3. "In case of positive test for SARS-CoV-2 infection, screening may be paused for an additional 2 weeks (ie, screening period of up to 12 weeks)". 4. "The screening period can be extended by 2 weeks for any reason (including but not limited to a repeat test requirement for select and predefined measurements) on a case-by-case basis with the sponsor's approval". 5. In case of positive test for SARS-CoV-2 infection, the total study period could be up to 48 weeks (ie, screening period of up to 12 weeks). 6. Revised the statement from "An individual who has been designated a screen failure may be rescreened once, except for participants who fail the histological evaluation of the liver biopsy." to "An individual who has been designated a screen failure may be rescreened once". • Schedule of Activities: Clarified in the Tables 1, 2 and 3. 1. Revised the table title from "Table 1. Schedule of Activities: Screening Period" to "Table 1. Schedule of Activities: Screening Period (Visit 1 and 2)". 2. Removed columns of Visit 4a and Visit 4a2 from Table. Schedule of Activities: Treatment Period, follow-up, and End of Study.		Section 5.4.1 Screen Failures Section 5.5 Criteria for Temporary Delaying Enrollment Section 6.1 Study Drug Administered Section 8 Study Assessments and Procedures Section 8.2.8 Liver Biopsy Section 8.3.11.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information Section 9.3 Biomarker and Noninvasive Test Analyses Section 10.1.5.2 Other Committees Section 10.3.1 Definition of Adverse Event Section 10.3.4.9 Pretreatment-emergent Adverse Events

Description of Each Change and Rationale			**Section(s) Affected by Change**
#	**Description of change(s)**	**Rationale for change(s)**	**Section**
	3. Added a table, "Table 2. Schedule of Activities: Screening Period (Visit 4a and 4a2)". 4. Revised the table numbers and footnote sequences. 5. Revised "footnote a" in Table 3. • Pro-C3/ELF score: Revised the statements on the liver biopsy eligibility in participants with Pro-C3 ≥12.6 ng/mL and ELF score ≥7.7. Other changes include: ○ From "During the screening period, Pro-C3, ELF, and other exploratory markers will be measured at 3 visits (including Day 1 predose) to determine intra-participant variability." to "Pro-C3, ELF, and other exploratory markers will be measured at 2 screening visits (SV1 and SV2) and Day 1 [D1] predose measurement during treatment period to determine intra-participant variability." • Screening visits: Changes include: 1. From "The following laboratory findings are exclusionary for all participants if found during either screening visit (Week -8 or Week -6)" to "The following laboratory findings are exclusionary for all participants if found during screening visits (Week -8 [SV1], Week -6 [SV2] or at Day -4 visit [Visit 4a2])" in Exclusion criterion #1. 2. From "For biomarkers except cT1 MRI, data from all available sampling during screening (including the Day 1 predose measurement) will be averaged to establish the stable baseline value." to "For biomarkers except cT1 MRI, data from all available sampling during screening period (SV1 and SV2) and D1 predose measurement during treatment period will be averaged to establish the stable baseline value." • Adverse Events: Added a statement to further define Adverse Event, "an adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation participant who		

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	has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment". Other changes include: 1. Revised "footnote b" for "Events NOT Meeting the AE Definition". 2. Added a subsection to define "Pretreatment-emergent Adverse Events" under section "Recording and Follow-up of Adverse Events". 3. Added "including pretreatment-emergent and treatment-emergent" in parenthesis.		
3.	Added a statement "not more than four participants with F1 fibrosis will be enrolled in this study" in order to define a capping on F1 fibrosis participants enrollment in the study.	To have a wider and diverse range of participants from all fibrosis stages (F1 through F4cc) enrolled in the study.	Section 1.1 Synopsis Section 4.1 Overall Design
4.	• Removed Inclusion Criterion #4 to eliminate the FibroScan-aspartate aminotransferase (FAST) Score as an eligibility criterion for liver biopsy. • Revised Inclusion Criterion #6 from: "The participant has a diagnosis of NASH confirmed via biopsy (NAS ≥4 with at least 1 point each in steatosis, ballooning, and lobular inflammation) and liver fibrosis stage F2, F3, or F4cc according to NASH CRN, and established according to appropriate guidelines" to "The participant has indication of NASH via biopsy (NAS ≥3 with at least 1 point in lobular inflammation) and liver fibrosis stage F1 through F4cc according to NASH CRN". • Revised the statement from "Enrollment of F2 and F3 participants at a 1:1 ratio will not be required" to "Enrollment of F1, F2 and F3 participants at a 1:1:1 ratio will not be required". • Revised the justification for the inclusion criteria.	To improve study feasibility by expanding the study inclusion parameters while maintaining a population that is optimal (meeting the same threshold for elevated Pro-C3 and ELF) for assessing the anti-inflammatory/ani-fibrogenic mechanism of this drug. 1. NAS ≥4 to NAS ≥3 to reduce screen failures on NAS subscores due to nonreliability of the ballooning score. 2. Retaining "with at least 1 point in lobular inflammation", as this is important for the mechanism of action. 3. To lower the fibrosis score requirement from F2 to F1, improving study eligibility.	Section 1.1 Synopsis Figure 1 Study Schema Section 1.3.1 Schedule of Activities: Screening Period Section 2.2.1 Indication and Current Treatment Options Section 3 Objectives and Endpoints Section 4.1 Overall Design Section 4.2 Scientific Rationale for Study Design Section 5.1 Inclusion Criteria, Criteria #4 and #6 Section 5.1.1 Justification of Inclusion Criteria Section 8.2.3 FibroScan-Aspartate Aminotransferase Score Section 9.3 Biomarker and Noninvasive Test Analyses
5.	Revised the Exclusion criterion #6a increasing HbA1c requirement of ≥8% to ≥9% at Week -8 (SV1).	To improve study feasibility, recognizing the study population to be enrolled.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria, Criteria #6a
6.	Removed "dose increased" and "dose reduced" from Action Taken Concerning Intervention(s).	To correct the list of possible actions that can be taken in response to an adverse event,	Section 10.3.4.4 Action Taken

Description of Each Change and Rationale			**Section(s) Affected by Change**
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		given that a single dose of ontamalimab (75 mg) is available for use in this study.	
7.	• Removed Exclusion Criteria #17 "severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection" from the exclusion criteria. • Specified the screening period requirement in case of symptomatic and asymptomatic SARS-CoV-2 patients to be included in the study. • Added a heading in Table 1 Schedule of Activities; Screening Period, as "SARS-CoV-2 infection[s]". • Revised the footnote sequence, added and explained "footnote s" in Table 1.	To provide clarification on acceptable conditions for including SARS-CoV-2–infected participants into the study and to allow adequate time for recovery of participants (symptoms are resolved) before completion of screening.	Section 1.1 Synopsis Section 1.3.1 Schedule of Activities: Screening Period Section 5.2 Exclusion Criteria, Criteria #17
8.	Removed "after 4 weeks of last sample taken at the initial screening" from Screen Failures.	To allow participants to rescreen on a case-by-case basis after discussion with the investigator.	Section 5.4.1 Screen Failures
9.	Added "and samples for immunogenicity should be collected when worsening of a disease is reported as an AE" in the section Study Assessments and Procedures.	To clarify the instructions for collection of samples for immunogenicity in case of worsening of a disease being reported as an AE.	Section 8 Study Assessments and Procedures
10.	• Revised and added an additional statement to Exclusion criterion #7 "Treatment with leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange 30 days before baseline (Day 1)". • Removed "within 6 months" from FAST Score subsection of Biomarker and Noninvasive Test Assessments. • Removed the word "baseline" and from "abdominal MRI visit" and added "Visit 4a" in parenthesis. • Removed "Visits 4a, 4a2, and 4b comprise the baseline visit" from footnote a of Table 3. • Replaced "before screening" to "before baseline (Day 1)" in Exclusion criteria #25 and #26. • Added "X" under Visit 2 (Table 1) for Blood sample-hematology panel. • Removed "footnote p to X" under Visit 1 (Table 1) for TB test. • Added "footnote p to X" under Visit 1 (Table 1) for Urine drug screening.	Correction.	Section 1.1 Synopsis Figure 1 Study Schema Section 1.3.1 Schedule of Activities: Screening Period, Table 1 (Visit 1 and 2) Section 1.3.1 Schedule of Activities: Screening Period, Table 2 (Visit 4a and 4a2) Section 1.3.2 Schedule of Activities: Treatment Period, Follow-up, and End of Study, Table 3 Section 4.1 Overall Design Section 5.2 Exclusion Criteria, Criteria #6a, #7, #25, #26 Section 8.2.3 FibroScan-Aspartate Aminotransferase Score Section 8.2.10 HepQuant-SHUNT Disease Severity Index

Description of Each Change and Rationale			Section(s) Affected by Change
#	Description of change(s)	Rationale for change(s)	Section
	• Revised "footnote h" in Table 1 and "footnote d" in Table 3. • Removed the sentence in parenthesis "optional if the site is unable to perform this assessment" related to HepQuant-SHUNT DSI.		
See Section 10.6 for protocol history, including all previous amendments.			

ADDITIONAL INFORMATION

The study operations manual contains additional contact information for:

- Medical monitor, for medical advice on the protocol and the study drug
- Sponsor's responsible medical officer
- Monitor assigned to the study site, for general advice on protocol procedures
- Serious adverse event (SAE) reporting
- Pregnancy reporting
- Product complaints

INVESTIGATOR AGREEMENT

I confirm that I have read and understand this protocol, the Investigator's Brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, life, dignity, integrity, confidentiality of personal information, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP).
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) as defined in this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the Investigator as described in this protocol.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a potential participant to obtain their informed consent to participate.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

ADMINISTRATIVE INFORMATION

CONTACTS

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers and instructions on specific requirements for sample collection, assessments, and process is given in the study operations manual and relevant guidelines provided to the site.

Takeda-sponsored investigators will be provided with emergency medical contact information cards to be carried by each participant, per individual country requirements.

PRODUCT QUALITY COMPLAINTS

A product quality complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, strength, purity, effectiveness, or performance of a product, device, or combination product after it is released for distribution.

Report product complaints using the form called “Clinical Trial Material Complaint Form.”

Send it to the following email address: ctmcomplaint@takeda.com

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor(s): Takeda Development Center Americas, Inc.		**Compound:** TAK-647 (ontamalimab)	
Study Number: TAK-647-1001	**Phase:** 1b	**IND No.:** 163193	**EudraCT No.:** Not Applicable
Title of Protocol: A Multicenter, Single-arm, Open-label, Phase 1b Study to Explore the Mechanism of Action and Evaluate the Safety of Ontamalimab in Participants With Nonalcoholic Steatohepatitis With Fibrosis Stage 1 Through 4			
Number of participants (total and per treatment arm): Approximately 30 participants are planned to be enrolled to ensure that at least 18 participants (approximately 12 participants with fibrosis stage [F] noncirrhotic (F1-F3) and approximately 6 participants with fibrosis stage 4 compensated cirrhotic [F4cc]) complete the 24-week treatment period. Not more than four participants with F1 fibrosis will be enrolled in this study.			
Investigator(s): Multicenter study			
Site(s) and Region(s): Up to 20 sites in the United States (US)			
Study period (planned): Approximately 2023 to 2024			
Objectives and Endpoints			

Objectives	**Endpoints**
Primary	

To evaluate safety and tolerability of ontamalimab 75 mg administered every 4 weeks (Q4W) in participants with nonalcoholic steatohepatitis (NASH) (defined as Nonalcoholic Fatty Liver Disease [NAFLD] Activity Score [NAS] ≥3 with at least 1 point in lobular inflammation) with different fibrosis stages (NASH Clinical Research Network [CRN] F1 through F4cc participants).	• Incidence of treatment-emergent adverse events (TEAEs)
	• Number of participants with clinically significant changes in the following parameters from baseline to the end of the follow-up period (Week 36):
	  • Laboratory tests
	  • Electrocardiograms (ECGs)
	  • Vital signs
	  • Body weight

Secondary	
To determine if the changes from baseline in key biomarkers (neoepitope-specific N-terminal propeptide of type III collagen [Pro-C3] and Enhanced Liver Fibrosis [ELF] test) and in iron-corrected T1 mapping (cT1) by magnetic resonance imaging (MRI) provide a signal of a potential role of the mucosal addressin cell adhesion molecule-1 (MAdCAM-1) pathway in participants with NASH (NAS ≥3 with at least 1 point in lobular inflammation) with different fibrosis stages (NASH CRN F1 through F4cc participants) after 24 weeks of administration of ontamalimab 75 mg Q4W.	• Percent change from baseline in Pro-C3 through Week 24 • Percent change from baseline in ELF through Week 24 • Change from baseline in liver cT1 MRI at Week 24

Rationale:
This study is designed to evaluate the safety and tolerability of ontamalimab 75 mg Q4W in participants with NASH with fibrosis stages F1 through F4cc and to explore the role of MAdCAM-1 in NASH by administering a MAdCAM-1 inhibitor (ontamalimab). Blocking MAdCAM-1 may disrupt the trafficking of $\alpha_4\beta_7^+$ lymphocytes into hepatic and portal vein endothelium and subsequent extravasation into the liver. Ontamalimab selectively binds MAdCAM-1 with high affinity and selectivity, preventing the MAdCAM-1/$\alpha_4\beta_7$-integrin interaction. This is expected to reduce lymphocyte trafficking to the liver, preventing hepatic inflammation and injury, and may slow, halt, or reverse fibrosis.

Study drug, dose, and mode of administration:
The study drug is ontamalimab (TAK-647, previously known as PF-00547659 or SHP647; a fully human immunoglobulin G2 kappa antihuman MAdCAM-1 monoclonal antibody), which will be provided as a sterile aqueous buffered solution for subcutaneous (SC) administration in a glass prefilled syringe (PFS) with a fixed needle. Each PFS contains 1 mL of ontamalimab solution for injection at a concentration of 75 mg/mL. A single syringe will be used to provide the intended dose of drug (75 mg). Ontamalimab will be administered SC Q4W starting on Day 1 and the last dose is administered at Week 20 (total treatment period is 24 weeks). Additional information is provided in the current ontamalimab investigator's brochure (IB).

Overall Design and Methodology:
This is a multicenter, single-arm, open-label, Phase 1b study to explore the role of MAdCAM-1 in NASH by administering a MAdCAM-1 inhibitor (ontamalimab) in participants with indication of NASH via biopsy (NAS ≥3 with at least 1 point in lobular inflammation) with different fibrosis stages (NASH CRN fibrosis stage F1-F3 and F4cc participants). The role of MAdCAM-1 will be evaluated by the changes in inflammatory and fibrosis biomarkers, liver histology and circulating inflammatory cells, and liver chemistry tests compared with baseline. Magnetic resonance imaging (MRI)-derived cT1 will be used to evaluate fibroinflammatory changes in the liver. Safety and tolerability of ontamalimab 75 mg will be assessed.
Approximately 30 participants are planned to be enrolled to ensure that at least 18 participants (approximately 12 participants with F1-F3 and approximately 6 participants with F4cc) complete the 24-week treatment period. Not more than four participants with F1 fibrosis will be enrolled in this study. Enrollment of F1, F2 and F3 participants at a 1:1:1 ratio will not be required. The study will be conducted at up to 20 sites in the US. Participants will be aged ≥18 and ≤70 years and diagnosed with NASH without decompensated cirrhosis or neoplasia.
The broad NASH population is targeted, and participants with documented stable type 2 diabetes mellitus or participants with high body mass index >25 kg/m^2 with ≥1 criterion of metabolic syndrome will be permitted to participate in the study.
Participants with neoepitope-specific N-terminal propeptide of type III collagen (Pro-C3) ≥12.6 ng/mL, and Enhanced Liver Fibrosis (ELF) score ≥7.7, who meet inclusion criteria and none of exclusion criteria for assessments and procedures at Screening Visit 1 (SV1; Week -8) will be eligible for liver biopsy that will be performed at Screening Visit 2 (SV2; Week -6). Indication for NASH (NAS ≥3 with at least 1 point in lobular inflammation) and liver fibrosis stage F1 through F4cc in the liver biopsy will enable these participants to enroll in the study.
Historical liver biopsy samples are acceptable for screening purposes if collected between 24 weeks and 4 weeks before the start of the screening period (maximum allowed time between historical liver biopsy and first dose of study drug is 34 weeks for any participant, except for the participants who test positive for SARS-CoV-2 at screening). For any F4cc participants who meet the inclusion and exclusion criteria before establishment of safety and tolerability in the first four noncirrhotic (F1-F3) participants, historical liver biopsy samples are acceptable for screening purposes if collected within 10 weeks before the start of the screening period (12 weeks if test positive for SARS-CoV-2 at screening). The first screening visit must occur at least 4 weeks after the historical liver biopsy to ensure that any biopsy-induced changes in liver function parameters or biomarkers have stabilized. If a qualifying historical liver biopsy sample or slides is available to be reviewed and read centrally by the study pathologists and if it meets all the criteria as defined in the histopathology manual, liver biopsy need not be repeated during screening. Historical liver biopsy samples must show indication for NASH (NAS ≥3 with at least 1 point in lobular inflammation) and liver fibrosis stage F1 through F4cc. Participants with qualifying historical liver biopsy must have adhered to restrictions on prohibited hepatotoxic medications during the specified period before historical liver biopsy sampling. For participants with qualifying historical liver biopsies, the abdominal MRI (Visit 4a), may occur as soon as possible after liver chemistry results from SV2 become available, and SV2 and the Day -4 visit (Visit 4a2) must be at least 2 weeks apart.

Pro-C3, ELF, and other exploratory markers will be measured at 2 screening visits (SV1 and SV2) and Day 1 [D1] predose measurement during treatment period to determine intra-participant variability. This will enable the correct interpretation of the posttreatment decrease in these biomarkers relative to the intra-participant variability at baseline.

After safety and tolerability have been established in the first four noncirrhotic (F1-F3) participants who have received at least 3 doses of ontamalimab 75 mg and have been monitored for at least 12 weeks after the first dose of study drug, eligible F4cc participants will be allowed to enroll into the study. The screening period may be extended for up to 24 weeks for participants with results consistent with F4cc fibrosis (ie, compensated cirrhosis) (ie, a combination of Fibrosis-4 Index [FIB-4] ≥3.48 and LSM ≥20 kPa or an Agile 4 score ≥0.57) after the first visit during the screening period, or have a screening liver biopsy or a historical liver biopsy that confirms F4cc NASH (NAS ≥3 with at least 1 point in lobular inflammation), until safety and tolerability data are evaluated in the first four noncirrhotic (F1-F3) participants.

All eligible participants (F1-F4cc) will enter a 24-week, single-arm, open-label treatment period with ontamalimab 75 mg. Ontamalimab will be administered SC Q4W starting on Day 1 and the last dose is administered at Week 20 (total treatment period is 24 weeks), followed by a 12-week safety follow-up period. Liver biopsy samples will be collected during screening and at Week 24. Fibro-inflammation will be assessed by cT1 MRI (iron-corrected T1 mapping by magnetic resonance imaging), liver stiffness by FibroScan, and hepatocellular function by the investigational HepQuant-SHUNT Disease Severity Index (DSI) at the start of the treatment period and at Week 24. At visits Q4W between baseline and Week 24, assessments of selected biomarkers (including but not limited to Pro-C3, ELF, soluble MAdCAM-1, high-sensitivity C-reactive protein [hsCRP], and calprotectin), liver chemistry tests, and specific safety data collection (laboratory, adverse events [AEs], neurological assessments) will be performed. Liver stiffness measurement by FibroScan will be also performed at Week 12. Safety and tolerability data will be continuously monitored and will be evaluated by the internal safety review committee (independent from the study team).

All participants, including those who discontinue, will undergo a safety follow-up period through 12 weeks after the last dose of study drug.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. The participant is willing and able to understand and fully comply with study procedures and requirements, in the opinion of the investigator.
2. The participant and/or the participant's legally acceptable representative has provided informed consent (that is, in writing, documented via a signed and dated informed consent form [ICF] or electronic consent [eConsent] if applicable) and any required privacy authorization prior to the initiation of any study procedures.
3. The participant is aged 18 to 70 years, inclusive, at the time of signing the ICF.
4. This criterion has been removed in Protocol Amendment 3.
5. The participant has signs of fibrogenic activity (Pro-C3 ≥12.6 ng/mL, ELF score ≥7.7) at the Week -8 (SV1) (applies to all participants regardless of whether historical biopsy results are available at screening).
6. The participant has indication of NASH via biopsy (NAS ≥3 with at least 1 point in lobular inflammation) and liver fibrosis stage F1 through F4cc according to NASH CRN.
7. This criterion has been removed in Protocol Amendment 2.
8. This criterion has been removed in Protocol Amendment 2.
9. The participant is a male participant or a nonpregnant, nonlactating female participant who, if sexually active, agrees to comply with the contraceptive requirements of the protocol, or a female participant of nonchildbearing potential. Participants of reproductive potential who are sexually active must agree to use appropriate contraception (ie, highly effective methods for female participants and medically appropriate methods for male participants) for the duration of the study and for at least 12 weeks after the last dose of study drug.
10. The participant, if capable of breastfeeding, agrees to forego breastfeeding for the period from informed consent until 12 weeks after the last dose of study drug.

Exclusion Criteria:

1. The following laboratory findings are exclusionary for all participants if found during screening visits (Week -8 [SV1], Week -6 [SV2] or at Day -4 visit [Visit 4a2]):
   a. AST levels >5×the upper limit of normal (ULN).
   b. ALT levels >5×ULN.
2. The following laboratory findings are exclusionary for all participants if found during either screening visit (SV1 or SV2):
   a. ALP ≥2×ULN.
   b. Serum creatinine ≥1.5×ULN, or has an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2.
   c. INR ≥1.3 (except for participants who are receiving anticoagulant treatment).
   d. TBL ≥ULN (except for patients with a documented history of Gilbert's syndrome if direct bilirubin is within normal reference range).
   e. Direct bilirubin ≥3×ULN.
   f. Platelet count <60×10^9/L.
3. The participant has been diagnosed with decompensated liver disease, or has new signs of decompensation and/or clinically meaningful change in disease status based on the judgment of the investigator (including but not limited to clinically significant changes in TBL, albumin, INR, creatinine, and/or AST and ALT levels*) are observed during the screening period, or has any of the following during screening period:
   a. Presence or history of ascites, hepatic encephalopathy, or variceal bleeding.
   b. Presence or history of Child-Pugh >6 (Class B or C), unless due to therapeutic anticoagulation.
   c. Presence or history of MELD score >12.

* Note: It is the investigator's decision, in consultation with the sponsor, to allow participants to enter the study who have clinically meaningful rising tendencies in liver chemistries or significantly elevated liver chemistries that do not yet satisfy Exclusion Criterion #1 but could be interpreted as clinically concerning (ie, AST or ALT >4×ULN) at any visit during the screening period.

4. The participant has other diagnosed causes of liver disease based on medical history and/or baseline evaluation of laboratory and/or histology results, including, but not limited to viral (eg, chronic hepatitis B, hepatitis B virus surface antigen [HBsAg] positive, or hepatitis B core antibody [HBcAB] positive; or chronic hepatitis C or hepatitis C virus antibody [HCVAb] positive and hepatitis C [HCV] RNA positive; or human immunodeficiency virus [HIV]-antibody positive)*, alcoholic (alcohol consumption greater than 4 units on any day or 14 units per week for male participants, or greater than 3 units on any day or 7 units per week for female participants [1 unit of alcohol is present in one 12 oz/355 mL beer (approximately 5% alcohol), one 5 oz/148 mL glass of wine (approximately 12% alcohol), and one 1.5 oz/44 mL measure of 80-proof liquor (approximately 40% alcohol)]), or autoimmune conditions (eg, primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, drug-induced hepatotoxicity), and other rare liver disease (eg, alpha-1-antitrypsin deficiency, Wilson disease, hemochromatosis).

* Note: If a participant tests negative for HBsAg but positive for HBcAb, the participant would be considered eligible if no presence of hepatitis B virus (HBV) DNA is confirmed by HBV DNA polymerase chain reaction (PCR) reflex testing performed by the central laboratory.
Participants who are HCVAb positive without evidence of HCV RNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCV RNA at least 12 weeks before baseline]).

5. The participant has a history of impaired hemostasis that, in the investigator's judgement, would increase the risk to the participant if he or she participates in the study.
6. The participant has a significant concurrent medical condition at the time of screening or baseline, including, but not limited to, the following:

a. Any major illness/condition or evidence of an unstable clinical condition (eg, hepatic, renal, hematologic, gastrointestinal, endocrine [eg, uncontrolled diabetes* or type 1 diabetes mellitus, or thyroid disease], neurological [pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening], cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness [any bacterial, fungal, or viral, eg, clinically active cytomegalovirus, Epstein-Barr virus, herpes simplex virus]) that, in the investigator's judgment will substantially increase the risk to the participant if he or she participates in the study.
* Note: Participants with hemoglobin A1c (HbA1c) of ≥6.5% at screening (SV1; Week -8) without a previous diagnosis of type 2 diabetes mellitus (T2DM) should be excluded from the study. Participants with a previous diagnosis for T2DM are permitted to enter the study if on a stable regimen of antidiabetic therapy for at least 90 days before screening. Participants who are on a stable regimen of antidiabetic therapy for at least 90 days before screening (SV1; Week -8) and have HbA1c of ≥9% at Week -8 (SV1) should be excluded.

b. Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening.

c. History of significant cerebrovascular disease within 24 weeks before screening.

d. Cancer or history of cancer, including hepatocellular carcinoma or cholangiocarcinoma, or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).

e. Any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

f. Transplanted organ or history of liver transplantation.

g. Significant trauma or major surgery within 4 weeks before the first screening visit, or with any major elective surgery planned to occur during the study.

7. The participant has severe active inflammatory bowel disease (IBD). Participants with inactive IBD or active of mild to moderate severity that was documented either by prior endoscopy or in previous medical records for >6 months are permitted to enter if they do not require biological treatment or JAK inhibitors. Treatment with leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange 30 days before baseline (Day 1).
8. The participant has a severe immune-mediated inflammatory disease (IMID) (eg, rheumatoid arthritis, spondylarthritis disease spectrum, connective tissue disorders, cutaneous inflammatory conditions such as psoriasis, atopic dermatitis, hidradenitis suppurativa, asthma, multiple sclerosis). Participants with inactive IMID or active IMID of mild to moderate severity are permitted to enter the study.
9. The participant has a change in body weight ≥5% three months before start of the screening or after qualifying liver biopsy. If the participant had a liver biopsy within 24 weeks of screening, but experienced a weight change of ≥5% since the date of liver biopsy, the liver biopsy must be repeated at screening.
10. The participant has any laboratory abnormality or condition that, in the investigator's opinion, could adversely affect the safety of the participant or impair the assessment of study results.
11. The participant has known hypersensitivity to ontamalimab or formulation excipient.
12. The participant has active or latent infection with *Mycobacterium tuberculosis* (TB) who have not completed a generally accepted full course of treatment before screening.
13. The participant has clinically significant abnormal chest X-ray findings at SV1 (or up to 12 weeks before the first screening visit if available), such as presence of active TB, general infections, heart failure, or malignancy.
14. The participant has a positive interferon-gamma release assay (IGRA) at screening or within 12 weeks before screening even in the absence of previously diagnosed active or latent TB. IGRA screening may

be repeated during the screening period if the initial result is indeterminate. The participant may be enrolled if confirmatory IGRA results from the central laboratory are negative. If the confirmatory IGRA results from the central laboratory are positive, the participant should be screen-failed. If both initial and confirmatory IGRA results are indeterminate, the participant may be enrolled after a Mantoux tuberculin skin test is negative and after consultation with the sponsor and a pulmonary or infectious disease specialist who determines low risk of infection (ie, the participant would be acceptable for immunosuppressant [eg, anti-tumor necrosis factor (TNF) treatment] without additional action). If the time for consultation exceeds the visit window, the participant should be screen-failed and can be rescreened after the consultation establishes eligibility for study participation. This consultation must be included in the participant's medical history.

15. The participant has any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy (PML) based on the targeted neurological assessment during the screening period.
16. The participant has HIV.
17. This criterion has been removed in Protocol Amendment 3.
18. The participant has a medical condition (eg, morbid obesity, claustrophobia) that prevent execution of protocol procedures including percutaneous liver biopsy, LSM by FibroScan, and MRI.
19. The participant is receiving treatment with vitamin E, thiazolidinediones, or glucagon-like peptide-1 receptor agonists (GLP-1 RA) unless on a stable dose for 3 months before qualifying liver biopsy and not initiated after qualifying liver biopsy and is anticipated to maintain the same dosing regimen throughout study participation.
20. The participant is using drugs, herbs, or supplements historically associated with causing or worsening NAFLD/NASH within 24 weeks before qualifying liver biopsy or any time after qualifying liver biopsy is performed, including the use of total parenteral nutrition.
21. The participant has a positive urine screen for amphetamines, cocaine, or opioids related to the use of these drugs at screening.
22. The participant is receiving methadone or buprenorphine unless on stable maintenance treatment for at least 6 months before screening. Participants with a positive urine drug screen due to prescription opioid-based medication are eligible if the prescription and diagnosis are reviewed and approved by the investigator.
23. The participant is using any prohibited concomitant medications as described in the protocol.
24. The participant has received a live (attenuated) vaccine within 4 weeks before baseline or is anticipated to receive a live vaccine during the study.
25. The participant has participated in another investigational study of a drug or device within 30 days before or within 5 half-lives of the prior investigational agent (whichever is longer) before baseline (Day 1).
26. The participant has participated in another investigational study targeting NASH, type 2 diabetes mellitus, or obesity within 6 months before baseline (Day 1).
27. The participant is concurrently participating in another therapeutic clinical study.
28. The participant has previously received ontamalimab.
29. The participant has had previous exposure to anti-integrin or anti-adhesion molecule treatment eg, natalizumab, efalizumab, etrolizumab, vedolizumab, or any other investigational anti-integrin/adhesion molecule within 90 days before baseline (Day 1).
30. The participant has had previous exposure to any other biologic drugs with immunomodulatory properties such as anti-TNF, including biosimilars or anti-interleukin (IL)-12/23, or any nonbiologic treatment with immunomodulatory properties such as JAK inhibitors within 90 days or 5 half-lives (whichever is longer) before baseline (Day 1).
31. The participant is unavailable for follow-up assessment or investigator concern for participant's compliance with the protocol procedures.

32. The participant is a study site employee, an immediate family member (eg, spouse, parent, child, sibling), or is in a dependent relationship with a study site employee who is involved in conduct of this study, or may consent under duress.

Intervention groups and duration including maximum duration of participant participation in the study:
The total duration of study participation for each participant includes:

- Planned duration of screening period: Up to 8 weeks (or up to 10 weeks on a case-by-case basis with the sponsor's approval). For F4cc participants who have met the inclusion and exclusion criteria before safety and tolerability have been established in four noncirrhotic (F1-F3) participants, the screening period may be extended for up to 24 weeks. However, in case of positive test for SARS-CoV-2 infection, screening may be paused for an additional 2 weeks (ie, screening period of up to 12 weeks).
- Planned duration of treatment period: 24 weeks
- Planned duration of follow-up: 12 weeks

The participant's maximum duration of participation in the study is expected to be approximately 46 weeks (11.5 months). In case of positive test for SARS-CoV-2 infection, the total study period could be up to 48 weeks (ie, screening period of up to 12 weeks). For any F4cc participants who have met the inclusion and exclusion criteria before safety and tolerability have been established in the first four noncirrhotic (F1-F3) participants. For these participants, the total study period is expected to be approximately 60 weeks (15 months).

Statistical analysis:

Analysis Sets

The screened set will consist of all participants who have signed informed consent(s).

The full analysis set (FAS) will consist of all participants who are enrolled in the study, have received at least 1 dose of study drug, and have at least 1 valid postbaseline assessment.

The safety analysis set will consist of all participants who are enrolled in the study and have received at least 1 dose of study drug.

The pharmacokinetic (PK) set will consist of all participants in the safety analysis set who have at least 1 evaluable postdose PK concentration value.

Primary Endpoint Analyses (Safety)

All safety analyses will be performed using the safety analysis set.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 25.0 or higher). Treatment-emergent AEs are defined as AEs with start dates at the time of or following the first exposure to the study drug. The number and percentage of TEAEs will be presented by system organ class and preferred term. Treatment-emergent AEs will be further summarized by severity and relationship to the study drug. Adverse events related to the study drug, AEs leading to study drug discontinuation, SAEs, and deaths will be similarly summarized or listed.

Clinical laboratory test results, vital signs, body weight, and ECG findings will be summarized by visit. Potentially clinically significant findings will also be summarized or listed.

Secondary Endpoint Analyses

The biomarker and noninvasive test analyses will be performed on the FAS based on data from participants in all fibrosis stages (F1 through F4cc) using an estimation approach. The biomarker and noninvasive test data will be summarized descriptively by visit as observed.

For biomarkers except cT1 MRI, data from all available sampling during screening period (SV1 and SV2) and D1 predose measurement during treatment period will be averaged to establish the stable baseline value. For cT1 MRI, only one measurement will be taken during screening, which will be used for the baseline value.

For Pro-C3 and ELF, which are collected at multiple postbaseline visits, the percent change from baseline at Week 24 will be analyzed using a mixed effects model for repeated measure (MMRM) with visit as the fixed effect, participants as the random effect, and baseline values as covariates. The least-squares means of the percent change from baseline at Week 24 along with the corresponding 95% confidence intervals (CIs) will be presented.

For cT1 MRI, which is collected at one postbaseline visit (Week 24), the change from baseline at Week 24 along with the corresponding 95% CI will be presented.

Determination of Sample Size

The planned sample size for this study is 18 participants who complete the 24-week treatment period. The sample size has been chosen to provide adequate number of participants to investigate the objectives of the study based on clinical experience for key biomarkers.

This study is not statistically powered to perform any formal hypothesis testing, and the analyses will be based on estimation approach.

Independent Review Committee(s): Yes

An internal safety review committee (independent from the study team) will review the overall safety of the study participants on an ongoing basis. This review will consist of monitoring of safety of participants throughout the study. Recommendations made on the basis of this review to alter the conduct of the study or to amend the protocol will be provided to the study team for review and for a final decision. The sponsor or its designee will notify investigative sites and regulatory authorities as appropriate, of recommendations based on this review. Details regarding this review and the frequency of this review will be established in a separate charter before the administration of study drug to any participant. In addition, this internal safety review committee will be responsible for:

- Evaluating safety and tolerability data from the first four noncirrhotic (F1-F3) participants who have received at least 3 doses of ontamalimab 75 mg and have been monitored for at least 12 weeks, to support the decision to include F4cc participants in the study.
- Engaging with an independent panel of experts to evaluate any liver-related events (eg, liver decompensation, significant deterioration of liver chemistry tests).
- Monitoring neurological safety and consulting a panel of leading PML experts, including a neurologist, neuroradiologist, and a virologist, in the event of a suspected case of PML.

1.2 Schema

Figure 1. Study Schema

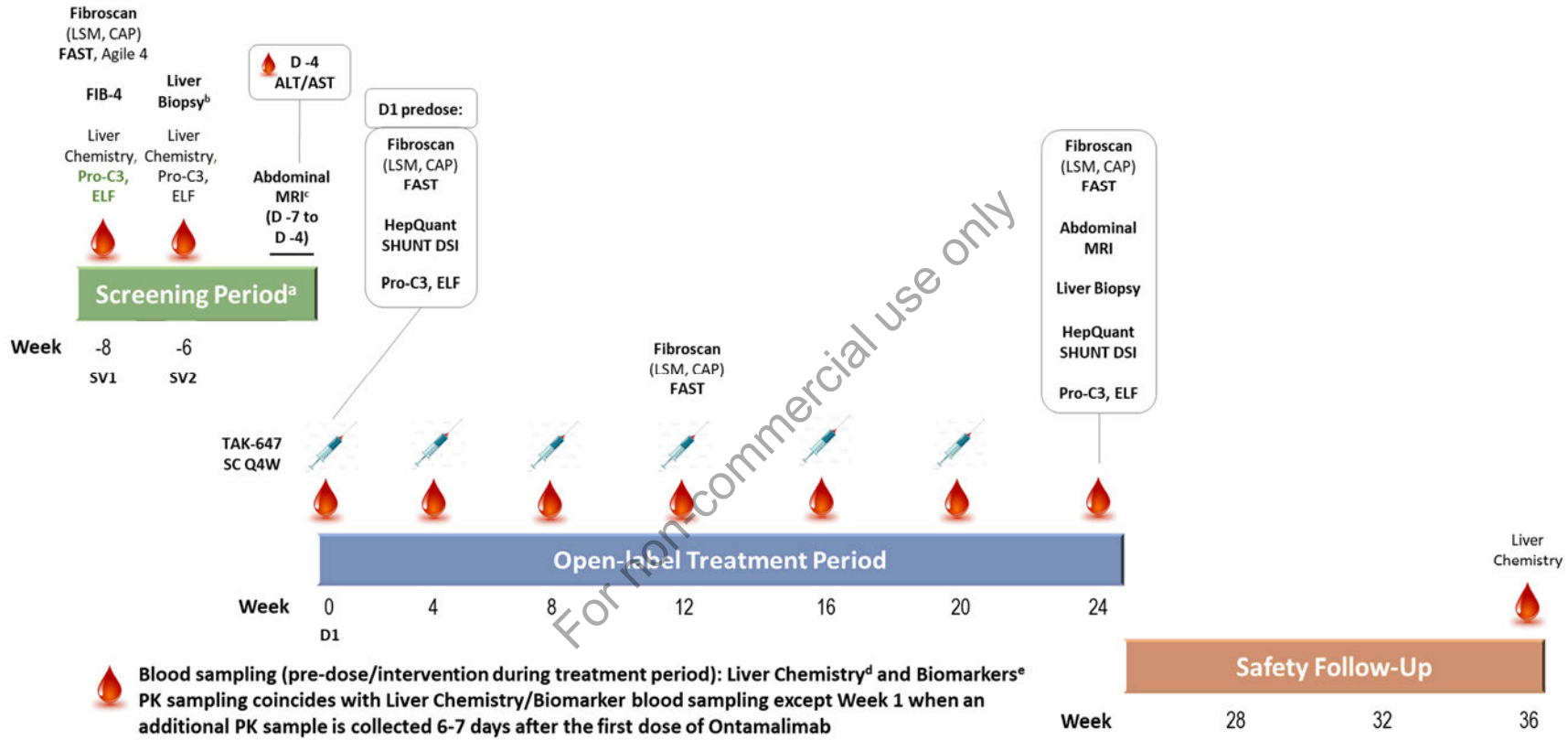

Figure 1. Study Schema (continued)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CAP=Controlled Attenuation Parameter; CCR9=C-C chemokine receptor type 9; cT1 MRI=iron-corrected T1 mapping by magnetic resonance imaging; CXCR3=C-X-C motif chemokine receptor 3; D=Day; DSI=Disease Severity Index; ELF=Enhanced Liver Fibrosis; F=fibrosis stage; F4cc=fibrosis stage 4 compensated cirrhotic; FAST=FibroScan-aspartate aminotransferase; FIB-4=Fibrosis-4 Index; hsCRP=high-sensitivity C-reactive protein; IL=interleukin; LSM=liver stiffness measurement; MRI=magnetic resonance imaging; NAS=Nonalcoholic Fatty Liver Disease Activity Score; NASH=nonalcoholic steatohepatitis; Pro-C3=neoepitope-specific N-terminal propeptide of type III collagen; Q4W=every 4 weeks; SC=subcutaneous(ly); sMAdCAM-1=soluble mucosal addressin cell adhesion molecule-1; SV=Screening Visit

[a] For participants with NASH (NAS ≥3) and F4cc fibrosis (ie, cirrhosis), the screening period may be extended up to 24 weeks until safety and tolerability information is available on first four noncirrhotic (F1-F3) participants who have received at least 3 doses of ontamalimab and have been monitored for at least 12 weeks after the first dose of study drug. Progression of screening is contingent on successful confirmation of eligibility along with the sponsor's approval.

[b] Eligibility for liver biopsy at Week -6 (SV2) will be established on the basis of results of Week -8 (SV1) assessments (including but not limited to Pro-C3 ≥12.6 ng/mL, ELF ≥7.7, and liver chemistry eligibility criteria as participants should meet all inclusion criteria and none of exclusion criteria for assessments and procedures at Week -8 (SV1) to be eligible for liver biopsy. For participants who meet other eligibility criteria at Week -8 (SV1), if ALT or AST is >4×ULN and <5×ULN at Week -8 (SV1), then the ALT/AST results at Week -6 (SV2) will also be evaluated before liver biopsy and the abdominal MRI can be performed. Only participants with indication of NASH via biopsy (NAS ≥3 with at least 1 point in lobular inflammation and liver fibrosis stage F1 through F4cc will be enrolled in the study. Green fonts indicate key inclusion criteria. Qualifying historical liver biopsies are acceptable for screening purposes if they are available to be reviewed and read centrally by the study pathologists and if they meet all the criteria as defined in the histopathology manual. For participants with qualifying historical liver biopsies, the abdominal MRI visit (Visit 4a) may occur as soon as possible after liver chemistry results from SV2 become available, and SV2 and the Day -4 visit must be at least 2 weeks apart.

[c] Abdominal MRI may be performed between Day -7 and Day -4.

[d] Liver chemistry tests include ALT, AST, total bilirubin, alkaline phosphatase, gamma-glutamyl transferase, and albumin.

[e] Biomarkers from blood samples include serum Pro-C3; ELF; serum sMAdCAM-1; serum and plasma markers of inflammation, fibrosis, and trafficking (including but not limited to hsCRP, IL-8, and calprotectin); whole blood T cell phenotyping (including but not limited to Th17/Th1 vs Th2 ratios, β_7^+ T cells, CCR9, and CXCR3) (treatment period only); and whole blood transcriptomics (treatment period only). Pro-C3 levels and ELF score at Week -8 (SV1) will be used to determine eligibility. Pro-C3 levels and ELF scores at Week -8 (SV1), Week -6 (SV2), and D1 predose measurement during treatment period will be used in calculating the baseline value for each parameter.

1.3 Schedule of Activities

1.3.1 Schedule of Activities: Screening Period

Table 1. Schedule of Study Activities: Screening Period (Visit 1 and 2)

Visit	1	2[a]
Week	**-8**	**-6**
Day	**-56**	**-42**
Visit Window (Days)	**NA**	**+14**
On-site Visit	Yes	Yes
Administrative Procedures		
Informed consent[b]	X	
Inclusion/exclusion criteria[c]	X	X
Demographics and medical history[d]	X	
Concurrent medical conditions	X	
Medication and procedure history	X	
Concomitant medication review[e]	X	*Throughout the study from the signing of informed consent form onwards*
Pregnancy avoidance counseling[f]	X	
Contraception and breastfeeding check[g]	X	X
Clinical Procedures		
AE assessment[h]	X	*Throughout the study from the signing of informed consent form onwards*
Height	X	
Body weight	X	X
Vital signs[i]	X	X
Complete physical examination[j]	X	X
Targeted neurological assessment[k]	X	X
12-lead ECG[l]	X	
Chest X-ray[m]	X	
Abdominal ultrasound[n]	X	
Clinical Laboratory Assessments		
Blood sample-clinical chemistry panel[o]	X[p]	X
Blood sample-hematology panel[o]	X[p]	X
Coagulation (INR)	X[p]	X
Serology[q]	X[p]	
Infectious disease panel[r]	X[p]	
SARS-CoV-2-infection[s]	X[p]	
HbA1c	X[p]	
eGFR (CKD-EPI)	X[p]	
Creatine kinase	X[p]	
Vitamin D	X[p]	
AMA	X[p]	
ANA, SMA, alpha-1-antitrypsin, and ceruloplasmin	X[p]	
IgG4	X[p]	
TB test[t]	X	
Serum α-fetoprotein	X[p]	

Table 1. Schedule of Study Activities: Screening Period (Visit 1 and 2)

Visit	1	2[a]
Week	**-8**	**-6**
Day	**-56**	**-42**
Visit Window (Days)	**NA**	**+14**
On-site Visit	Yes	Yes
FSH[u]	X[p]	
Serum β-hCG[v]	X[p]	
Urine β-hCG[v]		X
Urinalysis	X	X
Urine drug screening	X[p]	X
Alcohol screening (AUDIT)	X	
FIB-4 score	X	
FAST score	X	
Agile 4 score	X	
Child-Pugh score	X	
MELD score	X	
Noninvasive Tests and Liver Biopsy		
LSM, CAP (FibroScan)[w]	X	
Liver biopsy[x]		X
Biomarkers		
Serum sample for Pro-C3[y,z]	X	X^
Serum sample for ELF score[y,z]	X	X^
Serum sample for soluble MAdCAM-1[y]	X	X^
Serum sample for hsCRP[y]	X	X^
Plasma sample for calprotectin[y]	X	X^
Serum sample for circulating biomarkers[y]	X	X^

AE=adverse event; AMA=antimitochondrial antibody; ANA=antinuclear antibody; AUDIT=Alcohol Use Disorders Identification Test; β-hCG=beta-human chorionic gonadotropin; CAP=Controlled Attenuation Parameter; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; ECG=electrocardiogram; eCRF=electronic case report form; eGFR=estimated glomerular filtration rate; ELF=Enhanced Liver Fibrosis; FAST=FibroScan-aspartate aminotransferase; FIB-4=Fibrosis-4 Index; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1c; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCVAb=hepatitis C virus antibody; HIV=human immunodeficiency virus; hsCRP=high-sensitivity C-reactive protein; IGRA=interferon-gamma release assay; IgG4=immunoglobulin G4; INR=international normalized ratio; LSM=liver stiffness measurement; MAdCAM-1=mucosal addressin cell adhesion molecule-1; MELD=Model for Endstage Liver Disease; NA=not applicable; PML=progressive multifocal leukoencephalopathy; PPD=purified protein derivative; Pro-C3=neoepitope-specific N-terminal propeptide of type III collagen; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; SMA=smooth muscle antibody; TB=tuberculosis

[a] Procedures at this visit may be performed on different days within the visit window.

[b] The informed consent process (Section 10.1.3) must be completed, and the signed and dated informed consent form (or via an electronic system [eg, eConsent], if applicable) must be obtained before proceeding.

[c] Inclusion criteria (Section 5.1) and exclusion criteria (Section 5.2).

[d] Demography (Section 8.1), Medical history (Section 8.1).

[e] Concomitant medication review (Section 6.8).

[f] Lifestyle Restrictions: Contraception and Breastfeeding (Section 5.3.4).

Table 1. Schedule of Study Activities: Screening Period (Visit 1 and 2)

Visit	1	2[a]
Week	-8	-6
Day	-56	-42
Visit Window (Days)	NA	+14
On-site Visit	Yes	Yes

[g] Contraception and breastfeeding check should be performed for female participants of childbearing potential and who are capable of breastfeeding, as well as male participants who are with a partner of childbearing potential; see Section 5.3.4.

[h] AEs must be collected and assessed throughout the study from the time participant signs the informed consent form. Section 8.3.11).

[i] Vital signs (Section 8.3.2). Vital signs include blood pressure (resting more than 5 minutes), pulse, respiratory rate, and temperature.

[j] Physical examination (Section 8.3.1).

[k] Targeted neurological assessment (Section 8.3.2). Participants will be evaluated to reveal any potential abnormalities in the following neurological domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior. Participants with any unexplained positive item during screening that is suggestive of PML should be excluded.

[l] ECG (Section 8.3.5).

[m] A chest X-ray performed up to 12 weeks before the first screening visit may be used if available; the official reading must be located in the participant's source documentation.

[n] Abdominal ultrasound for screening evaluation of morphology of liver and other organs and structures.

[o] Laboratory tests (Section 8.3.8). Blood glucose and triglycerides are collected in a fasting state.

[p] Screening laboratory test results, if considered by the investigator to be transient and inconsistent with the participant's clinical condition, may be repeated once during the screening period for confirmation. Results of repeated tests must be reviewed and captured in the eCRF. The screening period can be extended by 2 weeks for any reason (including but not limited to a repeat test requirement for select and predefined measurements) on a case-by-case basis with the sponsor's approval. In case of positive test for SARS-CoV-2 infection, screening may be paused for an additional 2 weeks.

[q] Serology panel includes HIV (HIV-Ab/Ag), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C (HCVAb). Participants who test negative for HBsAg but positive for HBcAb would be considered eligible if HBV DNA results are negative (as confirmed by HBV DNA PCR reflex testing performed by the central laboratory). Participants with positive HBV DNA test results will not be eligible. Participants who are HCVAb positive without evidence of HCV RNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCV RNA at least 12 weeks before baseline]).

[r] Infection disease panel includes cytomegalovirus, Epstein-Barr virus, and herpes simplex virus. In case of suspicion of clinically active infection, additional testing should be performed at the investigator's discretion.

[s] Participants who test positive for SARS-CoV-2 and are asymptomatic or have mild to moderate symptoms not requiring SARS-CoV-2 targeted treatments may continue screening activities after 2 weeks, provided they have fulfilled the local, regional, or country-specific guideline for potential self-isolation. Participants who test positive for SARS-CoV-2 at screening and are symptomatic may be screened after 2 weeks of pause if SARS-CoV-2 symptoms are resolved. In case of prolonged symptoms and/or complications beyond the screening period, the participant will be considered as a screen failure and rescreened if applicable as described in Section 5.4. During the treatment period, in case of suspicion of clinically active infection with SARS-CoV-2, additional testing should be performed at the investigator's discretion.

[t] IGRA screening may be repeated during the screening period if the initial result is indeterminate. The participant may be enrolled if confirmatory IGRA results from the central laboratory are negative. If the confirmatory IGRA results are positive, the participant should be screen-failed. If both initial and confirmatory IGRA results are indeterminate, the participant may be enrolled after a Mantoux tuberculin skin test is negative and after

Table 1. Schedule of Study Activities: Screening Period (Visit 1 and 2)

Visit	1	2[a]
Week	-8	-6
Day	-56	-42
Visit Window (Days)	NA	+14
On-site Visit	Yes	Yes

consultation with the sponsor and a pulmonary or infectious disease specialist who determines low risk of infection and confirms no risk of immunosuppressive treatment. If the time for consultation exceeds the visit window, the participant should be screen-failed and can be rescreened after the consultation establishes eligibility for study participation. This consultation must be included in the participant's medical history.

[u] FSH will be assessed for postmenopausal participants. See Section 10.4.1 for definitions.

[v] Pregnancy tests only apply to participants of childbearing potential, as defined in the protocol (Section 10.4.1). A confirmatory serum β-hCG pregnancy test will be only required for participants who have a positive urine pregnancy test at any time.

[w] FibroScan results during screening will used to calculate FAST scores (Section 8.2.2).

[x] Participants who fulfilled all inclusion criteria and none of the exclusion criteria at Week-8 (SV1), eligibility for the liver biopsy at Week -6 (SV2) will be determined by data generated from Week -8 (SV1) assessments: Pro-C3 levels ≥12.6 ng/mL, and ELF score ≥7.7. Liver chemistry-related samples at Week -8 (SV1) must be evaluated and eligibility determined before the screening liver biopsy can be performed. For participants who meet other eligibility criteria at Week -8 (SV1), if ALT/AST results at Week -8 (SV1) are >4×ULN and <5×ULN, then the ALT/AST results at Week -6 (SV2) will also be evaluated before liver biopsy and the abdominal MRI (Visit 4a) can be performed.

[y] Additional Biomarkers (Section 8.2.12). Samples should be collected at approximately the same time of day at each screening visit. Samples for biomarker assessments may be repeated only if there are technical issues with the initial sample.

[z] Pro-C3 levels and ELF score at Week -8 (SV1) will be used to determine eligibility. Pro-C3 levels and ELF score at Week -8 (SV1), Week -6 (SV2), and D1 predose measurement during treatment period will be used in calculating the baseline values for each parameter. Progression of screening is contingent on successful confirmation of eligibility along with the sponsor's approval.

[^] Samples must be collected before the liver biopsy.

Table 2. Schedule of Activities: Screening Period (Visit 4a and 4a2)

Period	Screening Period	
Visit	4a Part 1[a]	4a2 Part 2
Week	-1	
Day	-7	-4
Visit Window (Days)	+3	-2
On-site visit	Yes	Yes
Administrative Procedures		
Concomitant medication review[b]	*Throughout the study from the signing of informed consent form onwards*	
Inclusion/exclusion criteria[b]		X

Table 2. Schedule of Activities: Screening Period (Visit 4a and 4a2)

Period	Screening Period	
Visit	4a Part 1[a]	4a2 Part 2
Week	-1	
Day	-7	-4
Visit Window (Days)	+3	-2
On-site visit	Yes	Yes
Clinical Procedures		
AE assessment[c]	*Throughout the study from the signing of informed consent form onwards*	
Clinical Laboratory Assessments		
Blood sample-clinical chemistry panel[d]		X
Noninvasive Tests and Liver Biopsy		
Abdominal MRI (for liver cT1 and other MRI-based exploratory biomarkers)[e]	X	

AE=adverse event; cT1=iron-corrected T1 mapping; MRI=magnetic resonance imaging; SV=Screening Visit

[a] Visit 3 is intentionally missing from the Schedule of Activities. Visits 4a and 4a2 may occur on the same day within the window specified for Visit 4a2. For participants with qualifying historical liver biopsies, the abdominal MRI visit (Visit 4a) may occur as soon as possible after liver chemistry results from SV2 become available, and SV2 and Visit 4a2 must be at least 2 weeks apart.

[b] Concomitant medication review (Section 6.8). Inclusion criteria (Section 5.1) and exclusion criteria (Section 5.2).

[c] AEs must be collected and assessed throughout the study from the time participant signs the informed consent form. (Section 8.3.11).

[d] Laboratory tests (Section 8.3.6). Blood glucose and triglycerides are collected in a fasting state.

[e] Abdominal MRI (Section 8.2.9). Participants will undergo the abdominal MRI to obtain liver cT1 MRI and other MRI-based exploratory biomarkers provided that the participant has no contraindications to MRI. Contraindication to oral or intravenous contrast agents should not exclude a participant from this assessment; this imaging procedure does not require use of such agents. The screening period can be extended by up to 2 weeks on a case-by-case basis with the sponsor's approval for participants who require a repeat MRI test.

1.3.2 Schedule of Activities: Treatment Period, Follow-up, and End of Study

Table 3. Schedule of Activities: Treatment Period, Follow-up, and End of Study

Period	Treatment Period							Follow-up			
Visit	4b Baseline	5	6	7	8	9	10	11/End of Treatment/ Early Termination[b]	12	13	14/End of Study
Week	0	1	4	8	12	16	20	24	28	32	36
Day	1	8	29	57	85	113	141	169	197	225	253
Visit Window (Days)[a]		±3	±3	±3	±3	±3	±3	±3	±7	±7	±7
On-site visit	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Administrative Procedures											
Concomitant medication review[c]	*Throughout the study from the signing of informed consent form onwards*										
Clinical Procedures											
AE assessment[d]	*Throughout the study from the signing of informed consent form onwards*										
Body weight	X		X	X	X	X	X	X	X	X	X
Vital signs[e]	X		X	X	X	X	X	X	X	X	X
Complete physical examination[f]	X		X	X	X	X	X	X	X	X	X
Targeted neurological assessment[g]	X		X	X	X	X	X	X	X	X	X
12-lead ECG[h]	X							X			
Contraception and breastfeeding check[i]	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments											
Blood sample-clinical chemistry panel[j]	X	X	X	X	X	X	X	X			X
Blood sample-hematology panel[j]	X	X	X	X	X	X	X	X			X
Coagulation (INR)	X							X			X
HbA1c[j]	X				X			X			X
eGFR (CKD-EPI)	X				X			X			X
Creatine kinase	X				X			X			X
Urine β-hCG[k]	X		X	X	X	X	X	X	X	X	X
Urinalysis	X		X	X	X	X	X	X	X	X	X
Urine drug screening	X		X	X	X	X	X	X			X
Alcohol screening (AUDIT)	X				X						X
FIB-4 score	X				X			X			
FAST score	X				X			X			
Child-Pugh score	X							X			
MELD score	X							X			

Table 3. Schedule of Activities: Treatment Period, Follow-up, and End of Study

Period	Treatment Period							Follow-up			
Visit	4b Baseline	5	6	7	8	9	10	11/End of Treatment/ Early Termination[b]	12	13	14/End of Study
Week	0	1	4	8	12	16	20	24	28	32	36
Day	1	8	29	57	85	113	141	169	197	225	253
Visit Window (Days)[a]		±3	±3	±3	±3	±3	±3	±3	±7	±7	±7
On-site visit	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Noninvasive Tests and Liver Biopsy											
LSM, CAP (FibroScan)	X				X			X			
Liver biopsy								X[l]			
Abdominal MRI (for liver cT1 and other MRI-based exploratory biomarkers)[m]								X			
HepQuant-SHUNT DSI[n]	X							X			
PK & Biomarkers											
Serum sample for PK[o]	X	X	X	X	X	X	X	X			
Serum sample for immunogenicity[p]	X				X			X	X	X	X
Serum sample for Pro-C3[q]	X	X	X	X	X	X	X	X			X
Serum sample for ELF score[q]	X	X	X	X	X	X	X	X			X
Serum sample for soluble MAdCAM-1[q]	X	X	X	X	X	X	X	X			X
Serum sample for hsCRP[q]	X		X	X	X	X	X	X			X
Plasma sample for calprotectin[q]	X		X	X	X	X	X	X			X
Serum sample for circulating biomarkers[q]	X		X	X	X	X	X	X			X
Blood sample for flow cytometry[q]	X				X			X			
Whole blood transcriptomics[q]	X				X			X			
Treatment Procedures											
Ontamalimab administration[r]	X		X	X	X	X	X				
Hypersensitivity monitoring[s]	X		X	X	X	X	X	X	X	X	X

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Visit Window (Days)[a]		±3	±3	±3	±3	±3	±3	±3	±7	±7	±7
On-site visit	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AE=adverse event; AUDIT=Alcohol Use Disorders Identification Test; β-hCG=beta-human chorionic gonadotropin; CAP=Controlled Attenuation Parameter; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; cT1=iron-corrected T1 mapping; DSI=Disease Severity Index; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; ELF=Enhanced Liver Fibrosis; FAST=FibroScan-aspartate aminotransferase; FIB-4=Fibrosis-4 Index; HbA1c=hemoglobin A1c; hsCRP=high-sensitivity C-reactive protein; Ig=immunoglobulin; INR=international normalized ratio; LSM=liver stiffness measurement; MAdCAM-1=mucosal addressin cell adhesion molecule-1; MELD=Model for Endstage Liver Disease; MRI=magnetic resonance imaging; PK=pharmacokinetics; Pro-C3=neoepitope-specific N-terminal propeptide of type III collagen; SAE=serious adverse event; SV=Screening Visit

[a] When the additional 2 weeks for screening are utilized, the visit window days may not be applicable anymore.

[b] Procedures at this visit may be performed on different days within the visit window.

[c] Concomitant medication review (Section 6.8). Inclusion criteria (Section 5.1) and exclusion criteria (Section 5.2).

[d] AEs must be collected and assessed throughout the study from the time participant signs the informed consent form. (Section 8.3.11).

[e] Vital signs (Section 8.3.2). Vital signs include blood pressure (resting more than 5 minutes), pulse, respiratory rate, and temperature.

[f] Physical examination (Section 8.3.1).

[g] Targeted neurological assessment (Section 8.3.2). Participants will be evaluated to reveal any potential abnormalities in the following neurological domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior.

[h] ECG (Section 8.3.5).

[i] Contraception and breastfeeding check should be performed for female participants of childbearing potential and who are capable of breastfeeding, as well as male participants who are with a partner of childbearing potential; see Section 5.3.4.

[j] Laboratory tests (Section 8.3.6). Blood glucose and triglycerides are collected in a fasting state.

[k] Pregnancy tests only apply to participants of childbearing potential, as defined in the protocol (Section 10.4.1). A confirmatory serum β-hCG pregnancy test will be only required for participants who have a positive urine pregnancy test at any time.

[l] Liver biopsy must be conducted as the last assessment for the Week 24/End of Treatment/Early Termination visit.

[m] Abdominal MRI (Section 8.2.9). Participants will undergo abdominal MRI to obtain liver cT1 MRI and other MRI-based exploratory biomarkers provided that the participant has no contraindications to MRI. Contraindication to oral or intravenous contrast agents should not exclude a participant from this assessment; this imaging procedure does not require use of such agents. The screening period can be extended by up to 2 weeks on a case-by-case basis with the sponsor's approval for participants who require a repeat MRI test.

[n] HepQuant-SHUNT DSI (Section 8.2.10).

Table 3. Schedule of Activities: Treatment Period, Follow-up, and End of Study

Period	Treatment Period							Follow-up			
Visit	4b Baseline	5	6	7	8	9	10	11/End of Treatment/ Early Termination[b]	12	13	14/End of Study
Week	0	1	4	8	12	16	20	24	28	32	36
Day	1	8	29	57	85	113	141	169	197	225	253
Visit Window (Days)[a]		±3	±3	±3	±3	±3	±3	±3	±7	±7	±7
On-site visit	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[o] Pharmacokinetics (Section 8.4).

[p] Immunogenicity assessments (Section 8.3.10). Sample should be collected predose at each visit.

[q] Additional Biomarkers (Section 8.2.12). Samples should be collected at approximately the same time of day, predose across each visit. Samples for biomarker assessments may be repeated only if there are technical issues with the initial sample.

[r] Study drug (Section 6.1, Section 6.2.5.2). At each visit, all other assessments, and procedures (other than hypersensitivity monitoring) must be completed before administration of study drug.

[s] Hypersensitivity monitoring (Section 8.3.3). Participants will be monitored for the presence of Type I (anaphylaxis) and Type III (immune complex) hypersensitivity reactions. Participants who experience AEs suggestive of Type I and Type III hypersensitivity reactions should have blood samples (3 mL and 4 mL, respectively) collected for anti-ontamalimab IgE antibody determination (Type I) and C3a and C5b-9 (Type III) determination, respectively; results of which will be available at the end of the study.

2. INTRODUCTION

2.1 Study Rationale

This study is designed to evaluate the safety and tolerability of ontamalimab 75 mg every 4 weeks (Q4W) in participants with nonalcoholic steatohepatitis (NASH) with fibrosis stage 1 (F1) through F4 compensated cirrhotic (F4cc) and to explore the role of mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in NASH by administering a MAdCAM-1 inhibitor (ontamalimab). Blocking MAdCAM-1 may disrupt the trafficking of $\alpha_4\beta_7^+$ lymphocytes into hepatic and portal vein endothelium and subsequent extravasation into the liver. Ontamalimab selectively binds MAdCAM-1 with high affinity and selectivity, preventing the MAdCAM-1/$\alpha_4\beta_7$-integrin interaction. This is expected to reduce lymphocyte trafficking to the liver, preventing hepatic inflammation and injury, and may slow, halt, or reverse fibrosis.

2.2 Background

2.2.1 Indication and Current Treatment Options

Nonalcoholic fatty liver disease (NAFLD) is generally viewed as a spectrum of liver disease in which hepatic steatosis, the accumulation of triglycerides in hepatocytes, develops in the absence of secondary causes (eg, medications, excessive alcohol consumption, or certain heritable conditions). Patients with NAFLD are at a high risk for cardiovascular morbidity and mortality (Chalasani et al. 2018). Nonalcoholic steatohepatitis is the inflammatory subtype of NAFLD, with steatosis, hepatocyte injury (ballooning) and lobular inflammation, with or without fibrosis (Chalasani et al. 2018). Although often clinically silent, NASH with fibrosis can progress to cirrhosis, end-stage liver disease, and in some patients, a need for a liver transplant. More than 20% of patients with NASH will develop cirrhosis in their lifetime (Matteoni et al. 1999) and patients with NASH also have increased risk of developing hepatocellular carcinoma (Stine et al. 2018). From 2004 to 2016, there was a 114% and 80% expansion in liver transplant waitlist registration due to NASH for men and women, respectively (Noureddin et al. 2018), and NASH is now the leading indication for liver transplant listing for women and is expected to overtake alcoholic liver disease as the leading liver transplant indication for all patients within the next few years (Noureddin et al. 2018). Nonalcoholic steatohepatitis has an annual mortality 1.7 times higher than NAFLD overall (25.56 vs 15.44 events per 1000 person-years), and liver-specific mortality is 15 times higher than in NAFLD (11.77 vs 0.77 events per 1000 person-years) (Younossi et al. 2016). In addition, NASH is closely related to the triple epidemic of obesity, prediabetes, and diabetes (European Association for the Study of the Liver (EASL) et al. 2016). However, symptoms are often silent or nonspecific to NASH, making it difficult to diagnose. As a result, patients with NASH can remain unaware of their condition until late stages of the disease (Polis and Fernandez 2015) (mayoclinic.org/diseases-conditions/nonalcoholic-fatty-liver-disease/symptoms-causes/syc-20354567?p=1; Mayo Clinic, accessed 25 July 2022).

Furthermore, NASH is associated with a significant socioeconomic burden; lifetime direct medical costs for patients in the US with NASH in 2017 were estimated at $222 billion (Younossi et al. 2019). This estimate does not include indirect medical or societal costs and will only increase as the prevalence of NASH rises.

Currently, the primary treatment for NAFLD/NASH is lifestyle modification for weight loss through diet and exercise (Guirguis et al. 2021; Sheka et al. 2020). A meta-analysis of studies showed the weight loss of 7% or greater was associated with improvement in the Nonalcoholic Fatty Liver Disease Activity Score (NAS) (Musso et al. 2012). Although dietary composition does appear to have an effect on hepatic fat deposition, no specific macronutrient diet has been shown to have a benefit for NASH. Therefore, caloric restriction is the most appropriate recommendation for these patients (Chalasani et al. 2018). To date, no pharmacotherapy is approved by US Food and Drug Administration (FDA) or European Medicines Agency (EMA) for NASH. However, vitamin E and pioglitazone has shown some benefits in clinical studies. Pioglitazone, a peroxisome proliferator-activator receptor-gamma (PPAR-γ) agonist, has demonstrated improvement in insulin sensitivity, aminotransferase levels, steatosis, inflammation and ballooning in patients with NASH and prediabetes or type 2 diabetes mellitus (T2DM) (Belfort 2006). Vitamin E treatment in a small pilot study showed improvement by reducing insulin resistance and PPAR-alpha (PPAR-α) expression in NASH (Yakaryilmaz et al. 2007). In the PIVENS trial, compared with placebo, vitamin E therapy was associated with a significantly higher rate (43% vs. 19%, p=0.001) of achieving the primary endpoint of an improvement in histological findings (ie, an improvement by 1 or more points in the hepatocellular ballooning score; no increase in the fibrosis score; and either a decrease in the NAS to a score of 3 or less or a decrease in the NAS of at least 2 points, with at least a 1-point decrease in either the lobular inflammation or steatosis score), whereas pioglitazone did not reach statistical significance (34% vs. 19%, p=0.04 [Bonferroni-adjusted p-values <0.025 were considered statistically significant]) (Sanyal et al. 2010). A combination therapy with pioglitazone and vitamin E assessed in patients with T2DM and NASH showed significant improvement in the NAS by 2 or more points and without any worsening in fibrosis versus placebo (54% vs 19%, p=0.003), but not with vitamin E alone (31% vs. 19%, p=0.2604) (Bril et al. 2019). No improvement in fibrosis was observed in any treatment group. For patients with NASH, pharmacotherapy options are currently limited to off-label use of pioglitazone and vitamin E as large, randomized studies evaluating these therapies are lacking.

2.2.2 Product Background and Mechanism of Action

Ontamalimab (TAK-647; previously known as PF-00547659 or SHP647) is a fully human immunoglobulin G2 kappa monoclonal antibody that inhibits binding of the $\alpha_4\beta_7$–integrin to human MAdCAM-1 (Pullen et al. 2009). Ontamalimab has been shown to reduce $CD4^+$ and $CD8^+$ memory T-lymphocyte homing to the gut in response to gastrointestinal (GI) inflammation

(Briskin et al. 1997; Liaskou et al. 2011; Shyjan et al. 1996). MAdCAM-1, while initially thought to be gut specific, has also been demonstrated to recruit mucosal lymphocytes to the liver and biliary tract (Graham et al. 2018; Grant et al. 2001; Hillan et al. 1999). In modified Stamper-Woodruff assays, MAdCAM-1 on hepatic vessels supported adhesion of $\alpha_4\beta_7$ from patients who had inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC) (Grant et al. 2001). A recent publication confirmed MAdCAM-1 expression in explanted livers of patients undergoing orthotopic liver transplantation for chronic liver disease (CLD) (Graham et al. 2022). Positive hepatic MAdCAM-1 immunoreactivity was described in more than 75% of patients with CLD regardless of etiology or disease severity and is largely universal in cases of later stages of CLD. There was increased expression of both C-C chemokine ligand 25 (CCL25) and MAdCAM-1, which can induce tissue infiltration of $\alpha_4\beta_7$- and C-C chemokine receptor type 9 (CCR9)-expressing CD4+ T cells and a concomitant reduction in peripheral frequencies (Graham et al. 2022), across all CLD groups compared with normal liver. The authors also found an increase in the number of $\alpha_4\beta_7^+$ $CD4^+$ T-effector memory cells in livers, an increase in $\alpha_E\beta_7^+$ $CD8^+$ cells, and that these $\beta7^+$ cells displayed an increased proinflammatory phenotype. Consistent with the work of Grant and colleagues (Grant et al. 2001), these findings were independent of the etiology of the liver disease.

The liver inflammatory lymphocytes of patients with PSC are mainly non-activated memory T lymphocytes, a substantial proportion of which expressed the co-receptors $\alpha_4\beta_7$ and/or CCR9 (Ponsioen et al. 1999). Hepatic MAdCAM-1 expression was shown in a variety of CLDs, particularly in patients with PSC and autoimmune hepatitis (AIH) (Grant et al. 2001). In addition, peripheral T lymphocytes from patients with PSC, patients with ulcerative colitis (UC), and healthy controls adhered to histologically MAdCAM-1–positive PSC liver sections, indicating that the aberrant hepatic expression of MAdCAM-1 was functional (Grant et al. 2001).

MAdCAM-1 expression is upregulated in the cirrhotic liver and immunolocalizes to the peribiliary plexus and lymphoid aggregates (Ala et al. 2013). MAdCAM-1 expression was evaluated in tissue sections from cirrhotic individuals who underwent orthotopic liver transplantation and was compared with precirrhotic, fulminant hepatitis B, and noncirrhotic portal hypertension tissue sections. Real-time PCR was used to quantify levels of MAdCAM-1 mRNA in the samples. MAdCAM-1 was expressed in 27 of 28 of the cirrhotic sections, and it was localized primarily to septal areas within the endothelium of the peribiliary vascular plexus and lymphoid aggregates but notably was absent from normal liver, noncirrhotic livers obtained from patients with portal hypertension, and precirrhotic livers. There was significant upregulation of MAdCAM-1 mRNA in cirrhosis ($p < 0.011$), consistent with immunohistochemical analysis.

Takeda's immunohistochemistry data on cirrhotic liver samples also support the key observations in the literature that MAdCAM-1 expression is increased in the liver of patients with cirrhosis, independent of the etiology.

Evidence for MAdCAM-1 immunoreactivity in diagnostic or other early-stage liver biopsies has not been shown consistently in PSC-IBD or other CLDs. This could be due to sampling limitations of biopsies. An alternate possibility is that aberrant hepatic MAdCAM-1 expression occurs in the later stages of CLD and thus does not mediate hepatic inflammation via gut lymphocyte recruitment in the early stages of disease. In line with this hypothesis, expression of MAdCAM-1 and α_4 and β_7 integrins were shown to be upregulated in the liver of patients with late-stage NASH (Ala et al. 2013; Rai et al. 2020; Riva et al. 2018).

The role of MAdCAM-1 in NASH progression is supported by several studies conducted in mice. MAdCAM-1 expression was induced in liver tissue of mice fed with a methionine- and choline-deficient (MCD) diet (NASH diet that promotes inflammation and fibrosis), and MAdCAM-1 knockout mice fed with a MCD diet for 4 weeks were protected from liver fibrosis, had reduced hepatic oxidative stress, and had decreased tissue inflammation, with a concomitant increase in regulatory T cells and anti-inflammatory macrophages (Drescher et al. 2017). Mice with a "leaky gut" phenotype (F11r knockout) developed more severe NASH and fibrosis on a Western diet, and had increased MAdCAM-1 expression and greater numbers and percentages of $\alpha_4\beta_7$ $CD4^+$ T cells in their livers (Rai et al. 2020). In addition, an inhibitory $\alpha_4\beta_7$ antibody blocked hepatic and colonic T-cell recruitment and attenuated hepatic inflammation and fibrosis in this model. In a different model of liver damage, Madcam-1 knockout mice were less susceptible to concanavalin A–induced hepatitis and intrahepatic thrombosis, and the adhesion of lymphocytes to liver sinusoids was dependent on MAdCAM-1 and that β_7 expression on T cells contributed to liver damage (Schippers et al. 2021).

Further understanding of the mechanisms and identification of the timing of hepatic MAdCAM-1 induction throughout the course of CLD could pave the way for the use of targeted anti-integrin therapies, as used in IBD, with the aim of blocking hepatic MAdCAM-1/$\alpha_4\beta_7$–mediated cell recruitment and inhibiting the progression of CLD. In support of pursuing similar therapeutic approaches in IBD and NASH, it is worthwhile to point out that there is a correlation between immune-mediated inflammatory diseases (IMIDs) and the prevalence of NAFLD and advanced liver fibrosis. It has been recently shown that IMIDs, such as IBD (Rodriguez-Duque et al. 2022), psoriasis (van der Voort et al. 2014), and hidradenitis suppurativa (Durán-Vian et al. 2019) represent independent risk factors for both NAFLD and NAFLD with advanced liver fibrosis. In a recent, cross-sectional, case-control study presented at the 2022 International Liver Congress (García-Nieto et al. 2022) involving 1567 patients with IMIDs and 3130 paired controls (paired by sex, age, body mass index, and T2DM), the presence of IMIDs significantly

increased the prevalence of NAFLD and NAFLD with advanced fibrosis. IMIDs have been found to be strong predictors of NAFLD with advanced fibrosis independent of metabolic risk factors (eg, obesity, T2DM). These emerging association studies suggest that chronic inflammation, which is known driver of IMIDs, may also play a role in progressive steatohepatitis in NAFLD and advanced liver fibrosis.

Fibrosis is the single most important determinant of clinical outcomes (Angulo et al. 2015) and the presence of lobular inflammation is an important risk factor for the development and progression of hepatic fibrosis. To justify the therapeutic rationale of MAdCAM-1 inhibition in fibrotic NASH, it is important to note that improvement of steatohepatitis has been shown to be associated with fibrosis regression (Kleiner et al. 2019). Based on the strong correlation between intrahepatic T-cell frequency and liver stiffness in patients with NASH (Van Herck et al. 2019), MAdCAM-1 inhibition may decrease fibrosis and liver stiffness, ultimately improving clinical outcome, by virtue of decreasing T-cell infiltration into the liver and resultant inflammation.

2.3 Benefit/Risk Assessment

As of 31 March 2022, the ontamalimab clinical program comprises 13 studies, including 6 completed studies for UC, 6 completed studies for Crohn's disease (CD), and 1 ongoing long-term safety extension study for participants with UC or CD previously enrolled in the Phase 3 induction and maintenance studies. As of 31 March 2022, 1468 participants enrolled in Phase 1 and induction studies received at least 1 dose of study drug in the clinical development program (1166 participants who received ontamalimab and 302 participants who received placebo), including 1094 participants with UC and 374 participants with CD. A total of 598 participants (330 participants with UC and 268 participants with CD) rolled over to Phase 2 long-term safety studies where they received ontamalimab, regardless of treatment assignment in previous studies. Overall, 406 participants enrolled in Phase 3 maintenance studies after completing the Phase 3 induction studies were further randomized to receive either ontamalimab or placebo (366 participants with UC and 40 participants with CD). A total of 557 participants have received ontamalimab in the ongoing Phase 3 long-term safety study, which includes participants previously enrolled in Phase 3 induction and maintenance studies.

The safety data across the ontamalimab development program shows ontamalimab to be generally well tolerated, with the majority of treatment-emergent adverse events (TEAEs) distributed at similar frequencies among treatment arms. Nasopharyngitis occurred at relatively high frequency during the long-term safety studies; however, it was not reported more frequently in the ontamalimab group compared with the placebo group in the induction studies. No liver-related safety signals have been observed in previous clinical studies of ontamalimab. Ontamalimab does not appear to be associated with impaired central nervous system immune

surveillance. No cases of progressive multifocal leukoencephalopathy (PML) or myocarditis have been reported. However, as continued mitigation for the potential risk of PML, targeted neurological assessments will be performed in this study to monitor any changes from baseline in the participant's status (Section 8.3.2).

To date, no clinical data with ontamalimab in patients with NASH have been gathered; participants with PSC or with impaired hepatic function were excluded from enrollment in clinical studies of ontamalimab in the treatment of UC and CD.

Refer to the latest version of the ontamalimab investigator's brochure (IB) for the overall benefit/risk assessment in the context of IBD and the most current information regarding drug metabolism, pharmacokinetics (PK), efficacy, and safety of ontamalimab in participants with IBD.

3. OBJECTIVES AND ENDPOINTS

The following are the objectives and endpoints of this study:

Objectives	Endpoints
Primary	

To evaluate safety and tolerability of ontamalimab 75 mg administered Q4W in participants with NASH (defined as NAS ≥3 with at least 1 point in lobular inflammation) with different fibrosis stages (NASH CRN) F1 through F4cc participants.	• Incidence of treatment-emergent adverse events (TEAEs)
	• Number of participants with clinically significant changes in the following parameters from baseline to the end of the follow-up period (Week 36):
	  • Laboratory tests
	  • Electrocardiograms (ECGs)
	  • Vital signs
	  • Body weight

Secondary	
To determine if the changes from baseline in key biomarkers (neoepitope-specific N-terminal propeptide of type III collagen [Pro-C3] and Enhanced Liver Fibrosis test [ELF]) and in cT1 MRI (iron-corrected T1 mapping by magnetic resonance imaging) provide a signal of a potential role of the MAdCAM-1 pathway in participants with NASH (defined as NAS ≥3 with at least 1 point in lobular inflammation) with different fibrosis stages (NASH CRN F1 through F4cc participants) after 24 weeks of administration of ontamalimab 75 mg Q4W.	• Percent change from baseline in Pro-C3 through Week 24 • Percent change from baseline in ELF through Week 24 • Change from baseline in liver cT1 MRI at Week 24
Exploratory	
To evaluate the changes from baseline in soluble MAdCAM-1 after 24 weeks of administration of ontamalimab 75 mg Q4W in participants with NASH (NAS ≥3 with at least 1 point in lobular inflammation) in each of the different fibrosis stages (NASH CRN F1 through F4cc) and overall in all participants.	Change from baseline to Week 24 in soluble MAdCAM-1 for each fibrosis stage group (fibrosis stage 1 through 4) and overall in all participants.
To evaluate the changes from baseline in inflammatory and cell trafficking markers in liver biopsy and blood samples after 24 weeks of administration of ontamalimab 75 mg Q4W in participants with NASH (NAS ≥3 with at least 1 point in lobular inflammation) in each of the different fibrosis stages (NASH CRN F1 through F4cc) and overall in all participants.	Change from baseline to Week 24 in each of the following biomarker readouts for each fibrosis stage group (fibrosis stage 1 through 4) and overall in all participants: • Serum or plasma biomarkers including but not limited to: high-sensitivity C-reactive protein (hsCRP) (serum), interleukin (IL)-8 (serum), and calprotectin (plasma) • T and immune cell trafficking in liver biopsy samples and circulating whole blood samples, including but not limited to: Th17/Th1 vs. Th2, β_7^+ T cells, CCR9, and C-X-C motif chemokine receptor 3 (CXCR3)

Objectives	Endpoints
	• Liver biopsy exploratory analyses including but not limited to markers of inflammation, fibrosis and artificial intelligence/machine learning methods • Transcriptomics in liver biopsy and whole blood samples
To evaluate the changes in fibrosis markers from baseline after 24 weeks of administration of ontamalimab 75 mg Q4W in participants with NASH (NAS ≥3 with at least 1 point in lobular inflammation) in each of the different fibrosis stages (NASH CRN F1 through F4cc) and overall in all participants.	Change from baseline to Week 24 in each of the following biomarker readouts for each fibrosis stage group (fibrosis stage 1 through 4) and overall in all participants: • Liver stiffness measure (LSM) by FibroScan • Fibrosis-4 Index (FIB-4) • FibroScan-aspartate aminotransferase (FAST) score
To evaluate the changes in liver fat content from baseline after 24 weeks of administration of ontamalimab 75 mg Q4W in participants with NASH (NAS ≥3 with at least 1 point in lobular inflammation) in each of the different fibrosis stages (NASH CRN F1 through F4cc) and overall in all participants.	Change from baseline to Week 24 in proton density fat fraction (PDFF) as measured by MRI-PDFF, part of the Liver *MultiScan*® for each fibrosis stage group (fibrosis stage 1 through 4) and overall in all participants.
To evaluate the changes in spleen cT1 MRI from baseline after 24 weeks of administration of ontamalimab 75 mg Q4W in participants with NASH (NAS ≥3 with at least 1 point in lobular inflammation) in each of the different fibrosis stages (NASH CRN F1 through F4cc) and overall in all participants.	Change from baseline to Week 24 in spleen cT1 MRI for each fibrosis stage group (fibrosis stage 1 through 4) and overall in all participants
To evaluate the changes from baseline in liver histology concerning NASH CRN fibrosis stage after 24 weeks of administration of ontamalimab 75 mg Q4W in participants with NASH (NAS ≥3 with at least 1 point in lobular inflammation) in each of the different fibrosis stages (NASH CRN F1 through F4cc participants) and overall in all participants.	Change from baseline to Week 24 in each of the following biomarker readouts for each fibrosis stage group (fibrosis stage 1 through 4) and overall in all participants: • Lobular inflammation grade • Hepatocyte ballooning grade • Steatosis grade • NAS
To evaluate the changes from baseline in liver function and biochemistry after 24 weeks of administration of ontamalimab 75 mg Q4W in participants with NASH (NAS ≥3 with at least 1 point in lobular inflammation) in each of the different fibrosis stages (NASH CRN F1 through F4cc participants) and overall in all participants.	Change from baseline to Week 24 in each of the following biomarker readouts for each fibrosis stage group (fibrosis stage 1 through 4) and overall in all participants: • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • AST/ALT ratio • Alkaline phosphatase (ALP) • Gamma-glutamyl transferase • Total bilirubin (TBL)

Objectives	Endpoints
	• International normalized ratio (INR) • Albumin • HepQuant-SHUNT – Disease Severity Index (DSI) (investigational assessment)
To evaluate the pharmacokinetics (PK) of ontamalimab 75 mg Q4W in participants with NASH (NAS ≥3 with at least 1 point in lobular inflammation) (NASH CRN F1 through F4cc participants).	Serum concentrations of ontamalimab over the treatment period.
To evaluate immunogenicity of ontamalimab 75 mg Q4W in participants with NASH (NAS ≥3 with at least 1 point in lobular inflammation) (NASH CRN F1 through F4cc participants).	Incidence of formation of antidrug antibodies (ADAs) through the end of the follow-up period (Week 36).

4. STUDY DESIGN

4.1 Overall Design

This is a multicenter, single-arm, open-label, Phase 1b study to explore the role of MAdCAM-1 in NASH by administering a MAdCAM-1 inhibitor (ontamalimab) in participants with indication of NASH via biopsy (NAS ≥3 with at least 1 point in lobular inflammation) with different fibrosis stages (NASH CRN F1 through F4cc participants). The role of MAdCAM-1 will be evaluated by the changes in inflammatory and fibrosis biomarkers, liver histology and circulating inflammatory cells, and liver chemistry tests compared with baseline. MRI-derived cT1 (iron-corrected T1 mapping) will be used to evaluate fibroinflammatory changes in the liver. Safety and tolerability of ontamalimab 75 mg will be assessed.

Approximately 30 participants are planned to be enrolled to ensure that at least 18 participants (approximately 12 participants with F1-F3 and approximately 6 participants with F4cc) complete the 24-week treatment period. Not more than four participants with F1 fibrosis will be enrolled in this study. Enrollment of F1, F2 and F3 participants at a 1:1:1 ratio will not be required. The study will be conducted at up to 20 sites in the US.

Participants will be aged ≥18 and ≤70 years and diagnosed with NASH without decompensated cirrhosis or neoplasia.

The broad NASH population is targeted, and participants with documented stable T2DM or participants with high body mass index ≥25 kg/m^2 with ≥1 criterion of metabolic syndrome will be permitted to participate in the study.

Participants with neoepitope-specific N-terminal propeptide of type III collagen (Pro-C3) ≥12.6 ng/mL, and Enhanced Liver Fibrosis (ELF) score ≥7.7, who meet inclusion criteria and none of exclusion criteria for assessments and procedures at Screening Visit 1 (SV1; Week -8) will be eligible for liver biopsy that will be performed at Screening Visit 2 (SV2; Week -6). Indication for NASH (NAS ≥3 with at least 1 point in lobular inflammation) and liver fibrosis stage F1 through F4cc in the liver biopsy will enable these participants to enroll in the study.

Historical liver biopsy samples are acceptable for screening purposes if collected between 24 weeks and 4 weeks before the start of the screening period (maximum allowed time between historical biopsy and first dose of study drug is 34 weeks for any participant, except for the participants who test positive for SARS-CoV-2 at screening). For any F4 participants who meet the inclusion and exclusion criteria before establishment of safety and tolerability in the first four noncirrhotic (F1-F3) participants, historical liver biopsy samples are acceptable for screening purposes if collected within 10 weeks before the start of the screening period

(12 weeks if test positive for SARS-CoV-2 at screening).The first screening visit must occur at least 4 weeks after the historical biopsy to ensure that any biopsy-induced changes in liver function parameters or biomarkers have stabilized. If a qualifying historical liver biopsy sample is available to be reviewed and read centrally by the study pathologists and if it meets all the criteria as defined in the histopathology manual, liver biopsy need not be repeated during screening. Historical liver biopsy samples must show indication for NASH (NAS ≥3 with at least 1 point in lobular inflammation) and liver fibrosis stage F1 through F4cc. Participants with qualifying historical liver biopsy must have adhered to restrictions on prohibited hepatotoxic medications during the specified period before historical liver biopsy sampling. For participants with qualifying historical liver biopsies, the abdominal MRI visit (Visit 4a) may occur as soon as possible after liver chemistry results from SV2 become available, and SV2 and the Day -4 visit (Visit 4a2) must be at least 2 weeks apart.

Pro-C3, ELF, and other exploratory markers will be measured at 2 screening visits (SV1 and SV2) and Day 1 [D1] predose measurement during treatment period to determine intra-participant variability. This will enable the correct interpretation of the posttreatment decrease in these biomarkers relative to the intra-participant variability at baseline.

After safety and tolerability have been established in the first four noncirrhotic (F1-F3) participants who have received at least 3 doses of ontamalimab 75 mg and have been monitored for at least 12 weeks after the first dose of study drug, eligible F4cc participants will be allowed to enroll into the study. The screening period may be extended for up to 24 weeks for participants with results consistent with F4 fibrosis (ie, compensated cirrhosis) after the first screening visit (ie, a combination of Fibrosis-4 Index [FIB-4] ≥3.48 and liver stiffness measurement (LSM) ≥20 kPa, or an Agile 4 score ≥0.57), or have a screening liver biopsy or a historical liver biopsy that confirms F4 NASH (NAS ≥3 with at least 1 point in lobular inflammation) with F4 fibrosis (ie, cirrhosis), until safety and tolerability data are evaluated in the first four noncirrhotic (F1-F3) participants.

All eligible participants (F1-F4) will enter a 24-week, single-arm, open-label treatment period with ontamalimab 75 mg. Ontamalimab will be administered subcutaneously (SC) Q4W starting on Day 1 and the last dose is administered at Week 20 (total treatment period is 24 Weeks), followed by a 12-week safety follow-up period. Liver biopsy samples will be collected during screening and at Week 24. Fibro-inflammation will be assessed by cT1 MRI, liver stiffness by FibroScan, and hepatocellular function by the investigational HepQuant-SHUNT Disease Severity Index (DSI) at the start of the treatment period and at Week 24. At visits Q4W between baseline and Week 24, assessments of selected biomarkers (including but not limited to Pro-C3, ELF, soluble MAdCAM-1, hsCRP, and calprotectin), liver chemistry tests, and specific safety data collection (laboratory, adverse events [AEs], neurological assessments) will be performed.

Liver stiffness measurement by FibroScan will also be performed at Week 12. Safety and tolerability data will be continuously monitored and will be evaluated by the internal safety review committee (independent from the study team).

All participants, including those who discontinue, will undergo a safety follow-up period through 12 weeks after the last dose of study drug.

The end of the study is defined as the date of the last visit (Week 36) of the last participant undergoing the study, unless the study is stopped earlier by the sponsor due to futility or for safety reasons (Section 4.4).

For a schematic of the study design, see Section 1.2. For the Schedule of Activities (SoA), see Section 1.3.

4.2 Scientific Rationale for Study Design

Blocking MAdCAM-1 may disrupt the trafficking of $\alpha_4\beta_7^+$ lymphocytes into hepatic and portal vein endothelium and subsequent extravasation into the liver. Ontamalimab selectively binds MAdCAM-1 with high affinity and selectivity, preventing the MAdCAM-1/$\alpha_4\beta_7$-integrin interaction.

This is expected to reduce lymphocyte trafficking to the liver, preventing hepatic inflammation and injury, and may slow, halt, or reverse fibrosis.

This study is designed to explore the role of MAdCAM-1 in NASH by administering a MAdCAM-1 inhibitor (ontamalimab) and to evaluate the safety and tolerability of ontamalimab 75 mg in participants with NASH with fibrosis stages F1 through F4cc.

Due to the potential mechanism of action on inflammation and secondary effects on fibrosis, the changes in fibrosis parameters in response to ontamalimab treatment may take longer to detect than would be expected for anti-fibrotic compounds. It is expected that 24 weeks is a sufficient duration to see changes in key fibrosis markers (Pro-C3, ELF score) as well as decreases in fibro-inflammation that can be detected by the cT1 parameter of the MRI. The investigational HepQuant-SHUNT DSI, which is thought to be a true measure of liver function, has been shown to be a dynamic biomarker that can change significantly after 12 weeks of obeticholic acid treatment (which is a mixed acting choleretic, anti-inflammatory and anti-fibrotic agent); therefore, it is likely that 24 weeks is long enough to detect a change in DSI following ontamalimab treatment that also targets fibro-inflammation albeit by a different mechanism.

Soluble MAdCAM-1 concentrations decreased significantly, in a dose-related manner, at Week 2 compared with baseline and remained low during Phase 2 ontamalimab IBD studies. After

12 weeks, median suppression of soluble MAdCAM-1 of 88.7%, 96.5%, and 97.8% was observed following monthly dosing of 22.5 mg, 75 mg, and 225 mg, respectively, whereas a median increase of 6.7% was seen with placebo. It is expected that there will be a decrease soluble MAdCAM-1 with ontamalimab treatment in participants with NASH, assuming the baseline levels in NASH are high, as was observed in IBD. The observed PK/pharmacodynamic properties and safety profiles of ontamalimab in participants with IBD support evaluation of the molecule in participants with NASH with fibrosis stages F1 through F4cc.

Baseline and after-treatment biopsy samples can help to understand the potential changes in liver immunology. Because this study is a single arm, open-label study, the estimated level of participant consent/interest (due to participant preference for active treatment versus placebo) may be higher than in a placebo-controlled study. Twenty-four weeks of treatment is reasonably long enough to expect changes in inflammatory and fibrosis biomarkers.

4.3 Justification for Dose

Ontamalimab has been evaluated for the treatment of UC and CD in 13 studies. There are 6 completed studies for UC, 6 completed studies for CD, and 1 ongoing study. After the Phase 2 program, the 25 mg and 75 mg doses were selected for the Phase 3 program based on efficacy and safety profile of the previously tested doses (22.5 mg, 75 mg, and 225 mg) in the Phase 2 program. The highest dose (225 mg) did not show efficacy benefit over the lower doses.

Based on (1) the pooled analyses results of the SHP647-301 and SHP647-302 UC induction Phase 3 studies showing an enhanced clinical and endoscopic benefit of the ontamalimab 75 mg dose over placebo (with no statistically significant difference in remission between the ontamalimab 25 mg group and placebo group at Week 12); and (2) the similar safety profile of the 25 mg and the 75 mg doses observed, the recommended dose of ontamalimab to induce remission in participants with moderate to severe UC is 75 mg. As the assumption is that ontamalimab will block tissue MAdCAM-1 in the liver in a similar way as in the gut, the 75 mg dose was selected for this Phase 1b study as the dose showing the best profile for inducing anti-inflammatory changes in IBD.

4.4 End of Study/Study Completion Definition

The end of the study is defined as the date of the last visit (Week 36) of the last participant undergoing the study, unless the study is stopped earlier by the sponsor due to futility or for safety reasons.

The final analyses for the primary endpoints and single final clinical study report (CSR) will be conducted after all participants enrolled in the study have had the opportunity to complete the Week 36 safety follow-up visit.

The participant's maximum duration of participation in the study is expected to be approximately 46 weeks (11.5 months). In case of positive test for SARS-CoV-2 infection, the total study period could be up to 48 weeks (ie, screening period of up to 12 weeks). For any F4 cirrhotic participants who have met the inclusion and exclusion criteria before safety and tolerability have been established in the first four noncirrhotic (F1-F3) participants. For these participants, the total study period is expected to be approximately 60 weeks (15 months).

5. STUDY POPULATION

Informed consent must be obtained before any screening procedures, other than activities the Institutional Review Board (IRB) has specifically approved for use as prescreening procedures. Specifically, informed consent must be obtained before the participant is asked to fast before a screening laboratory sample is collected. Informed consent requirements are described in Section 10.1.3.

All entry criteria, including test results, must be confirmed before enrollment. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Investigators must account for all individuals who sign informed consent forms (ICFs), regardless of the outcome of the screening, by completing the required electronic case report forms (eCRFs).

Rescreening will be allowed under circumstances described in Section 5.4.

5.1 Inclusion Criteria

Participants must meet *all* of the following criteria to be eligible for inclusion in the study:

Informed Consent

1. The participant is willing and able to understand and fully comply with study procedures and requirements, in the opinion of the investigator.
2. The participant and/or the participant's legally acceptable representative has provided informed consent (that is, in writing, documented via a signed and dated ICF or electronic consent [eConsent] if applicable) and any required privacy authorization prior to the initiation of any study procedures.

Age

3. The participant is aged 18 to 70 years, inclusive, at the time of signing the ICF.

Type of Participant and Disease Characteristics

4. This criterion has been removed in Protocol Amendment 3.
5. The participant has signs of fibrogenic activity (Pro-C3 ≥12.6 ng/mL, ELF score ≥7.7) at the Week -8 (SV1) (applies to all participants regardless of whether historical biopsy results are available at screening).

6. The participant has indication of NASH via biopsy (NAS ≥3 with at least 1 point in lobular inflammation) and liver fibrosis stage F1 through F4cc according to NASH CRN, and established according to appropriate guidelines.
7. This criterion has been removed in Protocol Amendment 2.
8. This criterion has been removed in Protocol Amendment 2.

Contraception and Breastfeeding

9. The participant is a male participant or a nonpregnant, nonlactating female participant who, if sexually active, agrees to comply with the contraceptive requirements of the protocol, or a female participant of nonchildbearing potential. Participants of reproductive potential who are sexually active must agree to use appropriate contraception (ie, highly effective methods for female participants and medically appropriate methods for male participants) for the duration of the study and for at least 12 weeks after the last dose of study drug.
10. The participant, if capable of breastfeeding, agrees to forego breastfeeding for the period from informed consent until 12 weeks after the last dose of study drug.

5.1.1 Justification of Inclusion Criteria

Elevated Pro-C3 and ELF signify active steatohepatitis and subsequently increased fibrogenic drive. The inhibition of MAdCAM-1 is expected to decrease steatohepatitis, reduce inflammatory cell infiltrate, and lower Pro-C3 and ELF levels. The Pro-C3 threshold (≥12.6 ng/mL) has been selected based on a recent publication (Erhardtsen et al. 2021) that indicates that participants with Pro-C3 values above this threshold are likely to have active fibrotic NASH. The ELF score threshold has been provided by the manufacturer (Siemens Healthineers) of this score; below this threshold, the participant is likely to have no fibrosis to mild fibrosis.

Progression of screening is contingent on successful confirmation of eligibility along with the sponsor's approval. All participants, independent from the timing of their liver biopsy (new or historical), are expected to have elevated Pro-C3 (≥12.6 ng/mL) and ELF (≥7.7), that indicate active fibrogenesis. For participants who are subject to liver biopsy during the screening period, these measurements are a part of the strategy to decrease biopsy screen failure rate, participant burden, and risks associated with performing liver biopsy.

The protocol allows the enrollment of up to four participants with stage 1 fibrosis with Pro-C3≥12.6 ng/mL and ELF≥7.7 who also satisfy all other inclusion and exclusion criteria, because based on available Pro-C3 information in each fibrosis stages (Nielsen et al. 2021) it is believed that these patients represent a subpopulation of F1 patients who likely have more active, ongoing fibrogenesis with a potential for faster progression and could benefit from TAK-647 that

is aimed to decrease this fibrogenic process. It has been recently shown that Pro-C3 is an independent prognostic factor for predicting clinical events (Nielsen et al. 2023).

5.2 Exclusion Criteria

The participant will be excluded from the study if any of the following exclusion criteria are met:

Medical Conditions

1. The following laboratory findings are exclusionary for all participants if found during screening visits (Week -8 [SV1], Week -6 [SV2] or at Day -4 [Visit 4a2]):
   a. AST levels >5×the upper limit of normal (ULN).
   b. ALT levels >5×ULN.
2. The following laboratory findings are exclusionary for all participants if found during either screening visit (SV1 or SV2):
   a. ALP ≥2×ULN.
   b. Serum creatinine ≥1.5×ULN, or has an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2.
   c. INR ≥1.3 (except for participants who are receiving anticoagulant treatment).
   d. TBL ≥ULN (except for patients with a documented history of Gilbert's syndrome if direct bilirubin is within normal reference range).
   e. Direct bilirubin ≥3×ULN.
   f. Platelet count <60×10^9/L.
3. The participant has been diagnosed with decompensated liver disease, or has new signs of decompensation and/or clinically meaningful change in disease status based on the judgment of the investigator (including but not limited to clinically significant changes in TBL, albumin, INR, creatinine, and/or AST and ALT levels*) are observed during the screening period, or has any of the following during the screening period:
   a. Presence or history of ascites, hepatic encephalopathy, or variceal bleeding.
   b. Presence or history of Child-Pugh >6 (Class B or C), unless due to therapeutic anti-coagulation.
   c. Presence or history of MELD score >12.

   * Note: It is the investigator's decision, in consultation with the sponsor, to allow participants to enter the study who have clinically meaningful rising tendencies in liver chemistries or significantly elevated liver chemistries that do not yet satisfy Exclusion Criterion #1 but could be interpreted as clinically concerning (ie, AST or ALT >4×ULN) at any visit during the screening period.

4. The participant has other diagnosed causes of liver disease based on medical history and/or baseline evaluation of laboratory and/or histology results, including, but not limited to viral (eg, chronic hepatitis B, hepatitis B virus surface antigen [HBsAg] positive, or hepatitis B core antibody [HBcAb] positive; or chronic hepatitis C or hepatitis C virus antibody [HCVAb] positive and hepatitis C virus [HCV] RNA positive; or human immunodeficiency virus [HIV]-antibody positive)*, alcoholic (alcohol consumption greater than 4 units on any day or 14 units per week for male participants, or greater than 3 units on any day or 7 units/week for female participants [1 unit of alcohol is present in one 12 oz/355 mL beer (approximately 5% alcohol), one 5 oz/148 mL glass of wine (approximately 12% alcohol), and one 1.5 oz/44 mL measure of 80-proof liquor (approximately 40% alcohol)]), or autoimmune conditions (eg, PSC, primary biliary cirrhosis, autoimmune hepatitis, drug-induced hepatotoxicity), and other rare liver disease (eg, alpha-1-antitrypsin deficiency, Wilson disease, hemochromatosis).
   * Note: If a participant tests negative for HBsAg but positive for HBcAb, the participant would be considered eligible if no presence of hepatitis B virus (HBV) DNA is confirmed by HBV DNA polymerase chain reaction (PCR) reflex testing performed by the central laboratory.
   Participants who are HCVAb positive without evidence of HCV RNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCV RNA at least 12 weeks before baseline]).
5. The participant has a history of impaired hemostasis that, in the investigator's judgement, would increase the risk to the participant if he or she participates in the study.
6. The participant has a significant concurrent medical condition at the time of screening or baseline, including, but not limited to, the following:
   a. Any major illness/condition or evidence of an unstable clinical condition (eg, hepatic, renal, hematologic, GI, endocrine [eg, uncontrolled diabetes* or type 1 diabetes mellitus, or thyroid disease], neurological [pre-existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening], cardiovascular, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness [any bacterial, fungal, or viral, eg, clinically active cytomegalovirus, Epstein-Barr virus, herpes simplex virus]) that, in the investigator's judgment will substantially increase the risk to the participant if he or she participates in the study.
      * Note: Participants with hemoglobin A1c (HbA1c) ≥6.5% at screening (SV1; Week -8) without a previous diagnosis of T2DM must not take part in the study. Participants with a previous diagnosis for T2DM are permitted to enter the study if on

a stable regimen of antidiabetic therapy for at least 90 days before screening. Participants who are on a stable regimen of antidiabetic therapy for at least 90 days before screening (SV1; Week -8) and have HbA1c of ≥9% at Week -8 (SV1) should be excluded.

b. Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening.

c. History of significant cerebrovascular disease within 24 weeks before screening.

d. Cancer or history of cancer, including hepatocellular carcinoma or cholangiocarcinoma, or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).

e. Any other severe acute or chronic medical or psychiatric condition or laboratory or ECG abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

f. Transplanted organ or history of liver transplantation.

g. Significant trauma or major surgery within 4 weeks before the first screening visit, or with any major elective surgery planned to occur during the study.

7. The participant has severe active IBD. Participants with inactive IBD or active of mild to moderate severity that was documented either by prior endoscopy or in previous medical records for >6 months are permitted to enter if they do not require biological treatment or JAK inhibitors. Treatment with leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange 30 days before baseline (Day 1).
8. The participant has a severe immune-mediated inflammatory disease (IMID) (eg, rheumatoid arthritis, spondylarthritis disease spectrum, connective tissue disorders, cutaneous inflammatory conditions such as psoriasis, atopic dermatitis, hidradenitis suppurativa, asthma, multiple sclerosis). Participants with inactive IMID or active IMID of mild to moderate severity are permitted to enter the study.
9. The participant has a change in body weight ≥5% three months before start of the screening or after qualifying liver biopsy. If the participant had a liver biopsy within 24 weeks of screening, but experienced a weight change of ≥5% since the date of liver biopsy, the liver biopsy must be repeated at screening.

10. The participant has any laboratory abnormality or condition that, in the investigator's opinion, could adversely affect the safety of the participant or impair the assessment of study results.
11. The participant has known hypersensitivity to ontamalimab or formulation excipient.
12. The participant has active or latent infection with *Mycobacterium tuberculosis* (TB) who have not completed a generally accepted full course of treatment before screening.
13. The participant has clinically significant abnormal chest X-ray findings at SV1 (or up to 12 weeks before the first screening visit if available), such as presence of active TB, general infections, heart failure, or malignancy.
14. The participant has a positive interferon-gamma release assay (IGRA) at screening or within 12 weeks before screening even in the absence of previously diagnosed active or latent TB. IGRA screening may be repeated during the screening period if the initial result is indeterminate. The participant may be enrolled if confirmatory IGRA results from the central laboratory are negative. If the confirmatory IGRA results from the central laboratory are positive, the participant should be screen-failed. If both initial and confirmatory IGRA results are indeterminate, the participant may be enrolled after a Mantoux tuberculin skin test is negative and after consultation with the sponsor and a pulmonary or infectious disease specialist who determines low risk of infection (ie, the participant would be acceptable for immunosuppressant [eg, anti- tumor necrosis factor (TNF)] treatment without additional action). If the time for consultation exceeds the visit window, the participant should be screen-failed and can be rescreened after the consultation establishes eligibility for study participation. This consultation must be included in the participant's medical history.
15. The participant has any unexplained symptoms suggestive of PML based on the targeted neurological assessment during the screening period.
16. The participant has HIV.
17. This criterion has been removed in Protocol Amendment 3.
18. The participant has a medical condition (eg, morbid obesity, claustrophobia) that prevent execution of protocol procedures including percutaneous liver biopsy, LSM by FibroScan, and MRI.

Prior/Concomitant Therapy

19. The participant is receiving treatment with vitamin E, thiazolidinediones (TZDs), or glucagon-like peptide-1 receptor agonists (GLP-1 RA) unless on a stable dose for 3 months before qualifying liver biopsy and not initiated after qualifying liver biopsy and is anticipated to maintain the same dosing regimen throughout study participation (see Section 6.8.3).

20. The participant is using drugs, herbs, or supplements historically associated with causing or worsening NAFLD/NASH within 24 weeks before qualifying liver biopsy or any time after qualifying liver biopsy is performed, including the use of total parenteral nutrition.
21. The participant has a positive urine screen for amphetamines, cocaine, or opioids related to the use of these drugs at screening.
22. The participant is receiving methadone or buprenorphine unless on stable maintenance treatment for at least 6 months before screening. Participants with a positive urine drug screen due to prescription opioid-based medication are eligible if the prescription and diagnosis are reviewed and approved by the investigator.
23. The participant is using any prohibited concomitant medications as described in Section 6.8.2.
24. The participant has received a live (attenuated) vaccine within 30 days before baseline (Day 1) or is anticipated to receive a live vaccine during the study.

Prior/Concurrent Clinical Study Experience

25. The participant has participated in another investigational study of a drug or device within 30 days before or within 5 half-lives of the prior investigational agent (whichever is longer) before baseline (Day 1).
26. The participant has participated in another investigational study targeting NASH, T2DM, or obesity within 6 months before baseline (Day 1).
27. The participant is concurrently participating in another therapeutic clinical study.
28. The participant has previously received ontamalimab.
29. The participant has had previous exposure to anti-integrin or anti-adhesion molecule treatment eg, natalizumab, efalizumab, etrolizumab, vedolizumab, or any other investigational anti-integrin/adhesion molecule within 90 days before baseline (Day 1).
30. The participant has had previous exposure to any other biologic drugs with immunomodulatory properties such as anti-TNF, including biosimilars or anti-IL-12/23, or any nonbiologic treatment with immunomodulatory properties such as JAK inhibitors, within 90 days or 5 half-lives (whichever is longer) before baseline (Day 1).

Other Exclusion Criteria

31. The participant is unavailable for follow-up assessment or investigator concern for participant's compliance with the protocol procedures.
32. The participant is a study site employee, an immediate family member (eg, spouse, parent, child, sibling), or is in a dependent relationship with a study site employee who is involved in conduct of this study, or may consent under duress.

5.2.1 Justification of Exclusion Criteria

Participants with active and severe IMIDs (including IBD, rheumatoid arthritis, psoriasis, etc.) are to be excluded from this study because IMIDs have been shown to be independent predictors of advanced fibrotic NASH and an active flare up during the study period would represent a confounder with uncertain implications on the outcome of the study.

5.3 Lifestyle Considerations

Participants should be encouraged to maintain their pre study exercise routine and diet throughout the study.

Participants must agree not to have weight loss surgery during the period of participation in the study.

5.3.1 Meals and Dietary Restrictions

Laboratory samples for blood sugar and triglycerides, including those during the screening, treatment, and follow-up periods, should be obtained in a fasting state.

For the purposes of this protocol, dietary supplements (such as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties) are considered to be concomitant medications (Section 6.8).

Restrictions on the consumption of other products with known pharmacological effects is also described in Section 5.3.2 (Alcohol and Tobacco), Section 6.2.5.2 (Administration), and Section 6.8.2 (Excluded Procedures and Treatments).

5.3.2 Alcohol and Tobacco

Consumption of alcohol more than 4 units on any day or more than 14 units per week for male participants, or more than 3 units on any day or more than 14 units per week for female participants (1 unit of alcohol is present in one 12 oz/355 mL beer [approximately 5% alcohol], one 5 oz/148 mL glass of wine [approximately 12% alcohol], and a 1.5 oz/44 mL measure of 80-proof liquor [approximately 40% alcohol]) is not permitted within 24 weeks before the first dose of study drug through the end of the safety follow-up period (Week 36).

Participants will be instructed to abstain from consuming alcohol for at least 48 hours before their clinic visit on dosing days, and during the clinic visit.

Use of nicotine-containing preparations should be recorded as concomitant medication.

For a comprehensive list of prohibited medications and procedures, see Section 6.8.2 and Table 4.

5.3.3 Activity

Participants should refrain from strenuous physical activity (eg, weightlifting, strenuous yard work, intensive exercise workouts) for 48 hours before study visits and laboratory evaluations.

5.3.4 Contraception and Breastfeeding

The potential effects of ontamalimab on embryofetal or postnatal development have not been assessed in humans. An enhanced pre- and postnatal development toxicity study of ontamalimab in nonhuman primates indicated that ontamalimab by intravenous injection once every 10 days from GD20-22 until parturition was tolerated in pregnant cynomolgus monkeys at levels up to 60 mg/kg (approximately 172 times the clinical exposure at the highest dose investigated in Phase 3 studies [75 mg Q4W]). For fetuses aborted, infants that died/euthanized early, and infants that survived until the scheduled terminal necropsy, there were no ontamalimab-related effects observed in the placenta (when available) or effects on fetal or infant morphometric measurements, or teratologic external, visceral, heart, or skeletal (infants only) evaluations. At 30 and 60 mg/kg, the abortion rate was similar to controls, but infant losses were increased in both ontamalimab dose groups. Histopathologic findings of mononuclear cell infiltration and/or inflammation mainly in the GI tract were observed in 1 infant decedent in each dose group as well as at the terminal necropsy. The weight of evidence suggests an ontamalimab-related effect on infant survival and GI histopathology, considered potentially secondary to the pharmacological effects of ontamalimab and ontamalimab-related decreased immune surveillance.

To minimize the risk of unintentional exposure of the embryo or fetus in the clinical study, all sexually active participants who, in the opinion of the investigator, are biologically capable of having children, or with their partners are at risk of pregnancy, must agree to use an appropriate form of contraception (ie, highly effective methods for participants capable of producing viable ova and/or becoming pregnant, and medically appropriate methods for participants capable of producing sperm), in accordance with the package instructions/leaflet.

Ontamalimab was detected in the milk of lactating monkeys. It is not known if ontamalimab is secreted in human milk.

During the screening visit (SV1), the investigator or designee in consultation with the participant will confirm the participant's childbearing potential status. For participants of childbearing potential, it must be confirmed and documented that the participant has selected the most appropriate method of contraception (ie, highly effective methods for female and medically appropriate methods for male study participants) from the permitted list of contraception methods (see Section 10.4). Participants must affirm the consistent and correct use of at least one of these selected methods. Participants who are capable of breastfeeding must affirm that

they are not using their breastmilk to feed an infant. Regular contraception and breastfeeding check discussions will take place at the time points specified in the SoA (Section 1.3) (ie, at each site visit) and will be documented. In addition, the participant must be instructed to call the site immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

5.3.4.1 Contraception for Participants Capable of Producing Viable Ova and/or Becoming Pregnant

Participants who are of childbearing potential (that is, capable of producing viable ova and/or becoming pregnant) must use highly effective contraception as agreed to in Inclusion Criterion #9. Section 10.4 defines childbearing potential and lists acceptable methods of contraception. If used, hormonal contraceptives should be administered according to the package insert.

5.3.4.2 Contraception for Participants Capable of Producing Viable Sperm

Participants who are capable of producing viable sperm must use medically appropriate contraception as agreed to in Inclusion Criterion #9. Section 10.4 provides further definitions and lists acceptable methods of contraception.

5.3.4.3 Restrictions on Breastfeeding

Participants capable of breastfeeding must forgo breastfeeding as agreed to in Inclusion Criterion #10.

5.4 Screening

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The screening period can be extended by 2 weeks for any reason (including but not limited to a repeat test requirement for select and predefined measurements) on a case-by-case basis with the sponsor's approval. In case of positive test for SARS-CoV-2 infection, screening may be paused for an additional 2 weeks.

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 the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

5.4.1 Screen Failures

An individual who has provided informed consent to participate in the study (but has not yet been allocated to receive study drug) may be categorized as a screen failure for any of the following reasons:

- Screen Failure (Did Not Meet Entrance Criteria)
- Adverse Event
- Lost to Follow-up
- Pregnancy
- Withdrawal by Subject
- Study Terminated by Sponsor
- Other (Specify)

Participants are **not** considered screen failures if they were allocated to receive study drug but not treated. See Section 7.2.

Participant identification numbers assigned to participants who fail screening should not be reused.

An individual who has been designated a screen failure may be rescreened once. Rescreening can be considered at the judgment of the investigator in consultation with the sponsor; however, a participant who has been designated as a screen failure may be rescreened up to one time. Rescreened participants must be reconsented, must begin the screening procedure again, and will be assigned a new participant number. Additionally, a participant's abnormal screening laboratory results may be repeated once for confirmation before designating a participant as a screen failure as long as the repeated assessment is conducted prior to the next scheduled screening visit. If the second attempt would also result in a screen failure, the participant cannot be further rescreened.

5.5 Criteria for Temporarily Delaying Enrollment

Enrollment may be delayed for the following reason:

- For F4 cirrhotic participants who have met the inclusion and exclusion criteria before safety and tolerability have been established in the first four noncirrhotic (F1-F3) participants, the screening period may be extended for up to 24 weeks. After the first four noncirrhotic (F1-F3) participants have received at least 3 doses with ontamalimab 75 mg and have been monitored for at least 12 weeks after the first dose of study drug, eligible F4cc participants may enroll in the study.

5.6 Enrollment

A participant is defined as enrolled when *all of* the following have occurred:

- The participant or the participant's legally acceptable representative has provided informed consent (that is, in writing, documented via a signed and dated ICF [or eConsent if applicable]).
- The participant has completed screening, having satisfied all entry criteria.
- The participant takes part in any study activity after screening.

6. STUDY DRUG AND CONCOMITANT THERAPY

6.1 Study Drug Administered

The study drug is ontamalimab (TAK-647, previously known as PF-00547659 or SHP647; a fully human immunoglobulin G2 kappa antihuman MAdCAM-1 monoclonal antibody), which will be provided as a sterile aqueous buffered solution for SC administration in a glass prefilled syringe (PFS) with a fixed needle. Each PFS contains 1 mL of ontamalimab solution for injection at a concentration of 75 mg/mL. Ontamalimab will be administered SC Q4W starting on Day 1 and the last dose is administered at Week 20 (total treatment period is 24 Weeks). Additional information is provided in the current ontamalimab IB.

6.2 Preparation, Handling, Storage, and Accountability

6.2.1 Accountability Throughout the Study

The investigator or designee must ensure that the sponsor-supplied study product is used in accordance with the protocol and is only used for participants enrolled in the study.

To document appropriate use of sponsor-supplied study product (Section 6.1), the investigator or designee must maintain 100% accountability for all sponsor-supplied study drugs that the site receives and dispenses during his or her entire participation in the study.

Proper drug accountability includes, but is not limited to:

- The investigator or designee must maintain records of all sponsor-supplied study drugs delivery to the site, current site inventory, dispensing for use by each participant, and return to the sponsor or designee.
- The investigator or designee must record this inventory on a sponsor-approved drug accountability log.
- Based on entries in the log, it must be possible to reconcile study products delivered with those used and returned.
- All study products must be accounted for, and all discrepancies investigated and documented to the sponsor's satisfaction.
- If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

6.2.2 Receiving Product at the Site

Investigators will be provided with sufficient amounts of the study drug to carry out this protocol for the agreed number of participants.

Upon receipt of sponsor-supplied study drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition.

This may include an examination of temperature-monitoring devices.

If quantity and conditions are acceptable, the investigator or designee should acknowledge the receipt of the shipment by signing the packing list, scanning the signed packing list, and returning the signed packing list per instructions provided on the form. If there are any discrepancies between the packing list and the actual product received, the sponsor must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

6.2.3 Handling and Storage at the Site

The investigator bears the overall responsibility for ensuring that the study drug is stored in an appropriate location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

An appropriate storage location is one that is secure, with access that is limited to the investigator and authorized site staff, and that is environmentally controlled (manually or automated) in accordance with labeled storage requirements.

The study drug must remain in the original container until dispensed.

The study drug should be protected from light and should not be frozen. Do not shake.

The investigator is responsible for ensuring that the study drug is maintained within an established temperature range of 2°C to 8°C, that the temperature is monitored throughout the duration of the study, and that records are maintained. The temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording.

The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the study drug and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to participants until the impact has been determined and the product is deemed appropriate for use by the sponsor.

Study drug must be kept in these conditions until it is used or returned to the sponsor for destruction.

The sponsor should be notified immediately if there are any changes to the storage area of the study drug that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.2.4 Labeling

The study drug is packaged in the following labeled containers: PFS with nominal fill volume of 1 mL. The PFS will be packaged in a labeled carton.

The sponsor will provide the investigator with packaged study drug labeled in accordance with local regulatory requirements.

Space is allocated on the label so that the site representative can record a unique participant identifier.

Changes to sponsor-supplied packaging, including the addition of labels prior to dosing, may not be made without full agreement in advance by the sponsor. Such additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the study drug in order to satisfy local or institutional requirements, but *must not*:

- Contradict the clinical study label.
- Obscure the clinical study label.
- Identify the study participant by name.

6.2.5 Dispensing/Administration

The investigator has overall responsibility for administering the study drug.

Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or their designee will administer the study drug only to participants enrolled in this study, following the procedures set out in the study protocol.

6.2.5.1 Dispensing

Please refer to the pharmacy manual for additional details regarding study drug supply dispensation and management and inventory management and supply ordering.

Participants will receive treatment according to the study schedule.

Participant numbers are assigned to all participants as they consent to take part in the study. Within each site (numbered uniquely within a protocol), a participant number is assigned to each participant according to the sequence of presentation for study participation.

Participants will be assigned to receive the next available medication identification (ID) number allocated to each study site. The medication ID number will be entered onto the eCRF.

The pharmacist/designee will enter the participant ID on the study drug carton labels as they are distributed. All administered medication will be documented in the participant's source and/or other study drug record.

No study drug stock or returned inventory may be removed from the site to which it was originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

6.2.5.2 Administration

The study drug (ontamalimab) will be administered SC Q4W by qualified site personnel at the time points specified in the SoA (Section 1.3). See Section 8 for the timing of dosing relative to other procedures.

The study drug should be administered in the anterolateral right or left thigh. The injection site should be rotated. If there are clinical reasons why the drug cannot be administered in the thigh, the drug may be administered in the deltoid area or abdomen with appropriate documentation.

After the first administration of study drug, the participant must be observed by a member of the study staff for at least 30 minutes (the total duration should be determined at the discretion of the investigator). For subsequent administrations, observation of the participant is at the discretion of the investigator. Injection site and allergic reaction monitoring should be completed by a member of the study staff.

Investigator-directed delays in dosing due to abnormal laboratory findings or AEs should be discussed with the medical monitor to determine whether the participant should continue with the treatment.

The investigator, or an approved representative (eg, pharmacist), will ensure that all study drug is administered by qualified staff members.

Additional information will be provided in a separate pharmacy manual.

6.2.6 Destruction or Return

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied product accountability and reconciliation before sponsor-supplied products are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied study drugs' accountability, return, and/or destruction. Originals will be sent to the sponsor or designee.

With the written agreement of the sponsor, at the end of the study all unused study drug may be returned to a local facility for destruction. Any empty/used study drug packaging must be destroyed at the site. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of study drug must be in accordance with local, state, and national laws.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

Further instructions regarding the final disposition of unused study drugs are provided in the study reference manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

This is not a randomized study; therefore, no randomization schedule will be generated.

6.3.2 Blinding the Treatment Assignment

Not applicable.

6.3.3 Unblinding

Not applicable.

6.4 Study Drug Compliance

When participants are dosed at the site, they will receive study drug directly from the investigator or designee under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

6.5 Dose Modification

Not Applicable.

6.6 Continued Access to Study Drug After the End of the Study

No aftercare is planned for this study.

6.7 Treatment of Overdose

In this study, an overdose is defined as a known deliberate or accidental administration of the study drug at a dose above that assigned to that individual participant, or intentional or unintentional administration of ontamalimab 75 mg at a dosing interval that is less than 2 weeks between doses.

There is no specific antidote for overdose with ontamalimab. In the event of a drug overdose, treatment should be symptomatic and supportive.

An overdose can occur as a result of abuse, misuse, or a medication error, as defined below. These terms are not mutually exclusive.

- Abuse: Persistent or sporadic intentional intake of study drug when used for a nonmedical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- Misuse: Intentional use of study drug other than as directed or indicated at any dose (Note: This includes a situation where the study drug is not used as directed at the dose prescribed by the protocol.)
- Medication Error: An error made in prescribing, dispensing, administration, and/or use of a study drug. Medication errors are reportable to the sponsor only as defined below.

The administration and/or use of an expired study drug should be considered as a reportable medication error.

Cases of participants missing doses of the study drug are not considered reportable as medication errors.

All cases of overdose, abuse, misuse, or medication error must be documented, including the quantity of the excess dose and the duration of the overdose. Because these events are not, in and of themselves, AEs, they should be reported regardless of whether any manifested signs or symptoms are considered AEs. If there are signs and symptoms meeting the criteria for reporting as AEs or SAEs, they should also be reported, as described in Section 10.3.

Overdose, abuse, misuse, or medication error must be reported to the sponsor according to the SAE reporting procedure *whether or not it resulted in an AE/SAE*.

6.8 Concomitant Therapy

6.8.1 Rescue Medicine

The use of rescue medications is not allowed at any time during the study.

6.8.2 Excluded Procedures and Treatments

Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Table 4 details the minimum required time before baseline (Day 1) for common prior treatments that are excluded medications for this study.

Table 4. Common Excluded Treatments

	Permanently Excluded	Minimum Required Time Before Baseline (Day 1)	
Prohibited Concomitant Medication or Therapy		**30 days**	**90 days**
Ontamalimab (TAK-647, SHP647, PF-00547659) in a previous study	X		
Anti-integrin or antiadhesion molecule treatment (eg, natalizumab, efalizumab, etrolizumab, vedolizumab, or any other investigational anti-integrin/adhesion molecule)			X
Investigational products		X[a]	
Live (attenuated) vaccine		X	
Leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange		X	
Biologics with immunomodulatory properties (such as anti-TNFs) including biosimilars (including ustekinumab)			X[a]
Nonbiologics with immunomodulatory properties[b] (such as JAK inhibitors)			X[a]

TNF=tumor necrosis factor

Table 4. Common Excluded Treatments

	Permanently Excluded	Minimum Required Time Before Baseline (Day 1)	
Prohibited Concomitant Medication or Therapy		**30 days**	**90 days**

[a] Or 5 half-lives if longer.
[b] With the exception of participants who are on stable doses of nonbiologic therapies with immunomodulatory properties (eg, azathioprine, 6-mercaptopurine, or methotrexate).

Antiplatelet and anticoagulant medications must be temporarily discontinued, if safe to do so, before liver biopsies during the study as described below (Neuberger et al. 2020), or according to local guidelines if more stringent:

- Clopidogrel, prasugrel, ticagrelor: stop for 7 days before liver biopsy.
- Aspirin: stop for 3 to 7 days before liver biopsy.
- Dual antiplatelet therapy (eg, aspirin/clopidogrel): stop clopidogrel as above but continue aspirin.
- Dipyridamole: omit on day of liver biopsy.
- Low molecular weight heparin: stop for 12 hours before liver biopsy for prophylactic dose; stop for 24 hours before liver biopsy for higher than prophylactic dose.
- Direct oral anticoagulants: stop for 2 days before liver biopsy.

Systemic administration of antibiotics that can potentially influence the composition of intestinal flora (including but not limited to clindamycin, ciprofloxacin, amoxicillin/clavulanic acid, cefprozil, imipenem, colistin/amoxicillin, amoxicillin/clavulanate potassium, tetracycline) are prohibited for more than 2 weeks sequentially within 3 months before first dose of study drug (and if applicable, within 3 months before a qualifying historical liver biopsy and not initiation after qualifying liver biopsy) and are excluded while on study.

The following list of prohibited drugs should not be taken within 6 months before the first dose of study drug (and if applicable, within 6 months before a qualifying historical liver biopsy and not initiated after qualifying liver biopsy) and are excluded while on study:

- Tamoxifen
- Amiodarone
- Alcohol as described in exclusion criterion #4 (Section 5.2)
- Griseofulvin
- Total parenteral nutrition

- Obeticholic acid
- Valproate
- Nucleoside analogues (except acyclovir)
- Estrogens at doses greater than 2 mg once daily used for hormone replacement
- Anabolic steroids
- Any known hepatotoxins including over-the-counter therapies and herbal therapies such as germander, chaparral, and ma-huang

This is not a comprehensive list. Treatments not listed above are generally considered allowable, unless considered a potential hepatotoxin.

6.8.3 Permitted Concomitant Medications and Procedures

Medications and supplements including but not limited to vitamin E, betaine, s-adenosyl-l-methionine, ursodeoxycholic acid, statins, milk thistle, fibrates (eg, gemfibrozil), probiotics, biguanides (metformin), bile acid sequestrants (eg, cholestyramine or colestipol), TZDs, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and GLP-1 RA that have been used to treat NAFLD/NASH are allowed during the course of the study if the participant has been on a stable dosing regimen (ie, same dose and frequency in the previous 3 months before the qualifying liver biopsy and not initiated after qualifying liver biopsy) and is anticipated to maintain this dosing regimen throughout study participation. Use of antiplatelet medications is also allowed, except when restricted before liver biopsy as described in Section 6.8.2. The investigator must contact the contract research organization (CRO) medical monitor to discuss any changes to concomitant medications that may impact the study.

Participants taking 5-aminosalicylic acid, glucocorticoids, or immunosuppressants (eg, azathioprine, 6-mercaptopurine, or methotrexate) for IMIDs should be on a stable dose for at least 12 weeks before screening and anticipated to remain stable throughout the study.

7. DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

This section describes the circumstances under which individual participants would withdraw or be discontinued from the study drug or from the study itself.

Section 10.1.9.2 describes circumstances in which specific sites or the study itself would be discontinued.

7.1 Discontinuation of Study Drug

In rare instances, it may be necessary for a participant to permanently discontinue study drug. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

See Section 7.1.1 for liver chemistry stopping criteria.

NOTE: Participants who do not qualify for the study (screen failures) are not considered to have discontinued; instead see Section 5.4.1.

If the study drug is discontinued, regardless of the reason, the evaluations listed for the Week 24/early termination visit will be performed as completely as possible.

Comments (spontaneous or elicited) or complaints made by the participant must be recorded in the source documents.

The investigator must determine the primary reason for discontinuation of study drug and/or the participant from the study, date of discontinuation of the study drug, and the total amount of study drug administered and record this information in the eCRF.

The primary reason for discontinuation or withdrawal should be recorded using 1 of the following categories:

Adverse event. The participant has experienced an AE that may require early termination if continued participation would impose an unacceptable risk to the participant's health or the participant is unwilling to continue because of the AE.

Death.

Protocol deviation. The discovery after the first dose of study drug that the participant did not meet protocol entry criteria or did not adhere to protocol requirements and continued participation poses an unacceptable risk to the participant's health.

Lost to follow-up. The participant did not attend visits and attempts to contact the participant were unsuccessful. Attempts to contact the participant must be documented in the participant's source documents. See Section 7.3 for additional procedures for participants lost to follow-up.

Withdrawal by subject. The participant (or participant's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (for example, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

Study terminated by sponsor.

Pregnancy. The participant is found to be pregnant.

Note: If the participant is found to be pregnant, the participant must be withdrawn immediately. The procedure is described in Section 10.4.3.

Other (specify).

7.1.1 Liver Chemistry Stopping Criteria

Liver-related decisions to discontinue or temporarily interrupt a study drug should be considered based on factors that include how much higher baseline ALT and AST were relative to ULN and how much the on-study ALT and AST levels increased relative to baseline, in addition to whether there is concomitant elevation of TBL or INR. In this study, the baseline measurement (BLM) for evaluating liver chemistry stopping criteria is determined by the last liver chemistry value before dosing.

For participants with ALT or AST <5×ULN at screening visits (SV1, SV2 and Visit 4a2) but have ALT or AST >5×ULN at Day 1 after having received the first dose of study drug, a repeat test should be performed as soon as possible, the participant should be closely monitored according to guidance provided below, and the participant's continued study participation should be evaluated by the internal safety review committee, in consultation with an independent panel of hepatic experts.

The investigator, after discussion with the sponsor, is responsible for making the final decision to discontinue study drug. The study drug will be discontinued if any of the following criteria are met (see Figure 2):

1. ALT ≥3×ULN, ALT ≥2×BLM (or nadir*) and TBL ≥2×ULN (exception for individuals with Gilbert's syndrome: doubling of direct bilirubin or INR >1.5, instead of TBL ≥2×ULN).
2. ALT ≥8×ULN, if ALT was normal at baseline.
3. ALT ≥5×BLM (or nadir), if ALT was abnormal at baseline.
4. ALT ≥500 IU/L.
5. ALT ≥5×ULN for participants with normal baseline value, or ALT ≥3×BLM for participants with abnormal baseline (or nadir), and symptoms (eg, severe fatigue, nausea, vomiting, right upper quadrant pain).

*Nadir is the lowest ALT value after-treatment initiation.

The decision to discontinue study drug does not mean discontinuation of the participant from the clinical study; safety evaluations, including assessments of vital signs and liver chemistry values, should continue to be made in accordance with the SoA (Section 1.3) (see Section 7.1).

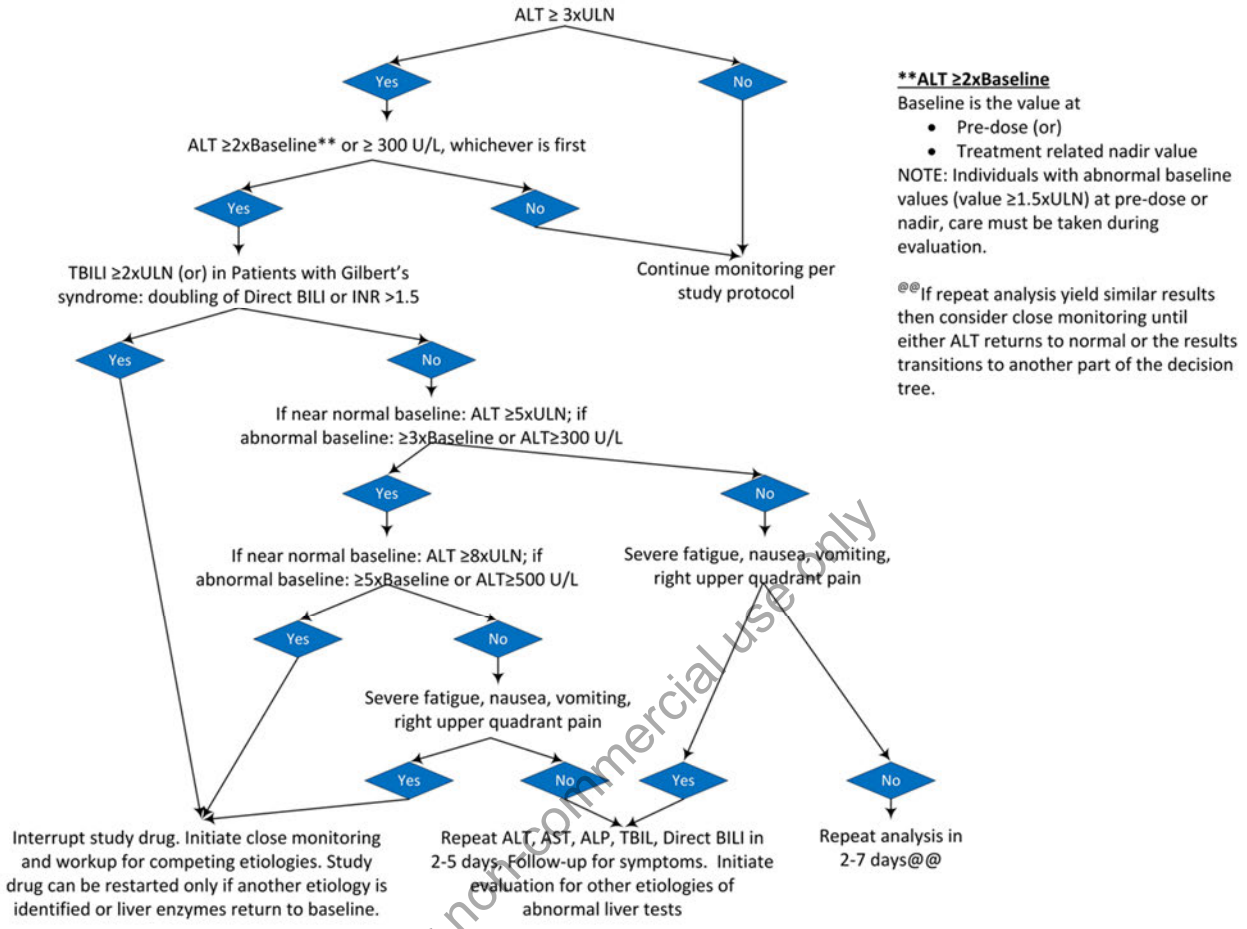
Discontinuation of an investigational drug is usually the only available therapy to treat suspected drug-induced liver injury and may not result in an immediate improvement, as test values and symptoms can last (sometimes even progress) for days or weeks after the drug has been discontinued.

Closer Monitoring Criteria

- ALT ≥3×ULN and ALT ≥2×BLM (or nadir*), but not meeting stopping criteria.
- ALT ≥5×ULN for participants with normal baseline value or ALT ≥3×BLM for participants with abnormal baseline (or nadir) without symptoms and who do not meet stopping criteria.

It is recommended to repeat with closer monitoring of ALT and bilirubin until levels return toward normal or until levels reach stopping criteria.

Figure 2. Abnormal Liver-associated Test Results: Algorithm for Study Drug Discontinuation



ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BILI=bilirubin; INR=international normalized ratio; TBIL=total bilirubin; ULN=upper limit of normal.
Source: Derived from (Regev et al. 2019).

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of participant safety). The investigator is encouraged to discuss withdrawal of a participant with the medical monitor when possible.

The investigator may discontinue a participant's study participation at any time during the study when the participant meets the study termination criteria described in Section 7.1.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). The primary criterion for termination must be recorded by the investigator. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3 Lost to Follow-up

A minimum of 3 documented attempts must be made to contact any participant (or their legally authorized representative) who is lost to follow-up at any time point prior to the last scheduled contact (in person or by phone or video). At least 1 of these documented attempts must include a written communication sent to the participant's last known address via courier or mail (with an acknowledgement of receipt request) asking that the participant be assessed for final safety evaluations.

8. STUDY ASSESSMENTS AND PROCEDURES

Written or electronic informed consent must be obtained (signed and dated) before study assessments and procedures can be performed, as described in Section 10.1.3.

The following sections describe the study procedures and data to be collected at planned time points per the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Repeat or unscheduled samples may be taken for safety reasons or due to technical issues with the samples at any time during the study and samples for immunogenicity should be collected when worsening of a disease is reported as an AE. For the screening laboratory tests indicated in the Schedule of Study Activities (Table 1 and Table 2), sampling may be repeated once during the screening period if a result is considered by the investigator to be transient and inconsistent with the participant's clinical condition, for confirmation before the participant is considered a screen failure as long as the repeated assessment is conducted prior to the next scheduled screening visit (see Section 5.4.1). The screening period can be extended by 2 weeks for any reason (including but not limited to a repeat test requirement for select and predefined measurements) on a case-by-case basis with the sponsor's approval. In case of positive test for SARS-CoV-2 infection, screening may be paused for an additional 2 weeks (Section 5.4). For biomarker assessments (Section 8.2.12), repeating a sample is not permitted for any reason other than technical issues with the sample.

Whenever possible, the same person should perform each assessment.

When timing of procedures and assessments coincide, the following order should be followed:

- Vital signs and ECG
- Laboratory sample collection
- Transient elastography and imaging techniques
- Prognosis and clinical scores (eg, Child Pugh, Model for End-stage Liver Disease [MELD])
- Study drug administration

Blood and tissue samples may be stored for up to the duration allowed by local regulations, but for no longer than 15 years.

8.1 Demographics, Medical History, and Medication History

8.1.1 Demographics

Participant demographic information will be collected prior to the participant receiving the first dose of study drug.

Demographic information to be obtained will include:

- Date of birth.
- Sex.
- Race.
- Hispanic ethnicity.
- Height and weight at screening.

8.1.2 Medical History

Medical and medication history, including concurrent medical conditions, will be collected and recorded in the participant's source documents and in the eCRF.

Medical history to be obtained will include determining whether the participant has any significant conditions or diseases relevant to the disease under study that resolved before, or at the time when, the participant provided informed consent. Ongoing conditions are considered concurrent medical conditions.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present when informed consent is provided. This includes clinically significant laboratory, ECG, physical examination, and/or vital signs abnormalities noted at screening examination, according to the judgment of the investigator. The condition (ie, diagnosis) should be described.

8.1.3 Prior and Concomitant Treatments/Medications

Prior and concomitant treatments and medications will be collected and recorded in the participant's source document.

Such treatments/medications include but are not limited to:

- medications or vaccines.
- over-the-counter or prescription medicines.
- recreational drugs.
- vitamins.

- herbal supplements.
- medications relevant to the eligibility criteria.
- other specific categories of interest.

Prior medications/treatments are defined as those that were received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the date of first dose of study drug.

Concomitant medications/treatments are defined as those given in addition to the study drug between the dates of the first dose of study drug and the end of the follow-up period, inclusive.

Concomitant medications may be prescribed by a physician or obtained by the participant over the counter. Concomitant medication is not provided by the sponsor.

At the time of the medical history, any available prior medication/treatment information will be collected.

At each study visit, participants will be asked whether they have taken any medication or received any treatment other than the study drug.

Information to be recorded will include:

- Identification of the medication or treatment.
- Reason for use.
- Dates of treatment/medication administration: start and end dates.
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

8.2 Biomarker and Noninvasive Test Assessments

8.2.1 Primary Efficacy Measurement

Not applicable.

8.2.2 Liver Stiffness Measurement and Liver Fat Content

Liver stiffness, as measured by elastography, is a marker for hepatic fibrosis. It will be quantified in the study by ultrasound-based transient elastography (FibroScan). Transient elastography correlates well with histology (Metavir and Ishak stages), performing best at extreme stages,

meaning severe fibrosis versus nonfibrosis (Corpechot et al. 2006; Muir et al. 2019). In addition, the rate of change over time has a correlation with clinical outcomes.

Assessments by FibroScan (LSM by FibroScan and liver fat content by Controlled Attenuation Parameter [CAP]) will be performed at the time points specified in the SoA (Section 1.3). The results will be read locally; the baseline reading at the first screening visit will be used to calculate FAST scores (see Section 8.2.3).

8.2.3 FibroScan-Aspartate Aminotransferase Score

The FAST score (>0.35) has been used to decrease biopsy screen failure rate as it is an efficient non-invasive tool to exclude patients who most likely do not have fibrotic NASH (Newsome et al. 2020) and thus would not benefit from potential pharmacologic therapy. The FAST score consists of LSM by vibration-controlled transient elastography and CAP, both measured by FibroScan, and AST (Newsome et al. 2020). The FAST score provides an efficient way to non-invasively identify patients at risk of progressive NASH for clinical trials, thereby reducing unnecessary liver biopsies.

The FAST score will be calculated by the following formula:

$$FAST = \frac{e^{-1.65+1.07\times ln(LSM)+2.66\times 10^{-8}\times CAP^3-63.3\times AST^{-1}}}{1+e^{-1.65+1.07\times \ln(LSM)+2.66\times 10^{-8}\times CAP^3-63.3\times AST^{-1}}}$$

To calculate the FAST score, LSM, and CAP should come from a single FibroScan exam. The FibroScan exam and blood collection for AST assessment should be performed. The FAST score will be calculated using the FibroScan software.

The FAST score will be calculated at the time points specified in the SoA (Section 1.3).

8.2.4 Agile 4 Score

The Agile 4 score was developed as a noninvasive test to identify cirrhosis in patients with NAFLD (Boursier et al. 2021). The Agile 4 score is a FibroScan-derived score that includes LSM, AST, ALT, platelets, diabetes status, and gender (Boursier et al. 2021). Agile 4 was externally and independently validated to identify patients with cirrhosis with a positive predictive value that is superior to FIB-4 or LSM alone. Agile 4's rule-out and rule-in cut-offs are associated with a much smaller indeterminate zone compared to FIB-4 and LSM alone to rule out or rule in cirrhosis. Agile 4 could be used in clinical practice to identify patients in need of hepatocellular carcinoma and esophageal varices screening.

An Agile 4 score ≥0.57 during screening is consistent with a high likelihood of F4 fibrosis (ie, cirrhosis).

The Agile 4 score will be calculated at the time points specified in the SoA (Section 1.3).

8.2.5 Fibrosis-4 Index

The FIB-4 index is a noninvasive test for liver fibrosis (Sterling et al. 2006). The FIB-4 score consists of age, ALT, AST, and platelet count, and is calculated using the following formula: age [years]×AST [U/L]/(platelet count [10^9/L]×√ALT [U/L]). FIB-4 has utility in identifying participants with advanced liver fibrosis (Srivastava et al. 2019) and prognosticating mortality and liver-related outcomes (Vieira Barbosa et al. 2022).

A FIB-4 score ≥3.48, along with LSM ≥20 kPa, at screening would indicate a high likelihood of F4 fibrosis (ie, cirrhosis).

The FIB-4 score will be calculated at the at the time points specified in the SoA (Section 1.3).

8.2.6 Child-Pugh Score

The Child-Pugh score is a scoring system to measure the severity of CLD inclusive of cirrhosis (Pugh et al. 1973). It consists of 5 clinical features, 3 of which assess the synthetic function of the liver (TBL level, serum albumin, and INR) and 2 of which are based on clinical assessment (degree of ascites and degree of hepatic encephalopathy).

The Child-Pugh score will be calculated at the time points specified in the SoA (Section 1.3).

8.2.7 Model for End-stage Liver Disease

The original MELD score is a prospectively developed and validated chronic liver disease severity scoring system that uses a patient's laboratory values for serum bilirubin, serum creatinine, and the INR for prothrombin time to predict 3-month survival. In patients with cirrhosis, an increasing MELD score is associated with increasing severity of hepatic dysfunction and increased 3-month mortality risk.

The MELD score changes over time depending on the course of the chronic liver disease and ranges from 6 to 40; increasing scores indicate progression/worsening of disease.

The MELD score will be calculated at the time points specified in the SoA (Section 1.3).

8.2.8 Liver Biopsy

Liver biopsies will be taken as described in both the SoA (Section 1.3) and the histopathology manual. The histopathology manual must be followed for all liver biopsies as study standard operating procedure. Reasonable attempts should be made to acquire a needle core liver biopsy specimen using a 16-gauge needle of at least 2.0 cm (expected to have ≥11 portal tracts) in length. Specimens less than 1.5 cm will not be accepted for evaluation. If the first sample is not a minimum of 1.5 cm, a second core sample should be collected. The anatomical location (right or left liver lobe) and the specimen adequacy (needle size, tissue length) should be recorded. All of the collected biopsy tissues should be submitted for central pathology review.

Liver biopsy samples will be processed into formalin fixed paraffin embedded blocks, routinely stained with hematoxylin and eosin (H&E) and Masson's trichrome (MTR) by a central laboratory. Stained slides will be used for confirmation of the diagnosis of NASH, assessment and grading of NAS activity including scoring of steatosis, lobular inflammation, ballooning, as well as fibrosis using the NASH CRN scoring system by a hepatopathologist. The NASH CRN fibrosis score and components of NAS (ie, lobular inflammation, hepatocyte ballooning, steatosis grade) will be used for comparison of pre- versus post treatment. Additional analyses of liver biopsies are outlined in Section 8.2.12.

A previous biopsy conducted between 24 weeks and 4 weeks before the start of the screening period (or within 12 weeks before the start of the screening period for any F4cc participants who met the inclusion and exclusion criteria before establishment of safety and tolerability in the first four noncirrhotic [F1-F3] participants) as part of standard of care that meets the above criteria for an adequate liver biopsy may substitute for a fresh biopsy, provided sufficient numbers of sections (stained or unstained) and uncut biopsy block, as outlined in the histopathology manual are made available to the sponsor. If the biopsy is found to be inadequate by the study pathologist, a fresh biopsy will be required. The Week 24 liver biopsy should be taken from the same lobe as the screening biopsy.

Leftover tissue samples may be retained and stored for RNA sequencing (transcriptomics) analysis or other possible additional future analyses. Any retained samples will be deidentified and will not be labeled with patient identifying information. After 15 years from the end of the study, or earlier as required by local regulations, samples may be returned to the sponsor repository or destroyed per local regulations. Additionally, with the participant's consent, samples may be used for further research by the sponsor or others, such as universities or other companies, to contribute to the understanding of NASH or other diseases, the development of related or new treatments, or development of research methods. Instructions for returns and destruction of tissue samples will be provided to the study sites in documentation outside of the protocol.

8.2.9 Magnetic Resonance Imaging-derived Iron-corrected T1 Mapping of the Liver

Liver *MultiScan*® MRI is a fast, contrast-free MRI scan that provides quantitative assessment of the whole liver tissue by measuring biomarkers for fibrosis and inflammation, fat, and iron. As part of the Liver *MultiScan*® technology, the owner company segments an entire slice of the liver parenchyma and quantifies iron-corrected T1 (cT1) relaxation time values across that slice of liver tissue, so capturing disease heterogeneity in analysis. The cT1 measurement has shown to be correlated with histopathological hallmarks of NASH (Dennis et al. 2021).

The abdominal MRI (to obtain liver cT1 as well as other MRI-based exploratory biomarkers described in Section 8.2.12) will be performed at the time points specified in the SoA (Section 1.3).

8.2.10 HepQuant-SHUNT Disease Severity Index

The dual cholate test (HepQuant®-SHUNT) is an investigational assay. The test yields a DSI that quantifies global liver function and physiology through the measurement of hepatic filtration rates that are defined from clearances of cholic acid-24-^{13}C (20 mg administered intravenously; "systemic") and cholic acid-2,2,4,4-d4 (40 mg administered orally; "portal"). The HepQuant-SHUNT DSI quantifies hepatic impairment and is thought to be reproducible over a broad spectrum of etiologies of liver disease, stages of fibrosis, and clinical severity.

The HepQuant-SHUNT DSI will be performed at the time points specified in the SoA (Section 1.3).

8.2.11 Alcohol Screening

The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems (nida.nih.gov/sites/default/files/audit.pdf). Both a clinician-administered version and a self-report version of the AUDIT are included in this assessment. Participants will be encouraged to answer the AUDIT questions in terms of standard drinks. A score of 8 or more is considered to indicate hazardous or harmful alcohol use. The AUDIT has been validated across genders and in a wide range of racial/ethnic groups and is well suited for use in primary care settings.

The AUDIT will be performed at the time points specified in the SoA (Section 1.3).

8.2.12 Additional Biomarkers

C-reactive protein and calprotectin are key biomarkers of inflammation. There is a significant relationship between hsCRP and risk of disease progression in NAFLD and NASH (Yoneda et al. 2007). Pro-C3 is a key biomarker of liver fibrosis. Mixed acting anti-metabolic agents

(FGF19/21 analogues) that affect inflammatory pathways (eg, NF-kB) decreased Pro-C3 within short trials ≤16 weeks by at least 20%, which is considered a clinically significant change (ie, associated with improvement in liver fibrosis by ≥1 stage improvement in longitudinal studies) (Luo et al. 2018). In the open label, 12-week Phase 2a trial with aldafermin, levels of Pro-C3 and ELF had greater reductions in patients who demonstrated histological response (histological response was defined as a 2-point or greater improvement in NAS without worsening of fibrosis or improvement in fibrosis of one stage or more without worsening of NASH [defined as no increase in NAS for ballooning, inflammation, or steatosis]), compared to non-responders (Harrison et al. 2021). Biomarkers of liver disease such as ELF will be derived as a composite score from serum levels of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA). The ELF is the first prognostic tool for patients with advanced fibrosis (F3 or F4) due to NASH to be granted De Novo marketing authorization by FDA. Elevated ELF levels are prognostic for progression to cirrhosis (ELF ≥9.8) and liver-related clinical events (ELF ≥11.3) in NASH patients with advanced fibrosis (Fagan et al. 2015; Harrison et al. 2017). Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) is a part of Liver *MultiScan*® and has an excellent correlation with histological steatosis across the spectrum of NAFLD and high diagnostic accuracy in stratifying all grades of hepatic steatosis (Dennis et al. 2021). Spleen cT1 significantly correlates with the hepatic venous pressure gradient (HVPG) and has an excellent diagnostic accuracy for portal hypertension (HVPG >5 mmHg) and clinically significant portal hypertension (HVPG ≥10 mmHg) with an area under the receiver operating characteristic (AUROC) curve of 0.92 for both (Levick et al. 2019).

Blood and liver biopsy samples will be collected at the time points specified in the SoA (Section 1.3) for each of the following biomarkers:

- Serum Pro-C3.
- Serum ELF and its components (TIMP-1, PIIINP, and HA).
- Serum soluble MAdCAM-1.
- Serum and plasma markers of inflammation, fibrosis, and trafficking including but not limited to: hsCRP, calprotectin (plasma), IL-8, CTXIII, C3M, TSP2, and Pro-C5.
- Exploratory analyses in liver biopsies including but not limited to markers of inflammation, fibrosis, and trafficking and may utilize artificial intelligence/machine learning methods.
- T and immune cell trafficking in liver biopsy samples (immunohistochemistry) and circulating whole blood samples, including but not limited to Th17/Th1 vs. Th2, β_7^+ T cells, CCR9, and CXCR3.

- Transcriptomics using residual liver biopsies and whole blood samples.
- Potential analyses of extracellular vesicles using residual serum samples.

Blood samples must be collected before administration of study drug. The ELF score is calculated from the concentrations of serum biomarkers: TIMP-1, PIIINP, and HA.

Details of sample collection, handling, shipment, and analysis will be provided in the laboratory manual.

The sponsor may store samples for up to 15 years after the end of the study to achieve study objectives. Additionally, with the participant's consent, samples may be used for further research by the sponsor or others, such as universities or other companies, to contribute to the understanding of NASH or other diseases, the development of related or new treatments, or development of research methods.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Physical Examinations

Complete physical examinations will be performed at the time points specified in the SoA (Section 1.3). Complete physical examination will include the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; eyes; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; back; and lymph nodes.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any changes from SV1 in physical examination results that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

8.3.2 Targeted Neurological Assessment

Targeted neurological assessments to monitor the development of signs and/or symptoms of PML will be performed at the time points specified in the SoA (Section 1.3). Participants will be evaluated to reveal any potential abnormalities in the following neurological domains: vision, motor, tactile sensation, coordination/cerebellar function, speech, verbal comprehension, and cognition/behavior.

If any abnormalities are indicated, participants will be further evaluated to help clarify any potential abnormal responses. Focus will be placed on possible alternative etiology (eg, fracture or stroke). If additional evaluation reveals an unexplained new abnormality, neurological examination(s), targeted to the abnormal domain, will be performed by the investigator or qualified personnel.

Participants with any unexplained positive neurological assessment item at the first screening visit that is suggestive of PML should be excluded from enrollment in the study (exclusion criterion #15, Section 5.2).

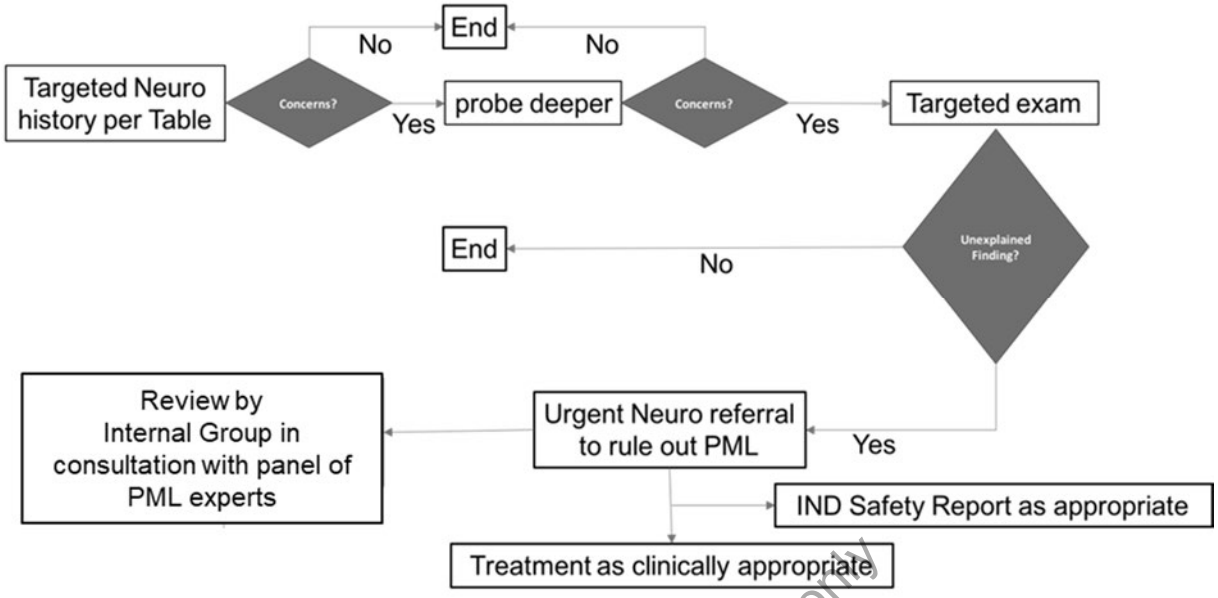
A step-wise approach for the proposed neurological assessment plan is summarized in Table 5.

Table 5. Neurological Assessment Plan

Domain	Step 1: Targeted Neurological History	Step 2: If Abnormal Response
Vision	Diplopia or visual/visual field loss	Perform visual field assessment
Motor	Major motor weakness (eg, legs, arms)	Test leg strength (hopping, foot tapping), finger tapping, pronator drift and bilateral muscle strength
Tactile sensation	Paresthesia, anesthesia in any domain (peripheral, central)	Pinprick test
Coordination/cerebellar	Clumsiness, difficulty with walking, writing, or fine motor skills, etc.	Finger-nose, heel-shin, heel-toe walk, writing sample, draw a clock
Speech	Dysarthria, expressive aphasia	Naming objects, repeat multipart phrase, observe for dysarthria or aphasia
Verbal comprehension	Agnosia, receptive aphasia	Test to follow routine commands, eg, close eyes, touch finger to ear
Cognition/behavior	New onset of difficulties with memory or thinking, important changes in behavior	Recall 3 objects over 1 minute, serial 7s, proverbs. Changes in activities of daily living over prior 24 weeks

Additionally, should there be any unexplained abnormal neurological findings, the participant is to be urgently referred to a neurologist. The sites will immediately inform the sponsor of any such occurrences. If the neurologist confirms the presence of PML, appropriate actions, including discontinuation of study drug, will be taken. Suspected PML cases will be reviewed promptly by the internal safety review committee with an external panel of PML experts and presented at the next meeting(s) of the internal safety review committee (Section 10.1.5.2). If PML is diagnosed, there will be an urgent meeting of the internal safety review committee with the PML expert panel. A flow diagram of the quarterly assessments and actions is presented in Figure 3. Any concerns from the internal safety review committee will be promptly communicated to the sponsor study team, investigator, and treating neurologist.

Figure 3. Flow Diagram for Quarterly Neurological Assessments



IND=investigational new drug; Neuro=neurological; PML=progressive multifocal leukoencephalopathy

It is important to note that assessments based on neurological evaluations are collected and evaluated in a different manner than observed or volunteered AEs. Given these differences, no attempt will be made to reconcile any apparent discrepancies between observed or volunteered AEs and data from neurological assessment collected from participants. Investigators will determine whether any finding on neurological testing constitutes an AE. At each visit, participants will be queried for adverse events of special interest (AESIs) related to PML (Section 8.3.11.6, Section 10.3.3.2.2, and Section 10.3.5). Adverse event incidence rates will not be calculated from these neurological evaluation data but rather from the AE information recorded by the investigator.

8.3.3 Hypersensitivity Monitoring

Participants will be monitored for the presence of Type I (anaphylaxis) and Type III (immune complex) hypersensitivity reactions at the time points specified in the SoA (Section 1.3).

Participants will be educated on the signs and symptoms of Type III hypersensitivity reactions (eg, fever, rash [including hives], arthralgia, myalgia, vasculitis, Arthus reaction, general ill feeling, itching, and swollen lymph nodes) and how to respond to them should they occur during the outpatient portion of the study. In addition, participants will be instructed to report hypersensitivity AEs to the investigator at the time of occurrence, and to seek immediate medical care if necessary. At each visit, the participant will be queried for AESIs related to hypersensitivity.

Participants who experience an AE suggestive of a Type I hypersensitivity reaction should have a blood sample (3 mL) collected for anti-ontamalimab immunoglobulin E antibody determination, results of which will be available at the end of the study. Participants who have a suspected Type III hypersensitivity reaction should have a blood sample (4 mL) collected for complement determination (C3a, C5b-9).

Further details of hypersensitivity reactions as AESIs are provided in Section 8.3.11.6 and Section 10.3.3.2.

8.3.4 Vital Signs

Vital signs will be collected before collection of blood samples for laboratory assessments, where applicable.

Additional collection times or changes to collection times will be permitted as necessary to ensure appropriate collection of safety data.

Vital signs will include:

- body temperature
- respiratory rate
- sitting blood pressure (systolic and diastolic, resting more than 5 minutes)
- pulse (bpm)

Single measurements of sitting blood pressure will be recorded at each time point. Blood pressure should be determined by cuff with the participant's arm supported at the level of the heart and recorded to the nearest mmHg using the same method, the same arm (preferably the dominant arm), and the same position throughout the study.

Respiratory rate will be measured with the participant in a comfortable position. The observer should hold the extremity of the participant as a distraction for the patient (ie, pretending he/she is taking the participant's radial pulse) and count the respiration for 1 minute.

Body temperature should be taken using a thermometer and reported in degrees Celsius or Fahrenheit.

The investigator will assess whether a change in vital signs from baseline (Day 1/Week 0) may be deemed clinically significant on the vital signs eCRF and whether the change should be considered and recorded as an AE on the AE eCRF.

8.3.4.1 Weight and Height

Weight and height will be measured at the time points specified in the SoA (Section 1.3).

A participant should have weight and height measured while wearing indoor clothing and with shoes off. Weight is collected in kilograms (kg). Height is recorded in centimeters (cm).

8.3.5 Electrocardiograms

A 12-lead ECG will be obtained as outlined in the SoA (Section 1.3).

A local ECG reader will be used in this study. The eligibility of the participant will be based on the assessment of the ECG by the investigator. If abnormal results are observed following assessment by the local reader, the investigator, in consultation with the appointed sponsor or CRO medical monitor, will reconfirm the participant's eligibility to continue.

8.3.6 Chest X-ray

A chest X-ray will be performed at the first screening visit; however, if a participant has had a chest X-ray performed up to 12 weeks before the first screening visit then it does not need to be repeated as a part of screening. The official reading must be located in the participant's source documentation.

8.3.7 Contraception and Breastfeeding Check

During the screening visit (Visit 1), the investigator or designee in consultation with the participant will confirm the participant's childbearing potential status. For participants of childbearing potential, it must be confirmed and documented that the participant has selected the most appropriate method of contraception (ie, highly effective methods for female and medically appropriate methods for male study participants) from the permitted list of contraception methods (see Section 10.4). Participants must affirm the consistent and correct use of at least one of these selected methods. Participants who are capable of breastfeeding must affirm that they are not using their breastmilk to feed an infant. Regular contraception and breastfeeding check discussions will take place at the time points specified in the SoA (Section 1.3) (ie, at each site visit) and will be documented.

8.3.8 Clinical Safety Laboratory Tests

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3). Details about these procedures and required safety monitoring will be given in the laboratory manual.

The maximum volume of blood at any single visit is approximately 100 mL, and the approximate total volume of blood for the study participant is 500 mL (approximate volumes do not include potential repeat measurements).

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis.

The central laboratory will return these results, along with their reference ranges, to the investigator. The investigator is responsible for reviewing the laboratory report, documenting this review, and filing the laboratory report with the source documents.

If serum liver chemistry measurements at Week -8 (SV1) or Week -6 (SV2) are repeated (ie, as described in the SoA), the Week -8 (SV1) or Week -6 (SV2) value will be calculated as the mean of the initial and repeat measurements for the given visit, except if the repeat sampling was conducted because of a technical issue with the initial sample.

Abnormal laboratory findings associated with the underlying disease should not be considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

Clinically significant abnormal laboratory values obtained during participation in the study or within 12 weeks after the last dose of study drug should be repeated until the values return to normal or the baseline value or are no longer considered clinically significant by the investigator or medical monitor. The investigator should evaluate whether the laboratory result meets the AE criteria in Section 10.3.1.

Abnormal clinical laboratory values that are unexpected or not explained by the participant's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

Investigators must document their review of each laboratory safety report.

The investigator must record the following types of laboratory test results on the laboratory eCRF and, if applicable, on the AE eCRF:

- any changes that are considered clinically significant by the investigator (eg, SAE or AE or dose modification)

- any laboratory test results (central laboratory, local laboratory, non-protocol-specific local laboratory) that are used to make a study drug decision, that require a change in participant management, or that are used to make a response evaluation.

8.3.9 Pregnancy Testing

A beta-human chorionic gonadotropin (β-hCG) pregnancy test will be performed on all participants of childbearing potential at times described in the SoA (Section 1.3); if pregnancy is suspected; or on withdrawal of the participant from the study.

A serum pregnancy test will be performed at the first screening visit; all other pregnancy tests will be urine tests (a confirmatory serum β-hCG pregnancy test will only be required for participants who have a positive urine pregnancy test at any time).

Pregnancy tests are not required for participants of nonchildbearing potential (see Section 10.4.1 for definitions).

If a participant or a participant's partner becomes pregnant during the study, the pregnancy must be followed as described in Section 10.4.3.

8.3.10 Immunogenicity Assessments

A blood sample for measurement of ADA will be collected at the time points specified in the SoA (Section 1.3). Blood samples must be collected before administration of the study drug at that visit. The detection and characterization of ADA will be performed using a validated assay method by or under the supervision of the sponsor.

8.3.11 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs are provided in Section 10.3.

The investigator and any qualified designees are responsible for collecting, detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for follow-up of these events (see Section 10.3.3.2.1).

8.3.11.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs (including pretreatment-emergent and treatment-emergent) will be collected from the signing of the ICF until the end of the 12-week safety follow up period at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately. Under no circumstance should this exceed 24 hours. The investigator will also submit any updated SAE data within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor via the reporting method described in Section 10.3.5.

8.3.11.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit specified in the SoA, the participant or the participant's legally authorized representative will be questioned in a general way to ascertain if AEs have occurred since the previous visit. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences without introducing bias. Participants will report AEs occurring at any time during the study.

8.3.11.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All participants experiencing AEs, whether considered associated with the use of the study drug or not, will be documented in the AE page of the eCRF.

All AEs must be monitored until the end of the study or until the event resolves, stabilizes, is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3.

SAEs must be monitored until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Information to be documented for each event is defined in Section 10.3.4.

Further information on follow-up procedures is provided in Section 10.3.

8.3.11.4 Regulatory Reporting Requirements for Serious Adverse Events

All SAEs must be recorded and reported to the sponsor or designee immediately, via the procedure described in Section 10.3.5. Under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study

drug 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 drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.

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

The sponsor or designee must prepare safety reports for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forward them to investigators as necessary.

8.3.11.5 Pregnancy in a Participant or Participant's Partner During the Study

Details about all pregnancies in participants or their partners will be collected after the start of study drug and until the end of the 12-week safety follow-up period. Collection of pregnancy data from a participant's partner requires the partner's informed consent.

To the extent possible, the investigator will collect follow-up information on the outcome of the pregnancy and the neonate, and the information will be forwarded to the sponsor.

Once a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours.

Pregnancy itself is not considered to be an AE or SAE; however, AEs or SAEs associated with pregnancy must be reported as such, including:

- Any pregnancy complication or elective termination of a pregnancy for medical reasons (to be reported as an AE or SAE)
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) (to be reported as SAEs)
- Any poststudy pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor as described in Section 10.3.5. Although the investigator is not obligated to actively seek poststudy pregnancy-related SAE information from former study participants or their partners, he or she may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.3.11.6 Adverse Events of Special Interest

Adverse events of special interest in this study include potential hypersensitivity, serum sickness, vasculitis, Arthus reactions to ontamalimab, and PML.

Participants will be monitored for the presence of Type I (anaphylaxis) and Type III (immune complex) hypersensitivity reactions at the time points specified in the SoA (Section 1.3).

Participants will be educated on the signs and symptoms of Type III hypersensitivity reactions (eg, fever, rash [including hives], arthralgia, myalgia, vasculitis, Arthus reaction, general ill feeling, itching, and swollen lymph nodes) and how to respond to them should they occur during the outpatient portion of the study. In addition, participants will be instructed to report hypersensitivity AEs to the investigator at the time of occurrence, and to seek immediate medical care if necessary. At each visit, the participant will be queried for AESIs related to hypersensitivity.

Participants who experience an AE suggestive of a Type I hypersensitivity reaction should have a blood sample (3 mL) collected for anti-ontamalimab immunoglobulin E antibody determination, results of which will be available at the end of the study. Participants who have a suspected Type III hypersensitivity reaction should have a blood sample (4 mL) collected for complement determination (C3a, C5b-9).

Further details of hypersensitivity reactions as AESIs are provided in Section 10.3.3.2.

Participants will be monitored for signs and symptoms of suspected PML at specified time points (Section 8.3.2). At each visit, the participant will be queried for AESIs related to PML.

Adverse events of special interest that occur during the treatment period or the follow-up period must be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

8.4 Pharmacokinetics

A blood sample for determination of serum ontamalimab concentrations will be collected at the time points specified in the SoA (Section 1.3). Blood samples must be collected before study drug administration. Details of sample collection, handling, shipment, and bioanalysis will be provided in the laboratory manual.

8.5 Genetics

Genetics will not be evaluated in this study.

8.6 Immunogenicity Assessments

See Section 8.3.10 for a description of immunogenicity assessments.

9. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be prepared and finalized before the first participant completes informed consent. The SAP will provide further details regarding the definition of analysis variables and the statistical analysis methodology to address all study objectives.

9.1 Statistical Hypotheses

No statistical hypothesis testing will be performed in this study.

9.2 Analysis Sets

- The screened set will consist of all participants who have signed informed consent(s).
- The full analysis set (FAS) will consist of all participants who are enrolled in the study, have received at least 1 dose of study drug, and have at least 1 valid postbaseline assessment.
- The safety analysis set will consist of all participants who are enrolled in the study and have received at least 1 dose of study drug.
- The PK set will consist of all participants in the safety analysis set who have at least 1 evaluable postdose PK concentration value.

9.3 Biomarker and Noninvasive Test Analyses

The biomarker and noninvasive test analyses will be performed on the FAS based on data from participants in all fibrosis stages (F1 through F4cc) using an estimation approach. The biomarker and noninvasive test data will be summarized descriptively by visit as observed.

For biomarkers except cT1 MRI, data from all available sampling during screening period (SV1 and SV2) and D1 predose measurement during treatment period will be averaged to establish the stable baseline value. For cT1 MRI, only one measurement will be taken during screening, which will be used for the baseline value.

9.3.1 Primary Endpoint

See Section 3 for the primary endpoints related to the assessment of safety. See Section 9.4 for a description of the safety analyses.

9.3.2 Secondary Endpoints

The secondary endpoints are presented in Section 3.

For Pro-C3 and ELF, which are collected at multiple postbaseline visits (SoA; see Section 1.3), the percent change from baseline at Week 24 will be analyzed using a mixed effects model for

repeated measure (MMRM) with visit as the fixed effect, participants as the random effect, and baseline values as covariates. The least-squares means of the percent change from baseline at Week 24 along with the corresponding 95% confidence intervals (CI) will be presented.

For cT1 MRI, which is collected at one postbaseline visit (Week 24), the change from baseline at Week 24 along with the corresponding 95% CI will be presented.

9.3.3 Exploratory Endpoints

The exploratory endpoints are presented in Section 3.

All continuous endpoints collected at multiple postbaseline visits will be analyzed using a MMRM with visit as the fixed effect, participants as the random effect, and baseline values as covariates. The least-squares means of the change from baseline at Week 24 along with the corresponding 95% Cis will be presented.

For binary endpoints, the count and proportion of participants achieving the endpoint status along with the corresponding 2-sided 95% Clopper-Pearson Cis will be presented.

9.3.4 Multiplicity Adjustment

Not applicable.

9.4 Safety Analyses

The primary endpoints of the study are related to the assessment of safety (see Section 3).

All safety analyses will be performed using the safety analysis set.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (version 25.0 or higher). Treatment-emergent AEs are defined as AEs with start dates at the time of or following the first exposure to the study drug. The number and percentage of TEAEs will be presented by system organ class and preferred term. Treatment-emergent AEs will be further summarized by severity and relationship to the study drug. Adverse events related to the study drug, AEs leading to study drug discontinuation, SAEs, and deaths will be similarly summarized or listed.

Clinical laboratory test results, vital signs, body weight, and ECG findings will be summarized by visit. Potentially clinically significant findings will also be summarized or listed.

Antidrug antibody data will be summarized by visit.

9.5 Other Analyses

9.5.1 Pharmacokinetic Analyses

Pharmacokinetic samples will be collected at predose on Day 1 and predose at Weeks 4, 8, 12, 16, 20, and 24 during the treatment period, and approximately 1 week after the dose on Day 1. Concentrations of ontamalimab over the sampling time will be descriptively summarized and graphed.

As part of the exploratory endpoints, PK properties of ontamalimab and relationships between PK and target engagement (as measured by soluble MAdCAM-1) in participants with NASH will be evaluated using a population PK/target engagement modeling and simulation approach and reported separately.

9.6 Interim Analysis

No interim analysis is planned.

9.7 Determination of Sample Size

The planned sample size for this study is 18 participants who complete the 24-week treatment period. The sample size has been chosen to provide adequate number of participants to investigate the objectives of the study based on clinical experience for key biomarkers (Anstee et al. 2022; Harrison et al. 2018; Jabor et al. 2018).

This study is not statistically powered to perform any formal hypothesis testing, and the analyses will be based on estimation approach.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted with the highest respect for the individual participants (ie, participants) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP). Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Section 10.1.11.2. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, participants' source documents, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of study drug for shipment to the site.

10.1.2 Financial Disclosure

The study is being funded by Takeda. Payments for the conduct of the study that will be made to study sites (and, if applicable, investigators and/or other study staff) will be specified in the Clinical Study Site Agreement(s). All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a form for the disclosure of their financial arrangements during the course of the study and for 1 year after the completion of the study. The financial disclosure form must be signed by each investigator and subinvestigator before the study starts at their study site; in addition, any potential conflicts of interests that are

not covered by this financial disclosure form should be disclosed separately to the sponsor prior to the start of the study at their site.

All institutional affiliations of the investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to the sponsor prior to the start of the study.

Upon submission of a marketing application to the US FDA for any drug, Takeda must provide the US FDA with a list of clinical investigators who conducted a Takeda-sponsored clinical study and certify or disclose financial arrangements.

Specific financial arrangements requiring disclosure would include any arrangement whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in study drug; any significant equity interest in the sponsor or subsidiaries as defined in 21 Code of Federal Regulations (CFR) 54 2(b) (1998).

10.1.3 Informed Consent Process

10.1.3.1 Informed Consent Requirements in This Study

The goal of the informed consent process is to provide a potential participant or their legally authorized representative with sufficient information about the research to allow for an informed decision about their voluntary participation in the research study. The informed consent process must facilitate the participant's comprehension of the information and allow adequate opportunity for the participant to ask questions and consider whether or not to participate. This process may extend beyond a participant's initial consent due to changing circumstances within the study, the therapeutic landscape, or the participant's situation.

When a participant or their authorized representative consents to participate in the study, their informed consent must be documented in writing via either a signed and dated ICF or via an eConsent system, if applicable. The date of the informed consent will also be collected in the eCRF along with the initial protocol version.

In this study, informed consent will be required from all participants and/or their legally authorized representatives.

A legally authorized representative is defined as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant, to the participant's participation in the procedure(s) involved in the study".

In this study, informed consent will be obtained using paper forms, an electronic system, or both (eg, eConsent, if applicable).

10.1.3.2 Standards the Informed Consent Follows

Informed consent documents, regardless of whether they are presented on paper or electronically, must embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations.

The ICF and related materials (eg, participant authorization form, participant information sheet):

- explain the nature of the study, its objectives, potential risks and benefits.
- describe the participant's rights and responsibilities, including what the study will require of the participant.
- describe the planned and permitted uses, transfers, and disclosures of the participant's personal and personal health information for purposes of conducting the study, including the use of electronic devices and associated technologies, if applicable.
- state the fact the participant is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

More specifically, in seeking informed consent, the following information shall be provided to each participant:

- A statement that the study involves research.
- An explanation of the purposes of the research.
- The expected duration of the participant's participation.
- A description of the procedures to be followed, including invasive procedures.
- The identification of any procedures that are experimental.
- The estimated number of participants involved in the study.
- A description of the participant's responsibilities.
- A description of the conduct of the study.
- A statement describing the treatment(s) and the probability for random assignment to each treatment.
- A description of the possible side effects of the treatment that the participant may receive.
- A description of any reasonably foreseeable risks or discomforts to the participant and, when applicable, to an embryo, fetus, or nursing infant.

- A description of any required restrictions related to contraception, pregnancy, and breastfeeding.
- Contraception requirements for participants of childbearing potential and for participants capable of making a partner pregnant.
- Definition of relevant terms such as "childbearing potential."
- Statement that participants of childbearing potential will undergo regular pregnancy tests during the study.
- Explanation of required actions (such as discontinuation or treatment or from the study) if a participant or their partner becomes pregnant during study.
- Statement that the participant must avoid breastfeeding during the study.
- A description of any benefits to the participant or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
- Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant and their important potential risks and benefits.
- A statement describing the extent to which confidentiality of records identifying the participant will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB, and the monitor may inspect the records. By signing an ICF, the participant or the participant's legally acceptable representative is authorizing such access.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
- The anticipated prorated payment(s), if any, to the participant for participating in the study.
- The anticipated expenses, if any, to the participant for participating in the study.
- An explanation of whom to contact for answers to pertinent questions about the research (investigator), participant's rights, and IRB and whom to contact in the event of a research-related injury to the participant.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant otherwise is entitled.
- A statement that the participant or the participant's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

- The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
- A statement that the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study.
- A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
- The foreseeable circumstances or reasons under which the participant's participation in the study may be terminated.
- A participant authorization (either contained within the ICF or provided as a separate document) describing to the participant the contemplated and permissible uses and disclosures of the participant's personal information (including personal health information) for purposes of conducting the study. The participant authorization must contain the following statements regarding the uses and disclosures of the participant's personal information:
    - That de-identified personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs;
    - That is possible that de-identified personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer participants the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    - That de-identified personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for participants, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    - That participants agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

- That the participant's identity will remain confidential in the event that study results are published.
- A statement that clinical trial information from this trial may be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.
- A description of the electronic devices and associated technology and its usage in the study.

10.1.3.3 Who Creates the Informed Consent Materials

The sponsor or designee will provide sample ICFs and related materials to the investigator.

The investigator is responsible for the preparation, content, and IRB approval of the ICF and related materials.

The principal investigator will provide the sponsor with a copy of the ICF and related materials that was reviewed by the IRB and received their favorable opinion/approval. A copy of the IRB's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB requires modification of the sample documents that the sponsor provided, the documentation supporting this requirement must be provided to the sponsor. Both the IRB and the sponsor must approve the ICF and related materials before use.

In the event that consent materials are provided electronically, and/or if consent is obtained electronically (eg, eConsent, if applicable), the sponsor or designee will provide the IRB-approved version of the ICF to the site in an electronic form with 21 CFR–compliant eConsent functionality.

10.1.3.4 Who Conducts the Informed Consent Process

It is the responsibility of the investigator and the study personnel to:

- explain the detailed elements of the ICF and related materials to the participant or the participant's legally authorized representative, as applicable.
- answer *all of* the participant's or participant's legally authorized representative's questions about the study.
- provide the participant or the participant's legally authorized representative, as applicable, ample time to decide whether or not to participate in the study.

- obtain written and/or electronic informed consent from all participants or the participants' legally authorized representatives, as applicable, prior to any study-related procedures including screening assessments.

Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. (Oral and written information may be provided via remote or virtual visits, eg, via telehealth [video, phone] and eConsent systems.) If the participant is not capable of rendering adequate written informed consent, then the participant's legally acceptable representative may provide such consent for the participant in accordance with applicable laws and regulations.

If the participant, or the participant's legally acceptable representative, determines they will participate in the study, then they must sign and date the ICF (and participant authorization form, as applicable) at the time of consent and prior to entering into the study.

For paper consent forms, the participant or the participant's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink in the case of written informed consent. If applicable, eConsent provides the same information as written consent forms, but in an electronic format that may include multimedia components. eConsent does not replace the important discussion between the study participant and site staff or investigator. Regardless of the consent format – written or eConsent – the investigational site is responsible for the consenting process.

A copy of the informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative.

The investigator must also sign and date the ICF or eConsent (if applicable) and the participant authorization form (if applicable) at the time of consent or after receipt of participant signature (in the case of eConsent) and before the participant enters the study. However, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Signed consent forms or certified copies of electronic signatures must remain in each participant's study file at the site and must be available for verification at any time.

The investigator must document the date the participant signs the ICF in the participant's source documents.

10.1.3.5 Reconsent

Participants or participants' legally authorized representatives, as applicable, are required to re-consent if changes are made to the protocol or if new information is made available that may affect the willingness of current participants (those who are already enrolled and actively participating) to continue in the clinical investigation. Re-consent should be obtained as described in Section 10.1.3.1.

Updated ICFs, individual consents, individual assents, individual re-consents and re-assents will be placed in the Trial Master File. Re-consent information including the protocol version and re-consent date will also be recorded in the eCRFs.

10.1.4 Data Protection

The confidentiality of records that may be able to identify participants will be protected in accordance with applicable laws, regulations, and guidelines.

After participants have consented to take part in the study, the sponsor and/or its representatives reviews their source documents and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market ontamalimab; national or local regulatory authorities; and the IRB(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of participants' identities. Participants are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing participants' unique identifying number, relevant source documents, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

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 which would make the participant identifiable will not be transferred.

The participant must be informed that their 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 who will be required to give consent for their data to be used as described in the ICF.

The participant must be informed that their source documents may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB or ethics committee members, and by inspectors from regulatory authorities.

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor or designee.

10.1.4.1 Notice Regarding the Use and Transfer of the Investigator's Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and telephone number, and other personally identifiable information such as education and professional details, payment-related details (if applicable), identity information (eg, medical registration number) and information relating to his or her interactions and activities with or involving Takeda. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and their licensing partners.
- Business partners assisting Takeda, its affiliates, and their licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and ethics committees.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.

- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

In addition, where required by law or industry codes of practice, Takeda and/or its affiliates may have to report or publicly disclose any payments or transfers of value made in connection with the study by or on behalf of Takeda and/or its affiliates or their service providers to the investigator or their institution.

The legal basis on which Takeda and its affiliates will process the Investigator's personal information for the above purposes are in order to comply with a legal obligation; or to perform any contract in place with the investigator (if applicable); or to meet the legitimate research, scientific and business interests of Takeda and its affiliates, including ensuring the proper performance of this study to the applicable standards, appropriate reporting of study results and archiving of study-related records and information, and further development and registration of the study drug or other compounds. The investigator may not be able to opt-out of this processing, or the investigator's choice to opt-out may impact his or her ability to continue to participate in this study and/or future studies involving Takeda and/or its affiliates.

Takeda and its affiliates will maintain physical, administrative, and technical safeguards to protect the Investigator's personal information from loss, misuse, unauthorized access, disclosure, alteration or destruction. Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

However, where Investigator's personal information is transferred to Takeda affiliates, licensing partners, business partners or service providers in such countries, Takeda will ensure that all adequate safeguards are in place and that all applicable laws and regulations are complied with in connection with such transfers.

The Investigator's personal information will only be stored as long as necessary for the purposes for which it was collected subject to local laws and regulations and legitimate scientific, research and business needs.

Investigator acknowledges and authorizes the use of his or her personal information by Takeda and other parties for the purposes described above.

10.1.5 Committees Structure

10.1.5.1 Institutional Review Board Approval

IRBs must be constituted according to the applicable state and federal requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRBs. If any member of the IRBs has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

Those sites in the US unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federalwide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRBs for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, participant recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRBs for approval.

The IRB's written approval of the protocol and participant ICF must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug).

The IRB's approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship drug once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives drug, no protocol activities, including screening, may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRBs regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by participants, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRBs, and submission of the investigator's final status report to IRBs. All IRBs approvals and relevant documentation for these items must be provided to the sponsor or designee.

Participant incentives should not exert undue influence for participation. Payments to participants must be approved by the IRBs and sponsor.

10.1.5.2 Other Committees

An internal safety review committee (independent from the study team) will review the overall safety of the study participants on an ongoing basis. This review will consist of monitoring of safety of participants throughout the study. Recommendations made on the basis of this review to alter the conduct of the study or to amend the protocol will be provided to the study team for review and for a final decision. The sponsor or its designee will notify investigative sites, and regulatory authorities as appropriate, of recommendations based on this review. Details regarding this review and the frequency of this review will be established in a separate charter before the administration of study drug to any participant. In addition, the internal safety review committee will be responsible for:

- Evaluating safety and tolerability data from the first four noncirrhotic (F1-F3) participants who have received at least 3 doses of ontamalimab 75 mg and have been monitored for at least 12 weeks, to support the decision to include F4cc participants in the study.
- Engaging with an independent panel of experts to evaluate any liver-related events (eg, liver decompensation, significant deterioration of liver chemistry tests).
- Monitoring neurological safety and consulting a panel of leading PML experts, including a neurologist, neuroradiologist, and a virologist, in the event of a suspected case of PML (see Section 8.3.2).

10.1.6 Dissemination of Clinical Study Data

10.1.6.1 Study Results Disclosure

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical trials and disclose the results of those trials in a manner and timeframe compliant with Takeda policy and all applicable laws and regulations. Clinical trial registration and results disclosures will occur on the applicable clinical trial registry(ies)/database(s) as required by law.

10.1.7 Data Quality Assurance

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

Guidance on completion of CRFs will be provided in the study CRF Completion Guidelines or similar.

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

Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan or contracts.

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

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time frame specified in the Clinical Study Site Agreement 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.

10.1.7.1 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The sponsor will assess any protocol deviation. If it is likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

The site should document all protocol deviations in the participant's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the participant, or confound interpretation of primary study assessment.

Protocol deviations should be captured in a Part 11–compliant clinical trial management system.

10.1.7.2 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site head guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

Alternative approaches may be used to ensure data quality, data integrity, and participant safety (eg, remote source data review/source data verification via phone or video) as permitted by regional and local regulations. See the monitoring plan for additional details.

10.1.7.3 Audits

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately.

The investigator and study site guarantee access for quality assurance auditors to all study documents as described in Section 10.1.8.

10.1.8 Source Documents

All key data must be recorded in the participant's source documents unless otherwise noted in the protocol. Source documents may be paper or electronic, including data obtained using electronic devices and associated technologies. Original source data to be reviewed during this study will include, but are not limited to: participant's medical file, appointment books, diaries, clinical outcome assessments, original clinical laboratory reports, histology reports, pathology

reports, X-rays. The investigator (as listed on the US FDA Form 1572) is responsible for maintaining adequate and accurate source documents.

The investigator must provide direct access to inspect facilities, including original source records relevant to this study (regardless of media), to: the sponsor or its authorized representatives; the respective national, local, or foreign regulatory authorities; the IRB/ethics committee; and auditors. These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, United Kingdom Medicines and Healthcare products Regulatory Agency) or an auditor. The ICF includes a statement granting this access to source data.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.1.8.1 Electronic Case Report Forms

Completed eCRFs are required for each participant who has completed the consent process. The eCRFs are designed to record all observations and other data pertinent to the clinical investigation unless otherwise noted in the protocol.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. eCRFs must be completed in English.

The investigator or the investigator's designee (ie, authorized site personnel, as stated in the site delegation log) must enter data from the source documents (Section 10.1.8) into the eCRF with guidance from the study CRF Completion Guidelines or similar.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

A study monitor from the sponsor or its designee will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Auditors, IRB members, or regulatory inspectors may also check the eCRF entries against the source documents.

Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel.

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should also be included. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

All data will have separate source documentation; no data will be recorded directly onto the eCRF.

The clinical research associate/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data. Alternative approaches may be used to ensure data quality, data integrity, and participant safety (eg, remote source data review via phone or video) as permitted by regional and local regulations. Additional details are in the monitoring plan.

10.1.8.2 Documentation and Retention of Records

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data 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 may need to request

previous source documents or transfer records, depending on the study. Also, current source documents must be available.

Study monitors will perform ongoing source data 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.

10.1.8.3 Data Handling

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

10.1.8.4 Record Retention

The investigator agrees to keep the records stipulated in Section 10.1.8 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating participants, source documents, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs (including consent to use digital tools and applications, if applicable), participant authorization forms regarding the use of personal health information (if separate from the ICFs), query responses/electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the participant's chart to ensure long term legibility. Furthermore, ICH E6(R2) Section 5.5.11 requires the investigator to retain essential documents specified in ICH E6(R2) (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6(R2) Section 5.5.11 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

10.1.9 Study and Site Start and Closure

10.1.9.1 First Act of Recruitment

The first act of recruitment is the first site open.

For clinical trial disclosure purposes, the study start date is the date when the first participant signed the ICF.

10.1.9.2 Study/Site Termination

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. The sponsor reserves the right to close the study site at its sole discretion. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- For study termination:
    - Discontinuation of further study drug development.
- For site termination:
    - Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines.
    - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
    - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

During this study, until the open access period, only Takeda may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation.

Both during and after this study, all public disclosures containing data/information from this study must undergo ***review and receive written approval*** by the appropriate Takeda representative(s) ***before*** any public disclosure (including but not limited to submission, presentation, posting on online platforms for archiving, and distribution of unpublished preprints).

This policy applies to all publication types, including: abstracts and presentations (oral and poster, including invited presentations) for scientific congresses; articles (original research manuscripts, review articles, invited articles), letters to the editor, and editorials, in scientific peer-reviewed journals; print, electronic and enhanced multimedia publications associated with traditional congress and journal publishing (such as, but not limited to, audio, visual/graphical or video abstracts or manuscript summaries; video or animated posters; augmented reality, etc.); books and book chapters.

Authorship will be determined in line with the requirements of the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, unless otherwise required by the journal or forum where the publication appears.

All publications must be developed with a dataset (such as statistical tables and listings, a CSR, and/or final report) that has been verified by a qualified Takeda employee per Takeda's internal standards. Data relevant to the development of Takeda publications must be shared with all authors via a secure site.

Publications derived from this study may never contain participants' direct identifiers (such as participant ID, initials) but may contain indirect/quasi identifiers (for example sex/gender, age/birth date, geographic indicators). Publications derived from this study may not include products' direct identifiers (lot numbers or batch numbers) unless specifically required by the journal or conference guidelines and if approved by Takeda.

Takeda requires the submission of all manuscripts resulting from this study, regardless of the intended audience or language, to journals that offer public availability via an Open Access platform.

The following types of information are required by ICH to be in the protocol if not addressed in another document (such as the site contracts):

The results of this study may be published or presented at scientific meetings. If this is foreseen, 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.

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.

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

10.1.11 Responsibilities of the Sponsor and the Investigator

10.1.11.1 Sponsor Responsibilities

10.1.11.1.1 Study-related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform these activities either in full or in partnership with the sponsor.

The study is being funded by Takeda. Payments for the conduct of the study that will be made to study sites (and, if applicable, investigators and/or other study staff) will be specified in the Clinical Study Site Agreement(s). All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and subinvestigator before the study starts at their study site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor before the start of the study at their site.

All institutional affiliations of the investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to sponsor before the start of the study.

10.1.11.1.2 Insurance

Each participant in the study must be insured in accordance with the regulations applicable to the site where the participant is participating. If a local underwriter is required, then the sponsor or sponsor’s designee will obtain clinical study insurance against the risk of injury to study participants. Refer to the study site agreement regarding the sponsor’s policy on participant compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor’s designee.

10.1.11.2 Investigator Responsibilities

Clinical research studies sponsored by the sponsor are subject to ICH GCP, FDA, and all other applicable local laws and regulations.

The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities:

- Conduct the study in accordance with the protocol.
- Personally conduct or supervise the staff who will assist in the protocol.
- If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
- Ensure that study related procedures, including study specific (non-routine/non-standard panel) screening assessments are NOT performed on potential participants, before the receipt of written approval from relevant governing bodies/authorities.
- Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
- Secure prior approval of the study and any changes by an appropriate IRB that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
- Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to participants. Make at least yearly reports on the progress of the study to the IRB, and issue a final report within 3 months of study completion.
- Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
- Obtain valid informed consent from each participant who participates in the study, and document the date of consent in the participant's medical chart. A valid ICF is the most current version approved by the IRB. Each ICF should contain a participant authorization section that describes the uses and disclosures of a participant's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a participant authorization, then the investigator must obtain a

separate participant authorization form from each participant or the participant's legally acceptable representative.

- Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
- Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
- Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
- Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

It is the investigator's responsibility to ensure that adequate time, appropriately trained personnel, and resources are available prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.

If a potential research participant has a primary care physician, the investigator should, with the participant's consent, inform them of the participant's participation in the study.

10.1.11.2.1 Protocol Adherence and Investigator Agreement

The investigator and any subinvestigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those participants who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRBs and provide them with a detailed written explanation. The investigator will also return all study drug, containers, and other study materials to the sponsor.

Upon study completion, the investigator will provide the sponsor, IRB, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.1.11.2.2 Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study.

Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research, as well as study participation.

The coordinating investigator will be required to review and sign the final clinical study report and by doing so agrees that it accurately describes the results of the study, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.1.11.2.3 Compliance With all Local, State, and National Controlled-substance Biohazard and Infectious Disease Regulations and Legislation

When using controlled substances, biohazardous material, or substances for infectious diseases, the investigator must at all times comply with all local, state, and national laws pertaining to registration and reporting with the appropriate regulatory body and control and handling of such substances.

10.1.12 Site Termination or Suspension

10.1.12.1 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement; is unable to ensure adequate performance of the study; or as otherwise permitted by the contractual agreement.

10.1.12.2 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for ontamalimab, such that the risk/benefit profile is no longer acceptable for participants participating in the study.

- Three participants develop the same TEAE or SAE considered possibly or probably related to study drug that is severe or medically significant, but not immediately life-threatening; or where hospitalization or prolongation of hospitalization is indicated; or is disabling; or limits self-care activities of daily living.
- Two participants develop any TEAE or SAE, regardless of attribution to study drug, that has life-threatening consequences or requires urgent intervention.
- Death of any participants at any time related to an AE.

- The internal safety review recommends that the study should be suspended or terminated or that cirrhotic participants are not to be enrolled in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises participant safety.

10.1.12.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an IRB, or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

10.2 Clinical Laboratory Tests

Table 6 lists the tests that will be obtained for each laboratory specimen. These tests will be performed by the central laboratory or other identified specialty laboratories (refer to laboratory manual for details).

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

Table 6. Protocol-required Laboratory Tests

Laboratory Tests	Parameters		
Hematology	Platelet count Hemoglobin Hematocrit	RBC count RBC indices: Mean corpuscular volume Mean corpuscular hemoglobin %Reticulocytes	White blood cell count with differential (both % and absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils

Table 6. Protocol-required Laboratory Tests

Clinical Chemistry[a]	Albumin Blood urea nitrogen Creatinine	Calcium Carbon dioxide Chloride Glucose[b] Magnesium Phosphate Potassium Sodium	AST ALT Alkaline phosphatase γ-Glutamyl transferase Lactate dehydrogenase	Total bilirubin Direct bilirubin Total protein Total cholesterol HDL-C LDL-C Triglycerides[b]
Coagulation	INR			
Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)			
Other safety tests	ADA HbA1c eGFR (CKD-EPI) Creatine kinase Anti-ontamalimab IgE[c] Complement determination (C3a, C5b-9)[d]			
Pregnancy Testing	For participants of childbearing potential only: Highly sensitive serum or urine human chorionic gonadotropin pregnancy test			
Other screening tests	If menopause is suspected: Follicle-stimulating hormone Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) Serology (HIV antibody, HbsAg, HbcAb, and HCVAb; HBV DNA reflex testing if HbsAg is negative and HbcAb is positive; HCV RNA polymerase chain reaction if HCVAb is positive) Infection disease panel (includes cytomegalovirus, Epstein-Barr virus, and herpes simplex virus) Vitamin D Serum α-fetoprotein AMA ANA, SMA, alpha-1-antitrypsin, and ceruloplasmin IgG4 TB (IGRA)			
PK and Biomarkers	Serum ontamalimab concentration Biomarkers: • Pro-C3 (serum) • ELF score (serum) • Soluble MAdCAM-1 (serum) • hsCRP (serum) • Calprotectin (plasma) • Whole blood T cell phenotyping • Whole blood transcriptomics			

Table 6. Protocol-required Laboratory Tests

ADA=antidrug antibody; ALT=alanine aminotransferase; AMA=antimitochondrial antibody; ANA=antinuclear antibody; AST=aspartate aminotransferase; CKD=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; ELF=Enhanced Liver Fibrosis; HbA1c=hemoglobin A1c; HbcAb=hepatitis B core antibody; HbsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCVAb=hepatitis C virus antibody; HDL-C=high-density lipoprotein cholesterol; HIV=human immunodeficiency virus; hsCRP=high-sensitivity C-reactive protein; Ig=immunoglobulin; IGRA=interferon-gamma release assay; IL=interleukin; INR=international normalized ratio; LDL-C=low-density lipoprotein cholesterol; MAdCAM-1=mucosal addressin cell adhesion molecule-1; PK=pharmacokinetic(s); Pro-C3=neoepitope-specific N-terminal propeptide of type III collagen; RBC=red blood cell; TB=tuberculosis

[a] Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 Liver Chemistry Stopping Criteria.

[b] To be collected under fasting conditions.

[c] For participants who experience an AE suggestive of a Type I hypersensitivity reaction (see Section 8.3.3).

[d] For participants who have a suspected Type III hypersensitivity reaction (see Section 8.3.3).

10.2.1 Clinical Laboratory Assessments and Other Safety Assessments

A change in the value of a clinical laboratory parameter, physical examination finding, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of study drug, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the study drug, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), physical examination, vital sign, or ECG values that were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of the participant, whether a change in a clinical laboratory value, physical examination, vital sign, or ECG parameter is clinically significant and represents an AE. The assessment of clinical significance is recorded on the eCRF related to the assessment (for example, the clinical laboratory value eCRF), but an event that is also classified as an AE will be recorded on the AE page.

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

Table 7. Adverse Event Subtypes Defined in This Section

Type	Nested Subtypes				Report Within[1]	Sponsor Reports[2]
Adverse Event (AE) – collection timing per SoA—Section 1.3					--	--
	AE of special interest/clinical interest (AESI)—Section 8.3.11.6, Section 10.3.3.2				24 hours	TBD
	Pretreatment-emergent adverse event				--	--
	Treatment-emergent adverse event (TEAE)—Section 10.3.4.9				--	--
	Serious adverse event (SAE)—Section 8.3.11.4				24 hours	TBD
	Related adverse event–any study drug (whether the study drug or another intervention) – Section 6.1, Section 10.3.4.3				--	--
		Related adverse event (adverse drug reaction [ADR]) (related to the study drug)			--	--
	Expected adverse event—Section 10.3.4.7				--	--
	Unexpected adverse event—Section 10.3.4.7				--	--
		Suspected, unexpected serious adverse reaction (SUSAR) (ie related to study drug)—Section 10.3.5.1				
			Fatal/Life threatening		24 hours	7 days
			Nonfatal/Non–life threatening		24 hours	15 days

(--)=not expedited; AE=adverse event; CRO=contract research organization; eCRF=electronic case report form; SAE=serious adverse event; SoA=Schedule of Activities; TBD=to be determined (to be evaluated at the sponsor. Reporting requirements vary); TEAE=treatment-emergent adverse event

The specific timeframes on this chart apply to expedited AE/SAE reporting periods and procedures for which this protocol provides additional instructions. Reporting via the eCRF is *required but is not sufficient* to expedite a report.

[1] This is the required, expedited reporting period for the site to report the event to the sponsor/CRO.

[2] This is the required, expedited reporting period for the sponsor to notify other parties including but not limited to regulatory agencies. For some studies, partner agreements may exist that have different reporting timelines, as specified in the individual pharmacovigilance agreement.

10.3.1 Definition of Adverse Event

Adverse Event Definition
An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation participant who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment. An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of the study drug, whether or not the occurrence is considered related to the study drug. 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 the study drug. An untoward finding generally may necessitate therapeutic intervention, require an invasive diagnostic procedure, or require discontinuation or a change in dose of study drug or a concomitant medication. (Repeated or additional noninvasive testing [eg, laboratory or ECG retests] for verification, evaluation, or monitoring of an abnormality is not considered a therapeutic intervention.)

Events Meeting the AE Definition
• New condition detected or diagnosed after the use of the study drug, even though it may have been present before the start of the study. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition. • Event that is of greater intensity, frequency, or duration than expected for the individual participant or an event with a reasonable possibility that it was related to the study drug. • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, physical examinations, vital signs measurements) that are clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease), including those that worsen from baseline.

Events NOT Meeting the AE Definition

- Situations in which an untoward medical occurrence did not occur (eg, preplanned or elective surgery[a]).
- Presence or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- 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[b].
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Cases of overdose with any medication without manifested side effects[c] .

[a] Preplanned and elective surgeries are defined as those that were scheduled prior to signing of the informed consent form. See exceptions in Section 10.3.3.1. While these procedures are not considered AEs, they should be documented in the participant's source documents as described in Section 8.1.3.

[b] Preexisting conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. However, any untoward medical occurrence (eg, signs and symptoms) in a clinical study participant which occurred between SV1 and D1 predose should be recorded as pretreatment-emergent AE (eg, COVID-19 infection). The results of the first evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless they are related to study procedures. However, any clinically significant change (worsening) between screening and following visits evaluations up to D1 predose should be recorded as pretreatment-emergent AEs.

[c] Overdoses should be documented in the participant's source documents.

AE onset and resolution dates are defined as follows:

- Start date: the date when the first signs/symptoms were noted by the participant and/or investigator
- End date: the date when the participant recovered, the event resolved but with sequelae, or the participant died

10.3.2 Definition of Serious Adverse Event

Serious adverse events (SAEs) are events that meet BOTH the AE criteria described in Section 10.3.1 AND the criteria for seriousness below.

SAE Definition
An SAE is defined as any untoward medical occurrence that meets 1 or more of the criteria listed:
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 that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
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 (for example, 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
f. Is a suspected transmission of any infectious agent via an authorized medicinal product

SAE Definition
g. Other situations: • Is an important medical event • May require intervention to prevent one of the outcomes listed above • May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

10.3.3 Additional Considerations in Identifying and Defining Adverse Events

10.3.3.1 Defining Discrete Adverse Events

Each reported AE should represent a single diagnosis, if the diagnosis is known. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs UNLESS the diagnosis is unknown. Specific examples are as follows:

Laboratory values and ECG findings:

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis should be reported as the AE.

Worsening of a condition:

If the participant experiences a worsening or complication of a medical condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…"). This includes:

- Pre-existing conditions present at the time of signing of informed consent.
- Pre-existing episodic concurrent medical conditions (eg, asthma, epilepsy): An episode should only be recorded as an AE if the condition becomes more frequent, serious, or severe in nature.

- A degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis): Worsening of the condition should only be recorded as an AE if it occurs to a greater extent than expected.
- Worsening or complication of an AE after any change in study drug: The worsening or complication should be recorded as a new AE.

Complications associated with preplanned procedures:

- Changes in plan and surgical complications associated with preplanned or elective surgeries, therapies, or procedures should be recorded as AEs.
- If a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE.
- Complications resulting from an elective surgery should be recorded as AEs.

Changes in intensity of AEs:

- If the participant experiences changes in intensity of an AE, the event should be recorded once with the maximum intensity recorded.

10.3.3.2 Adverse Events of Special Interest

An AESI (serious or nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest will be captured and monitored during this study. Investigators will report all AESIs to the sponsor, regardless of causality, using the same timelines as described for SAE reporting (see Section 10.3.5). The following text describes the AESIs and the criteria for reporting AESIs.

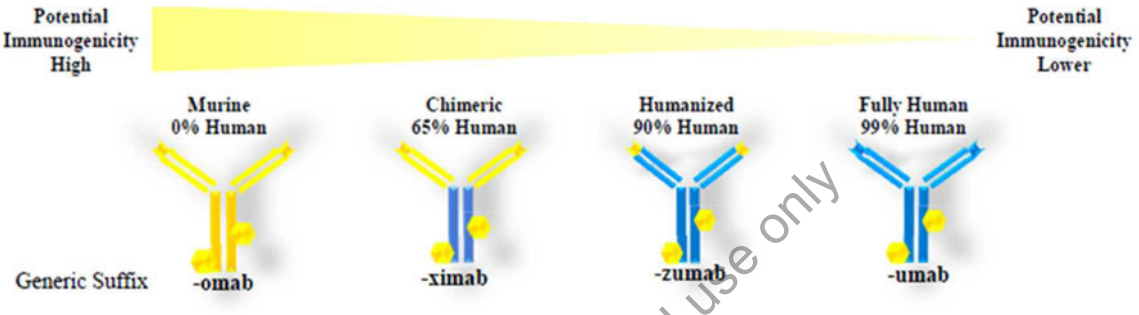
10.3.3.2.1 Hypersensitivity

Potential hypersensitivity reactions to ontamalimab will be regarded as AESIs. These events must be reported using the process described for SAEs and within the time frame mandated for SAEs (see Section 10.3.5).

It is well known that the administration of foreign proteins can cause immune responses including hypersensitivity reactions such as anaphylaxis and serum sickness. Other immune responses to foreign proteins include the development of ADA and neutralizing antibodies.

Monoclonal antibodies have been used in human therapeutics since the 1980s. The first monoclonal antibody approved for human use (Orthoclone OKT3®), was a murine protein which caused rapid production of neutralizing antibodies. Since then, much effort has been expended to reduce the immunogenicity of these useful therapeutic proteins by reducing the extent of "foreignness" from chimeric antibodies such as infliximab, to humanized antibodies such as vedolizumab, and finally to fully human antibodies such as adalimumab and ontamalimab (Isabwe et al. 2018) (see Figure 4).

Figure 4. Potential Immunogenicity of Therapeutic Monoclonal Antibodies



Ontamalimab is a fully human antibody of the immunoglobulin G2 subclass. In Phase 1 and Phase 2 clinical trials of ontamalimab, in which over 700 participants were treated for up to 3 years, there has been no case of anaphylaxis. There have been 2 reported cases of drug hypersensitivity: serum sickness attributed to concomitant administration of penicillin; and a reaction characterized by dyspnea, facial erythema, and chest pain with onset 2 days after administration of the fifth dose of ontamalimab. The latter event mimicked a reaction that the participant had previously experienced after 4 doses of infliximab. In addition, low titer activity has been observed in ADA assays, including pretreatment samples and placebo-treated participants, and no participant has had a 2-fold or greater increase in ADA titer. Analysis of pharmacokinetic and clinical parameters has shown no difference between participants whose ADA assay results are positive as compared with those whose are negative.

Nonetheless, the possibility of a hypersensitivity reaction occurring after drug exposure cannot be fully ruled out. The reactions of concern in this clinical trial are Type I (anaphylaxis) and Type III (immune complex) reactions. The clinical presentation of anaphylactic reactions is described below in Table 8.

Table 8. Clinical Criteria for Diagnosing Anaphylaxis (Type I Hypersensitivity)

Anaphylaxis is highly likely when below criterion and at least any one of the following criteria a and b are fulfilled:
Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:
Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
Reduced BP[a] or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

BP=blood pressure; mmHg=millimeters of mercury; PEF=peak expiratory flow.
[a] Low systolic BP for children is defined as less than 90 mmHg from 11 to 17 years.
Source: Adapted from Sampson et al. 2006 (Sampson et al. 2006).

Type III hypersensitivity responses, including those mediated by immune complexes and T cells (also referred to as delayed hypersensitivity responses), are relatively rare with respect to therapeutic protein products and a high degree of clinical suspicion is necessary for the diagnosis (US FDA Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products, August 2014). Type III hypersensitivity reactions involve the formation of biologic/ADA immune complexes in the circulation which, when present in the correct stoichiometric ratio, become deposited in tissues. Once immune complexes are deposited, they can elicit complement activation and inflammation, leading to tissue damage. When immune complexes are deposited in tissues, they tend to localize in small postcapillary venules where there is loss of laminar blood flow, in sites of ultrafiltration where there is high pressure and fenestrated endothelium (eg, choroid plexus, ciliary body, synovium, and glomeruli), in sites of turbulent blood flow (eg, coronary artery branches off aorta, aortic bifurcations, and cardiac valve leaflets), and in renal glomerular endothelium.

Signs and symptoms of immune complex deposition typically have onset 1 to 3 weeks after exposure (Warrington et al. 2018) usually improving in 7 to 10 days, with full recovery in 2 to 4 weeks and may include fever, rash (including hives), arthralgia, myalgia, vasculitis, Arthus reaction, general ill feeling, itching, and swollen lymph nodes.

10.3.3.2.2 PML

Suspected PML/PML will be regarded as an AESI. These events must be reported using the process described for SAEs and within the time frame mandated for SAEs (see Section 10.3.5).

Ontamalimab prevents the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM-1 expressing sites with high affinity and selectivity. Although the selective targeting of MAdCAM-1 is a novel anti-inflammatory approach, the basic interference of lymphocyte homing by preventing the

binding of these $\alpha_4\beta_7^+$ lymphocytes to MAdCAM-1, and the resultant efficacy in CD is well established by natalizumab and more recently by vedolizumab. The main difference between ontamalimab and other agents that interfere with the MAdCAM-1:integrin axis is that ontamalimab selectively binds to endothelial MAdCAM-1 rather than to the $\alpha_4\beta_7^+$ integrin on lymphocytes to block the interaction. Principal organs of MAdCAM-1 expression include intestine, pancreas, stomach, esophagus, spleen, and nasopharyngeal tissue and to a lesser extent lung, liver, and bladder but not in normal central nervous system. Ontamalimab also does not bind to vascular cell adhesion molecule and is, therefore, expected to be ineffective for multiple sclerosis, and it is not expected to increase the risk of PML since it does not affect lymphocyte homing or surveillance in the central nervous system.

No cases of PML have been reported with ontamalimab in previous clinical studies. However, as continued mitigation for the potential risk of PML, targeted neurological assessments will be performed in this study to monitor any changes from baseline in the participant's status (Section 8.3.2).

10.3.4 Recording and Follow-up of Adverse Events and/or Serious Adverse Events

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 reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information. Each event must be categorized in terms of the attributes below, over the entire course of the event, including the start and stop dates. It is **not** acceptable for the investigator to send photocopies of the participant's source documents to the sponsor or designee in lieu of completion of the required form. There may be instances when copies of source documents for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the source documents before submission to the sponsor or designee. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.4.1 Frequency

Assessment of Frequency
The investigator should assess and record the frequency of the event. Episodic AEs (eg, vomiting) or those that occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.3.4.2 Intensity

Assessment of Intensity	
The investigator will assess the intensity for each AE and SAE (including any laboratory abnormality) reported during the study and assign it to 1 of the following categories:	
Mild:	An AE that is usually transient, easily tolerated by the participant, and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	An AE that is usually alleviated with additional specific therapeutic intervention. The event causes discomfort and interferes with usual activities of daily living, but poses no significant or permanent risk of harm to the research participant.
Severe:	An AE that interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.
Please note: Intensity and seriousness are separate concepts. The terms "severe" and "serious" are not synonymous. Because serious events usually pose a threat to a participant's life or ability to function, seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.	

10.3.4.3 Causality/Relatedness

Assessment of Causality	
The investigator must assess the relationship between the study drug and each occurrence of each AE/SAE based on the criteria below:	
Related:	An AE that follows a reasonable temporal sequence from administration of the study drug (including the course after withdrawal of the study drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications, and concurrent treatments, may also be responsible. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
Not Related:	An AE that does *not* follow a reasonable temporal sequence from administration of the study drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.
The investigator will also consult the IB in their assessment. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. 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. The causality assessment is one of the criteria used when determining regulatory reporting requirements. 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.	

10.3.4.4 Action Taken

Action Taken Concerning Intervention(s)
The investigator must make note of the action taken concerning the study drug: • Dose not changed. • Drug interrupted. • Drug withdrawn. • Dose delayed. • Unknown. • Not applicable: a study drug was stopped for a reason other than the particular AE (eg, the study has been terminated, the participant died, dosing with study drug was already stopped before the onset of the AE). For any AE that was ongoing at the time of a participant's death, the study drug action should reflect the most recent action that had been taken at the time of death (eg, drug interrupted, withdrawn). If the participant had never received the study drug, the action taken should be recorded as "dose not changed" or "not applicable." The study drug action of "withdrawn" should not be selected solely as a result of the participant's death.

10.3.4.5 Outcome

Outcome
The investigator must make note of the outcome of any AEs that occur during the course of the study: • Recovered/resolved: The participant returned to first assessment status with respect to the AE. • Recovered/resolved with sequelae: The participant recovered from an acute AE but was left with permanent/significant impairment. • Recovering/resolving: The intensity has decreased by 1 or more stages; the diagnosis or signs/symptoms have almost disappeared; the abnormal laboratory value has improved, but has not returned to the normal range or to baseline; the participant died from a cause other than this particular AE. • Not recovered/not resolved: There is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms, or laboratory value on the last day of the observed study period is now worse than when it started; is an irreversible congenital anomaly; the participant died from another cause. • Fatal: The AE is considered to be the cause of death or contributed to the participant's death. • Unknown: The course of the AE cannot be followed up due to hospital change or residence change at the end of the participant's participation in the study.

10.3.4.6 Follow-up

Follow-up of AEs and SAEs
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee 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. If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings, including histopathology. New or updated information will be recorded in the originally submitted documents. The investigator will report any updated AESI/SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4.7 Reference Safety Information

The reference safety information (RSI) for this study is the IB, which the sponsor has provided under separate cover to all investigators.

10.3.4.8 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the RSI. "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but will not be based on what might be anticipated based on the pharmacological properties of a product.

10.3.4.9 Pretreatment-emergent Adverse Events

For reporting purposes in the study, a pretreatment-emergent AE is defined as any event that occurs after signing ICF up to the initiation of the study drug. Pre-existing conditions present at the time of signing of informed consent and pre-existing episodic concurrent medical conditions (eg, asthma, epilepsy) and laboratory tests, ECG, X-rays etc. related to first screening procedures

should NOT be recorded as AEs unless they are related to study procedures. As described in Section 1.3, these AEs will be collected in the study from the time when the ICF is signed.

10.3.4.10 Treatment-emergent Adverse Events

As described in Section 1.3, all AEs will be collected from the time when the ICF is signed. For reporting purposes in the study, a TEAE is defined as any event emerging or manifesting at or after the initiation of treatment with a study drug or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the study drug or medicinal product.

10.3.5 Expedited Reporting of Serious Adverse Events and Adverse Events of Special Interest

This section describes the expedited reporting required for certain types of events, in addition to eCRF completion:

Sites must report SAEs/AESIs immediately, and in no case in more than 24 hours.

SAE/AESI Reporting to the Sponsor via an Electronic Data Collection Tool
The primary mechanism for reporting an SAE/AESI to the sponsor will be the electronic data collection tool. If the electronic system is unavailable, then the site will use a paper SAE form to report the event within 24 hours. The site will enter the SAE/AESI data into the electronic system as soon as it becomes available. After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE/AESI from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or to the medical monitor by telephone. Contacts for SAE reporting can be found in the study operations manual.

10.3.5.1 Safety Reporting to Investigators, Institutional Review Boards, and Regulatory Authorities

The sponsor will be responsible for identifying and reporting all SUSARs and any other applicable SAEs to regulatory authorities including the FDA, investigators, and IRB in accordance with national regulations in the US. Adverse events that are already classified as expected (and therefore are not SUSARs) are listed in the RSI (see Section 10.3.4.7 for the location of the RSI).

The following specialized types of events have their own reporting windows:

Suspected unexpected serious adverse reactions will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, relative to the first awareness of an event by/or further provision to the sponsor or sponsor's designee, unless otherwise required by national regulations.

The sponsor will prepare an expedited report for other safety issues that might materially alter the current benefit-risk assessment of a study drug/sponsor-supplied drug or that would be sufficient to consider changes in the study drug/sponsor-supplied drug administration or in the overall conduct of the trial.

The study site will forward a copy of all expedited reports to its IRB in accordance with local regulations.

10.4 Contraceptive and Barrier Guidance

10.4.1 Definitions

For the purposes of this study, reproductive status is defined as follows:

- **Nonpregnant:** Negative urine and/or serum β-hCG pregnancy test result.
- Person who ***is*** **not of childbearing potential**:
  - Premenarchal and 1 of the following:
    - Tanner stage 1
    - Less than 9 years of age
  - Surgically sterile for at least 6 weeks at screening (defined as having undergone one of the following procedures: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy).

- Postmenopausal at screening (defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient).

- Person who ***is* of childbearing potential**: following menarche and until becoming postmenopausal unless permanently sterile by the definition above.
- Male who ***is* not fertile**: prepuberty OR post puberty but permanently sterile by bilateral orchidectomy.
- Male who ***is* fertile**: post puberty, unless permanently sterile by the definition above.

10.4.2 Contraception Guidance

In this study, the use of highly effective contraception is generally required unless otherwise noted. In addition, contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

The failure rates of contraceptives that are used consistently and correctly may differ in typical use. Therefore, when study participation requires any of these methods of contraception to be used, participants must commit to using them:

- consistently throughout the required period.
- correctly, as described below and in any labeling associated with the method.

Contraception requirements depend in part on the reproductive status of the participant and the participant's partner.

10.4.2.1 Contraceptive Methods for Participants Capable of Producing Viable Ova and/or Becoming Pregnant

This section describes contraception methods appropriate for participants capable of producing viable ova and/or becoming pregnant in the present study, as well as pregnancy and lactation-related guidance, based on guidance provided by the Clinical Trial Facilitation Group.

Table 9. Acceptable Contraception Methods and Lactation Guidance in This Study for Participants Capable of Producing Viable Ova and/or Becoming Pregnant

Highly Effective Contraceptives **Failure rate of <1% per year when used consistently and correctly**
User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[a] - Oral - Intravaginal - Transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation - Oral - Injectable • Sexual abstinence[b]
Low User Dependency
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner[c]
Measures Intended to Prevent Neonatal Exposure via Breastmilk
• Participants who are lactating must agree not to use their breastmilk to feed an infant.

IUD=intrauterine device; IUS=intrauterine hormone-releasing system.
[a] Hormonal contraceptives must be stabilized for at least 30 days prior to the start of the screening period.
[b] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[c] For participants of childbearing ability, having a vasectomized partner is a highly effective contraception method provided that the partner is the participant's sole partner and that the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Table 10. Unacceptable Contraception Methods for Participants Capable of Producing Viable Ova and/or Becoming Pregnant

Methods that are unacceptable in *any* study requiring contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods) • Withdrawal (*coitus interruptus*) • Spermicides only • Lactational amenorrhea method • Use of both female condom and male condom together at the same time
Contraceptives that are effective but have a failure rate of >1% per year when used consistently and correctly are unacceptable in a study requiring *highly effective contraception (ie, <1% failure rate)*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm, or sponge with spermicide

10.4.2.2 Contraceptive Methods for Participants Capable of Producing Viable Sperm

This section describes contraception methods appropriate for participants capable of producing viable sperm in the present study and for their partners of childbearing potential.

Table 11. Acceptable Contraception Methods in This Study for Participants Capable of Producing Viable Sperm and Their Partners

Acceptable Methods For Male Participants
• Sexual abstinence[a] • Male condom with spermicide • Combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) • Male sterilization (vasectomy) with documented absence of sperm in the postvasectomy ejaculate • Refraining from donating sperm[c]
Acceptable Methods For Female Sexual Partners of Male Participants (Unless Not of Childbearing Potential)
• Highly effective method of contraception listed in Table 9[b] • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action[b] • Female condom with spermicide • Cap, diaphragm, or sponge with spermicide

Table 11. Acceptable Contraception Methods in This Study for Participants Capable of Producing Viable Sperm and Their Partners

• Combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)
Measures Intended to Prevent Fetal and Neonatal Exposure via Sperm or Breastmilk
• Participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the treatment period and for at least 12 weeks after the last dose of study treatment.

[a] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[b] Hormonal contraceptives must be stabilized for at least 30 days prior to the start of the screening period.
[c] Refrain from donating sperm for the duration of the study and for 12 weeks after the last dose of study treatment.

In addition, male participants must be advised not to donate sperm from signing of the ICF to 12 weeks after the last dose of study drug.

10.4.3 Pregnancy

If any participant is found to be pregnant during the study, the participant should be withdrawn and any sponsor-supplied study drug should be immediately discontinued.

If a participant's partner becomes pregnant during the study or for 12 weeks after the last dose, the participant's partner should be asked for consent to record and follow the pregnancy.

If the pregnant participant or the participant's pregnant partner agrees, the investigator should notify their primary care physician that the participant/participant's partner was participating in a clinical study when they became pregnant and provide details about the study drug the participant received.

If the pregnancy occurs from the time of informed consent until the end of the 12-week follow-up period, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in the study operations manual.

All pregnancies in participants on study drug or their partners will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

10.5 Abbreviations and Definitions

10.5.1 Abbreviations

ADAs	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
AUROC	area under the receiver operating characteristic
β-hCG	beta-human chorionic gonadotropin
BLM	baseline measurement
CAP	Controlled Attenuation Parameter
CCR9	C-C chemokine receptor type 9
CD	Crohn's disease
CFR	Code of Federal Regulations
CLD	chronic liver disease
cm	centimeters
CRN	Clinical Research Network
CRO	contract research organization
CSR	clinical study report
cT1	iron-corrected T1 mapping
cT1 MRI	iron-corrected T1 mapping by magnetic resonance imaging
CXCR3	C-X-C motif chemokine receptor 3
DSI	disease severity index
ECG	electrocardiogram
eConsent	electronic consent
eCRF	electronic case report form(s)
ELF	Enhanced Liver Fibrosis
EMA	European Medicines Agency
F	fibrosis stage

F4cc	fibrosis stage 4 compensated cirrhotic
FAS	full analysis set
FAST	FibroScan-aspartate aminotransferase
FDA	Food and Drug Administration
FIB-4	Fibrosis-4 Index
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HA	hyaluronic acid
HbA1c	hemoglobin A1c
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein
HVPG	hepatic venous pressure gradient
IB	investigator's brochure
IBD	inflammatory bowel disease
ICF	informed consent form(s)
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identification
IGRA	interferon-gamma release assay
IL	interleukin
IMID	immune-mediated inflammatory disease
INR	international normalized ratio
IRB	Institutional Review Board
LSM	liver stiffness measurement
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MCD	methionine- and choline-deficient
MELD	Model for End-stage Liver Disease

MMRM	mixed effects model for repeated measure
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NAS	Nonalcoholic Fatty Liver Disease Activity Score
NASH	nonalcoholic steatohepatitis
PDFF	proton density fat fraction
PFS	prefilled syringe
PIIINP	amino-terminal propeptide of type III procollagen
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PPAR	peroxisome proliferator-activator receptor
Pro-C3	neoepitope-specific N-terminal propeptide of type III collagen
PSC	primary sclerosing cholangitis
Q4W	every 4 weeks
RSI	reference safety information
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SAP	statistical analysis plan
SC	subcutaneous(ly)
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
SV	screening visit
T2DM	type 2 diabetes mellitus
TB	tuberculosis
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TIMP-1	tissue inhibitor of metalloproteinases 1
TZD	thiazolidinedione
UC	ulcerative colitis
ULN	upper limit of normal
US	United States

10.6 Protocol Amendment History

Date	Document	Global/Country/Site Specific
02 Nov 2022	Original Protocol	Global
15 Dec 2022	Amendment 1	Global
25 Apr 2023	Amendment 2	Global
18 Sep 2023	Amendment 3	Global

Summary of Change(s) Since the Last Version of the Approved Protocol	
Protocol Amendment 2	
Amendment Date: 25 Apr 2023	**Global/Region/Country/Site Specific:** Global

Overall Reason for the Amendment

The overall reasons for this protocol amendment are to:

- Revise inclusion and exclusion criteria to improve feasibility of study conduct at a variety of clinical sites.
- Clarify contraception methods for male study participants and for female sexual partners of male participants.
- Add an additional part to the baseline visit to allow confirmation of eligibility on the basis of liver chemistry tests before dosing.
- Clarify acceptable conditions for repeating screening laboratory samples.
- Allow flexibility to perform Week -6 and Week 24 assessments on different days within the specified visit window.

Description of Each Change and Rationale			Section(s) Affected by Change
#	Description of change(s)	Rationale for change(s)	Section
1.	Removed Inclusion Criteria #7 and #8 and revised Exclusion Criteria #1 and #2 to eliminate separate entry criteria for fibrosis stage (F)2/F3 versus F4 compensated cirrhotic (F4cc) staging. Criteria for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total and direct bilirubin, albumin, international normalized ratio (INR), creatinine, and platelet count for all study participants were removed from Exclusion Criterion #1 and revised under Exclusion Criterion #2. Removed biopsy-confirmed fibrosis stage F4cc from Exclusion Criterion #2, so the subcriteria apply to all study participants.	To provide uniformity so that all study participants, regardless of biopsy-confirmed staging (F2/F3/F4cc), will have the same laboratory requirements for study entry, with no required presence or history of previously defined hepatic and abdominal diagnoses.	Section 1.1 Synopsis Section 5.1 Inclusion Criteria, Criteria #7 and #8 Section 5.2 Exclusion Criteria, Criteria #1 and #2

Description of Each Change and Rationale			Section(s) Affected by Change
#	Description of change(s)	Rationale for change(s)	Section
2.	Revised the inclusion criterion to lower the FibroScan-aspartate aminotransferase (FAST) score for eligible participants from ≥0.5 to >0.35. Revised justification for the FAST score threshold of >0.35.	To allow easier influx of participants into the study while maintaining the same neoepitope-specific N-terminal propeptide of type III collagen (Pro-C3) and Enhanced Liver Fibrosis (ELF) threshold to determine ultimate eligibility for liver biopsy, by identifying participants who do not have NASH with NAS≥4 and fibrosis F≥2.	Section 1.1 Synopsis Figure 1 Study Schema, footnote b Table 1 Schedule of Study Activities: Screening Period, footnote w Section 4.1 Overall Design Section 5.1 Inclusion Criteria, Criterion #4 Section 5.1.1 Justification of Inclusion Criteria Section 8.2.3 FibroScan-Aspartate Aminotransferase Score
3.	Changed the maximum age of eligible participants from 65 to 70 years at the time of providing informed consent.	To improve feasibility of study conduct at a variety of clinical sites where the proportion of newly retired people is significant.	Section 1.1 Synopsis Section 4.1 Overall Design Section 5.1 Inclusion Criteria, Criterion #3
4.	Specified that ALT/AST values at Week -8 will determine eligibility for liver biopsy at Week -6, and that ALT/AST results at Week -6 will be evaluated for eligibility for liver biopsy and abdominal magnetic resonance imaging (MRI) if Week -8 results are between 4×upper limit of normal (ULN) and 5×ULN. Noted that it is the investigator's decision, in consultation with the sponsor, the to allow participants to enter the study who have clinically meaningful rising tendencies in liver chemistries or significantly elevated liver chemistries that do not yet satisfy Exclusion Criterion #1 but could be interpreted as clinically concerning (ie, AST or ALT >4×ULN) at any visit during the screening period.	To clarify the liver chemistry-related assessments that determine eligibility for the screening liver biopsy and abdominal MRI, and to provide guidance for cases of borderline elevations in ALT or AST during screening.	Figure 1 Study Schema, footnote b Table 1 Schedule of Study Activities: Screening Period, footnote w Section 4.1 Overall Design Section 1.1 Synopsis Section 5.2 Exclusion Criteria, Exclusion Criterion #3
5.	Added an additional baseline visit on Day -4 (Visit 4a2; Baseline Part 2) to assess liver chemistry.	To allow for confirmation of eligibility on the basis of ALT and AST before dosing and to reduce constraint of conducting all baseline assessments at a single visit.	Figure 1 Study Schema Table 2 Schedule of Activities: Treatment Period, Follow-up, and End of Study

Description of Each Change and Rationale			Section(s) Affected by Change
#	Description of change(s)	Rationale for change(s)	Section
6.	Extended the Visit 2 (Week -6) window to up to 14 days.	To allow adequate time for processing of Week -6 study assessments during screening.	Table 1 Schedule of Study Activities: Screening Period
7.	Added new subsection to list acceptable contraception methods for male study participants and their female sexual partners.	To specify the contraception methods that are considered medically appropriate for male study participants, and to clarify contraception requirement for female sexual partners of male participants.	Section 10.4.2.2 Contraceptive Methods for Participants Capable of Producing Viable Sperm Table 10 Acceptable Contraception Methods in This Study for Participants Capable of Producing Viable Sperm and Their Partners
8.	Revised tables to reflect contraception information applicable only to participants of childbearing potential.	Clarification.	Section 10.4.2.1 Contraceptive Methods for Participants Capable of Producing Viable Ova and/or Becoming Pregnant Table 8 Acceptable Contraception Methods and Lactation Guidance in This Study for Participants Capable of Producing Viable Ova and/or Becoming Pregnant Table 9 Unacceptable Contraception Methods for Participants Capable of Producing Viable Ova and/or Becoming Pregnant
9.	Removed a footnote requiring 2 highly effective methods of contraception during the treatment period from the table of acceptable contraception methods of participants of childbearing potential.	To correct the table to accurately reflect the requirements for a single highly effective method of contraception during the treatment period.	Table 8 Acceptable Contraception Methods and Lactation Guidance in This Study for Participants Capable of Producing Viable Ova and/or Becoming Pregnant
10.	Specified that if liver chemistry measurements at the Week -8 or Week -6 visits are repeated, the Week -8 or Week -6 value will be calculated as the mean of the initial and repeat measurements for the given visit, except if the repeat sampling was conducted because of a technical issue with the initial sample.	To clarify instructions for repeat liver chemistry laboratory measurements during the screening period.	Section 8.3.8 Clinical Safety Laboratory Tests

Description of Each Change and Rationale			Section(s) Affected by Change
#	Description of change(s)	Rationale for change(s)	Section
11.	Clarified that for the screening laboratory tests indicated in the Schedule of Study Activities, sampling may be repeated once during the screening period if a result is considered by the investigator to be transient and inconsistent with the participant's clinical condition, for confirmation before the participant is considered a screen failure as long as the repeated assessment is conducted during the screening window. Revised "Repeat samples" to "Samples" in the footnote applicable to biomarker samples. Added statement that for biomarker assessments, repeating a sample due to reasons other than technical issues with the sample is not permitted.	To provide clarification on acceptable conditions for repeating a screening laboratory sample, and to specify that repeated sampling for biomarkers is not permitted for reasons other than technical issues.	Table 1 Schedule of Study Activities: Screening Period, footnote x Table 2 Schedule of Activities: Treatment Period, Follow-up, and End of Study, footnote q Section 8 Study Assessments and Procedures
12.	Added statement to allow for extension of the screening period by up to 2 weeks based on select measurements that require a repeat test (case-by-case basis with the sponsor's approval).	To reduce potential screen failures due to a lack of adequate time for select repeat measurements.	Section 1.1 Synopsis Table 1 Schedule of Study Activities: Screening Period Table 2 Schedule of Activities: Treatment Period, Follow-up, and End of Study Section 5.4 Screening Section 8 Study Assessments and Procedures
13.	Added that for participants with qualifying historical liver biopsies, the baseline abdominal MRI visit may occur as soon as possible after liver chemistry results from Screening Visit 2 become available, and Screening Visit 2 and the Day -4 visit (Visit 4a2) must be at least 2 weeks apart.	To reduce participant burden by shortening the screening period when a qualifying historical biopsy is available.	Section 1.1 Synopsis Figure 1 Study Schema, footnote b Table 2 Schedule of Activities: Treatment Period, Follow-up, and End of Study, new footnote a Section 4.1 Overall Design
14.	Added that for participants with ALT or AST <5×ULN at both screening visits and Visit 4a2 but have ALT or AST >5×ULN at Day 1 after having received the first dose of study drug, a repeat test should be performed as soon as possible, the participant should be closely monitored according to guidance provided in Section 7.1.1, and the participant's continued study participation should be evaluated by the internal safety review committee.	To ensure participant safety if liver chemistry abnormalities emerge at the Day 1 of the study.	Section 7.1.1 Liver Chemistry Stopping Criteria
15.	Changed the maximum duration of the screening period from 20 weeks to 24 weeks for participants with F4cc fibrosis (either based on screening tests at Screening Visit 1 or based on	To increase flexibility in screening and enrolling F4cc participants.	Section 1.1 Synopsis Figure 1 Study Schema, footnote a Section 4.1 Overall Design

Description of Each Change and Rationale			Section(s) Affected by Change
#	Description of change(s)	Rationale for change(s)	Section
	screening biopsy or historical biopsy results) who start screening before safety and tolerability data after 12 weeks of treatment are evaluated in the first four F2/F3 participants.		Section 5.5 Criteria for Temporarily Delaying Enrollment
16.	Changed the participant's maximum duration of study participation from approximately 44 weeks to approximately 46 weeks, or from 56 to 60 weeks for F4cc participants who are eligible before safety and tolerability are established in the first four F2/F3 participants.	To increase flexibility of maximum duration of study participation for all participants.	Section 1.1 Synopsis Section 4.4 End of Study/Study Completion Definition
17.	Added a footnote to specify that procedures at the Week -6 and Week 24 visits may be performed on different days within the visit window.	To increase flexibility and improve feasibility of the protocol at diverse study sites.	Table 1 Schedule of Study Activities: Screening Period, new footnote a Table 2 Schedule of Activities: Treatment Period, Follow-up, and End of Study, new footnote b
18.	Changed the restriction on antibiotic use from 6 months to 3 months before first dose of study drug (or before qualifying historical liver biopsy). Limited the restriction of antibiotic use to systemic administration of antibiotics that can potentially influence the composition of intestinal flora. Changed the requirement of stable regimen for permitted medications, including antidiabetic therapies, from 6 months to 3 months before the qualifying liver biopsy.	To improve feasibility of the protocol while maintaining participant safety, and to align the exclusion criterion with Food and Drug Administration (FDA) recommendations for enrolling participants with type 2 diabetes mellitus (T2DM) (FDA, Draft Guidance: Nonalcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for Treatment Guidance for Industry, June 2019).	Section 1.1 Synopsis Section 5.2 Exclusion Criteria, Exclusion Criteria #19 Section 6.8.2 Excluded Procedures and Treatments Section 6.8.3 Permitted Concomitant Medications and Procedures
19.	Added a footnote to specify that the liver biopsy must be conducted as the last assessment for the Week 24/End of Treatment/Early Termination visit.	To provide clarity to ensure that the liver biopsy procedure does not impact other assessments, such as serum liver chemistry measurements.	Table 2 Schedule of Activities: Treatment Period, Follow-up, and End of Study, new footnote l
20.	Revised Exclusion Criterion #13 to exclude participants with abnormal chest X-ray at screening or within 12 weeks before the screening visit (if available), and to remove the requirement of Mantoux tuberculin skin test for all participants at screening or within 12 weeks before screening.	To simplify exclusion criteria related to *Mycobacterium tuberculosis* (TB) infection and to provide guidance for retesting to ensure absence of TB infection during screening.	Section 1.1 Synopsis Table 1 Schedule of Study Activities: Screening Period, footnote s Section 5.2 Exclusion Criteria, Exclusion Criteria #13 and #14

Description of Each Change and Rationale			Section(s) Affected by Change
#	Description of change(s)	Rationale for change(s)	Section
	Specified that interferon-gamma release assay (IGRA) screening may be repeated during the screening period if the initial result is indeterminate. Included statements regarding screen failure procedure and permitting entry of participants if initial and confirmatory IGRA results are in determinate, after a negative tuberculin skin test and a consultation with the sponsor and a pulmonary or infectious disease specialist who determines low risk of infection.		
21.	Added exclusion of participants who may have new signs of liver decompensation and/or clinically meaningful change in disease status based on the judgment of the investigator during the screening period.	To ensure participants whose liver disease is progressing to decompensation are excluded from the study and receive appropriate treatment.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria, Exclusion Criterion #3
22.	Added hemochromatosis to the list of examples of excluded liver diseases.	To ensure participants with hemochromatosis are excluded from this study.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria, Exclusion Criterion #4
23.	Revised Exclusion Criterion #5 and Table 3 to remove restriction of anticoagulant medication. Added temporary restrictions on antiplatelet and anticoagulant medications before liver biopsy.	To improve feasibility of the protocol while ensuring participant safety in line with published guidelines on anticoagulant and antiplatelet medication restrictions before liver biopsy.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria, Exclusion Criterion #5 Table 3 Common Excluded Treatments Section 6.8.2 Excluded Procedures and Treatments Section 6.8.3 Permitted Concomitant Medications and Procedures
24.	Included clinically active infections of cytomegalovirus, Epstein-Barr virus, and herpes simplex virus as examples of local active viral infection/infectious disease that would be exclusionary. Added that in case of suspicion of clinically active bacterial, fungal, or viral infection, additional testing should be performed at the investigator's discretion.	To clarify exclusion related to infections and allow for additional testing at the investigator's discretion if active infection is suspected.	Section 1.1 Synopsis Table 1 Schedule of Study Activities: Screening Period, footnote r Section 5.2 Exclusion Criteria, Exclusion Criterion #6a
25.	Revised Exclusion Criterion #6a to exclude participants with hemoglobin A1c (HbA1c) ≥6.5% at screening (Week -8) with no previous diagnosis of T2DM, and to exclude participants with HbA1c of ≥8% at screening (Week -8) with a previous diagnosis of T2DM on a stable regimen of antidiabetic therapy for at least 90 days before screening.	To define the acceptable range of HbA1c levels and disease status at baseline for participants with T2DM and to exclude participants with HbA1c ≥8% at screening with a previous diagnosis of	Section 1.1 Synopsis Section 5.2 Exclusion Criteria

Description of Each Change and Rationale			Section(s) Affected by Change
#	Description of change(s)	Rationale for change(s)	Section
		T2DM on a stable regimen of antidiabetic therapy for at least 90 days before screening.	
26.	Added exclusion of participants who are anticipated to receive a live vaccine during the study.	To specify that live vaccines are not permitted during the study, in addition to the 4 weeks before baseline.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria, Exclusion Criterion #24
27.	Corrected the table to apply the footnote including 5 half-lives (if longer than 90 days) to biologics with immunomodulatory properties. Corrected Exclusion Criterion #30 to reflect the minimum required washout time of both biologic drugs and nonbiologic drugs with immunomodulatory properties of 90 days or 5 half-lives (whichever is longer) before baseline, in line with Table 3.	Correction.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria, Exclusion Criterion #30 Table 3 Common Excluded Treatments
28.	Clarified that the FAST score criterion does not apply participants with a qualifying historical liver biopsy that provides evidence of F2, F3, or F4cc staging.	Clarification	Section 5.1 Inclusion Criteria, Criterion #4
29.	Added that the baseline measurement for evaluating liver chemistry stopping criteria is determined by the last liver chemistry value before dosing.	To add the definition of baseline measurement for evaluating liver chemistry stopping criteria.	Section 7.1.1 Liver Chemistry Stopping Criteria
30.	Changed the name of the internal group responsible for evaluating the overall safety of the study participants to the internal safety review committee.	To provide a more precise committee name in line with the committee's charter.	Section 1.1 Synopsis Section 4.1 Overall Design Section 7.1.1 Liver Chemistry Stopping Criteria Section 8.3.2 Targeted Neurological Assessment Section 10.1.5.2 Other Committees
31.	Specified that the approximate daily and overall blood volumes do not include potential repeat measurement samples.	Clarification	Section 8.3.8 Clinical Safety Laboratory Tests

Description of Each Change and Rationale			Section(s) Affected by Change
#	Description of change(s)	Rationale for change(s)	Section
32.	Changed reporting procedure for adverse events of special interest (AESIs) from using the serious adverse event (SAE) form to reporting as an adverse event (AE) in the electronic case report form (eCRF). Clarified that investigators will report AESIs, in addition to SAEs, to the sponsor or designee within 24 hours of receipt of the information. Included AESIs in the expedited reporting procedures for SAEs. Corrected the procedures for SAE/AESI reporting via telephone to the medical monitor rather than an SAE coordinator. Removed the statement that initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper form.	To clarify AESI procedures for reporting AESIs via the electronic data capture, which will notify the sponsor's safety team.	Section 8.3.11.6 Adverse Events of Special Interest Section 10.3.4.6 Follow-up Section 10.3.5 Expedited Reporting of Serious Adverse Events and Adverse Events of Special Interest
33.	Addition of progressive multifocal leukoencephalopathy (PML) as an AESI, including instructions for monitoring and event reporting.	To clarify the procedure by which suspected PML cases are immediately reported to the sponsor, following the timeline for SAE reporting.	Section 8.3.2 Targeted Neurological Assessment Section 8.3.11.6 Adverse Events of Special Interest Section 10.3.3.2.2 PML Section 10.3.5 Expedited Reporting of Serious Adverse Events and Adverse Events of Special Interest
34	Added "approximately" to footnote w.	To align with the analogous footnote for the treatment period regarding time of day of biomarker sampling across visits.	Table 1 Schedule of Study Activities: Screening Period, footnote x
35.	Specified that the Week -1 visit can occur on Day -7 to -4. Changed the visit window of ±5 days to +3 days for the abdominal MRI at the Week -1 visit.	To clarify the acceptable timing of the baseline abdominal MRI.	Figure 1 Study Schema Table 2 Schedule of Activities: Treatment Period, Follow-up, and End of Study
36.	Added a footnote stating that abdominal ultrasound at screening is intended for morphological evaluation of liver and other organs and structures during screening.	Clarification	Table 1 Schedule of Study Activities: Screening Period, new footnote n
37.	Revised footnote to remove exclusion criterion of liver stiffness >25 kPa and to provide cross-reference to methodology section related to FibroScan.	To align footnote with revised exclusion criterion.	Table 1 Schedule of Study Activities: Screening Period, footnote v
38.	Removed "Caffeine" from section heading.	To correct the heading to accurately reflect the content of the section.	Section 5.3.2 Alcohol and Tobacco

Description of Each Change and Rationale			Section(s) Affected by Change
#	Description of change(s)	Rationale for change(s)	Section
39.	Removed "previous" from the statement regarding a fresh biopsy being required if a biopsy being found to be inadequate by the study pathologist.	To clarify that a fresh biopsy is required if any biopsy, whether historical or performed as part of this study, is found to be inadequate by the study pathologist.	Section 8.2.8 Liver Biopsy
40.	Added statement that instructions for returns and destruction of tissue samples will be provided to the study sites in documentation outside of the protocol.	Clarification	Section 8.2.8 Liver Biopsy
41.	Added that analyses of extracellular vesicles may be performed using residual serum samples.	To describe additional biomarker analyses to support exploratory objectives of the study.	Section 8.2.12 Additional Biomarkers

Summary of Change(s) Since the Last Version of the Approved Protocol			
Protocol Amendment 1			
Amendment Date: 15 Dec 2022			**Global/Region/Country/Site Specific:** Global
Overall Reason for the Amendment The overall reason for this protocol amendment is to update study stopping criteria.			
Description of Each Change and Rationale			**Section(s) Affected by Change**
#	**Description of change(s)**	**Rationale for change(s)**	**Section**
1.	Updated stopping criteria for safety-related events that would trigger temporary suspension or early termination of the study.	To specify safety-related criteria that would trigger temporary suspension or early termination of the study.	Section 10.1.12.2 Criteria for Premature Termination or Suspension of the Study

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