TVB-2640

PROTOCOL SB2640-CLIN-007

A PHASE 2B, MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF TVB-2640 IN SUBJECTS WITH NONALCOHOLIC STEATOHEPATITIS

(FASCINATE-2)

IND Number:	138506
Protocol Version:	4.0
Date:	06 September 2023

[redacted]

Version 4.0

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for TVB-2640. I have read the protocol for Study SB2640-CLIN-007 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

SPONSOR APPROVAL SIGNATURE PAGE

On behalf of the sponsor, I confirm that I have read and understood this protocol. We will meet the requirements of the protocol, abide by ethical standards stated by the Declaration of Helsinki, and follow the guidelines for ethical clinical practice (Good Clinical Practice).

Approved by:

[redacted]

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1 Emergency Contact Information

Role in Study	Name	Address and Telephone number
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Serious Adverse Event Reporting	*SAEs are to be reported within 24 hours of discovery via the electronic data capture (EDC) system, which will trigger email notifications to the* [redacted] *team.* [redacted]	

2. SYNOPSIS

Name of Sponsor/Company:
Sagimet Biosciences

Name of Investigational Product:
TVB-2640

Name of Active Ingredient:
TVB-2640

Title of Study:
A Phase 2b, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of TVB-2640 in Subjects with Nonalcoholic Steatohepatitis (FASCINATE-2)

Study Center(s):
This study will be conducted at approximately 100 centers in North America and other regions.

Coordinating Investigator:
The Coordinating Investigator is Rohit Loomba, MD, MHSc, University of California, San Diego, CA.

Studied Period (years):	**Phase of Development:**
Estimated date first subject dosed: May 2021 Estimated date last subject completed: September 2023	2b

Objectives:

Primary Objectives

- To evaluate the effect of TVB-2640 50 mg PO QD compared with matching placebo in noncirrhotic subjects with nonalcoholic steatohepatitis (NASH) and F2-F3 fibrosis by either:
  - Histological improvement at Week 52 in nonalcoholic fatty liver disease (NAFLD) activity score (NAS) (ie, ≥2 points improvement in NAS with ≥1 point improvement in ballooning or inflammation) and without worsening of fibrosis (by NASH Clinical Research Network [CRN] fibrosis score)

  OR

  - Resolution of steatohepatitis and no worsening of liver fibrosis (by NASH CRN fibrosis score). Resolution of steatohepatitis is defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis.
- To evaluate the safety and tolerability of TVB-2640 50 mg PO QD in subjects with confirmed NASH and liver fibrosis.

Secondary Objectives

- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on the proportion of subjects with ≥8% liver fat content at Baseline who achieve a ≥30% relative reduction in liver fat content as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) at Week 26.

- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on the proportion of subjects with ≥8% liver fat content at Baseline who achieve a ≥30% relative reduction in liver fat content as assessed by MRI-PDFF at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on fibrosis as assessed by ≥1 stage of fibrosis improvement by NASH CRN score without worsening of steatohepatitis (no increase in NAS for ballooning, inflammation, or steatosis) at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on fibrosis as assessed by ≥1 stage of fibrosis improvement by NASH CRN score without worsening of NAS (defined as no increase in any component of NAS) at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on fibrosis as assessed by ≥1 stage of fibrosis improvement by NASH CRN score without increasing of total NAS scores at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on fibrosis as assessed by ≥1 stage of fibrosis improvement by NASH CRN score without any worsening of NASH (no worsening of ballooning and lobular inflammation, a 1 grade change in steatosis may be acceptable) at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on the proportion of subjects experiencing **both** of the following at Week 52:
    - Resolution of steatohepatitis on overall histopathological reading and no worsening of liver fibrosis on NASH CRN fibrosis score. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis

    AND

    - Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on the proportion of subjects experiencing **both** of the following at Week 52:
    - Histological improvement at Week 52 in NAFLD NAS (ie, ≥2 points improvement in NAS with ≥1 point improvement in ballooning or inflammation) and without worsening of fibrosis (by NASH CRN fibrosis score)

    AND

    - Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on the proportion of subjects experiencing **both** of the following at Week 52:
    - Resolution of steatohepatitis and no worsening of liver fibrosis (by NASH CRN fibrosis score). Resolution of steatohepatitis is defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis.

    AND

    - Histological improvement in NAS (≥2 points improvement in NAS).
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on histological improvement at Week 52 in NAS.

- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on liver fat content as assessed by MRI-PDFF at Week 26.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on liver fat content as assessed by MRI-PDFF at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on NASH resolution (defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis) at Week 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on change from Baseline at 26 and 52 weeks in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT).
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on the change from Baseline at 26 and 52 weeks in low-density lipoprotein cholesterol (LDL-C) and other lipid levels.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on the change from Baseline at 52 weeks in the amount of collagen/fibrous area and fibrosis score, assessed by digital pathology.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on the change from Baseline at 26 and 52 weeks in fasting insulin, fasting glucose, homeostatic model assessment of insulin resistance (HOMA-IR), adipose tissue insulin resistance (adipo-IR), and glycosylated hemoglobin (HbA1c) levels.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on the change from Baseline at 26 and 52 weeks in fibroblast growth factor 21 (FGF-21), adiponectin, and other NASH biomarker levels.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on change from Baseline at 26 and 52 weeks in FibroScan® and controlled attenuation parameter (CAP) score.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on N-terminal type III collagen propeptide (PRO-C3) levels and other fibrosis biomarkers on change from Baseline at Weeks 4, 13, 26, and 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on change from Baseline at 26 and 52 weeks on enhanced liver function (ELF) score.
- To evaluate the pharmacokinetics (PK) of TVB-2640 in subjects with NASH over 52 weeks of treatment using sparse sample collection, and serial sample collection in a subset of subjects.

Exploratory Objectives

- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on the proportion of subjects with ≥8% liver fat content at Baseline who achieve a ≥30% relative reduction in liver fat content as assessed by MRI-PDFF **AND** achieve ≥17 U/L reduction in ALT at Week 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on FibroScan-AST (FAST) score at Weeks 26 and 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on select fibrosis biomarkers (including at least tissue inhibitor of metalloproteinase-1 [TIMP-1]) at Weeks 4, 13, 26, and 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on

lipidomic biomarkers (including tripalmitin, ceramides, bile acids, diacylglycerols, and other classes of metabolites) at Weeks 4, 13, 26, and 52.

- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on glycosylated hemoglobin (HbA1c) levels among subjects with type 2 diabetes mellitus (T2DM) at Weeks 13, 26, 39, and 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on Fibrosis 4 score (FIB-4) at Weeks 4, 13, 26, and 52.
- To use digital pathology to perform zonal analysis of fibrosis at Week 52.
    - To use digital pathology to evaluate the concurrence of fibrosis with components of the NAS score.
    - To use digital pathology to evaluate the NAS components.
- To correlate changes in MRI-PDFF with changes in, or baseline levels of, serum biomarkers and explore predictive markers of response.
- To explore the relationship between changes in, or Baseline levels of, serum biomarkers and histology results, and explore predictive markers of response.
- To explore the relationship between MRI-PDFF results and histology results.
- To correlate the presence of relevant single-nucleotide polymorphisms (SNPs) or other genes relevant to NAFLD or NASH with clinical and histopathologic response.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on gut microbiome change from Baseline to Weeks 26 and 52 in a subset of subjects.
- To explore the relationship between nutrition, as measured by the HepVita Nutritional Survey, and clinical, histopathological, and biomarker changes in NASH at Weeks 26 and 52 in a subset of subjects.

Methodology:

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-design study to evaluate the safety and efficacy of TVB-2640 compared with matching placebo in subjects with NASH who are aged ≥18 years at Screening. Histological eligibility will be determined during the Screening period or prior to Screening but within 180 days of the Screening visit in 1 of 2 ways:

- If an 'eligible' and adequate (this refers to the quality and quantity of remaining tissue) liver histology specimen, in the judgement of the central pathologist, exists from the time period within 180 days before the subject's Screening visit, the subject may participate so long as other eligibility criteria are satisfied.
- If no liver histology specimen exists from the period within 180 days of the Screening visit, the subject must undergo liver biopsy during the Screening period.

Approximately 162 unique subjects with liver fibrosis stage F2-F3 will be enrolled and randomized to achieve a 2:1 ratio with approximately 108 subjects on TVB-2640 50 mg and 54 subjects on placebo. Dynamic allocation is used for the randomization, stratified by 3 factors: T2DM status (yes or no), region (North America or not North America), and amount of fibrosis (F2 or F3).

Subjects will be screened for study eligibility within 90 days before randomization (randomization is within 3 days of Baseline [Day 1]). Subjects who are determined to be eligible for the study based on Screening assessments are to be randomized into the study within 3 days before Baseline (ie, Day 1, the first day of study drug administration). Subjects who are randomized are considered to be enrolled in the study.

Subjects will receive TVB-2640 or matching placebo PO QD for 52 weeks, with the first dose administered on Day 1. During the 52-week Treatment period, subjects are to attend study center visits at Weeks 4, 8, 13, 26, 39, and 52. After completion of the 52-week Treatment period, subjects are to attend a Follow-up visit at Week 56 for posttreatment safety and efficacy assessments.

In the event a subject is unable to complete the end of treatment MRI-PDFF and/or liver biopsy within the protocol-specified window (Week 52 +/- one week), extended dosing is permitted to maintain continuous dosing up to the time both assessments are completed, to a maximum total of 56 weeks of dosing. In this instance, the Follow-up visit at Week 56 for post treatment safety and efficacy assessments is to be adjusted to occur four weeks after the last dose (+/- one week).

In the instance of a dose hold due to an AE or SAE, the decision to resume study drug will require consultation with the Investigator, the CRO's Medical Monitor, and the Sponsor's Chief Medical Officer.

Improvement of NAS and improvement of fibrosis score will be evaluated by comparison of Baseline and Week 52 liver histology specimens. Subjects will also undergo MRI-PDFF prior to the start of treatment, at Week 26, and at Week 52 or Early Termination. Other efficacy and pharmacodynamic (PD) assessments include FibroScan with CAP, and measurement of liver aminotransferases, lipid parameters, and other noninvasive biomarkers of NASH and liver fibrosis throughout the study.

During the study, safety will be assessed by vital signs, 12-lead electrocardiograms (ECGs), physical examinations including eye examinations, and clinical laboratory testing. Subjects will be evaluated for AEs and concomitant medication use throughout the study.

[redacted]

An independent data monitoring committee (IDMC) will be established by charter to provide independent review and assessment of study data and to monitor the overall study conduct in a systematic manner to safeguard the safety of study subjects. The IDMC will be tasked with making recommendations to the Sponsor to continue, amend, or stop the study based on these assessments.

A single secondary endpoint efficacy interim analysis (IA) is planned when approximately 60 subjects with MRI-PDFF value of ≥8% liver fat at Baseline have completed Week 26 or an Early Termination visit after Week 22. The purpose of the proposed interim analysis is to examine the TVB-2640 benefit over placebo based on a Week 26 secondary efficacy endpoint consisting of "proportion of MRI-PDFF ≥30% responders at Week 26, where an MRI-PDFF ≥30% responder is defined as a subject with ≥8% liver fat content at Baseline who achieves a percent change (reduction) from Baseline in MRI-PDFF ≥30%."

Interim safety summaries will accompany the interim analysis of the secondary efficacy endpoint.

Number of Subjects (planned):

Approximately 162 unique subjects with liver fibrosis stage F2-F3 will be enrolled and randomized to achieve a 2:1 ratio to receive TVB-2640 50 mg or placebo (approximately 108 for TVB-2540 50 mg and approximately 54 subjects for placebo) PO QD for 52 weeks.

Diagnosis and Main Criteria for Inclusion:

Unless otherwise specified, repeat testing for laboratory and clinical Screening assessments may be performed in consultation with the Medical Monitor.

Inclusion Criteria

1. Must be willing and able to participate in the study and provide written informed consent.
2. Male and female adults ≥18 years of age on the date that written informed consent to take part

in the study is provided.

3. Body mass index (BMI) ≥23 kg/m^2 for Asians and ≥25 kg/m^2 for other races.
4. Female subjects must be either:
    a. Not of childbearing potential (ie, surgically [bilateral oophorectomy, hysterectomy, or tubal ligation] or naturally sterile [>12 consecutive months without menses]).

    OR

    b. Female subjects of childbearing potential (must have a negative serum pregnancy (beta-human chorionic gonadotropin [β-HCG]) test during Screening, a negative urine pregnancy test within 24 hours before the first dose of study drug on Day 1, and must agree to perform urine home pregnancy tests monthly between study visits. Female subjects of childbearing potential must not be breastfeeding, not plan to become pregnant during the study, and must use 2 forms of birth control, one being a barrier method (ie, condoms, diaphragm, nonhormonal intrauterine device [IUD]) throughout the study and for at least 3 months after the final study drug dose. Hormonal contraception (stable ≥3 months) and hormonal IUDs are permitted if used with a secondary barrier birth control method (e.g., condoms).
5. Male subjects who have sexual intercourse with a female partner of childbearing potential from the first dose of study drug until 3 months after completion of study drug intake must be either surgically sterile (confirmed by documented azoospermia >90 days after the procedure) OR agree to use a condom with spermicide. All male subjects must agree not to donate sperm from the first dose of study drug until 3 months after completion of study drug intake.
6. Must have liver stiffness measurement ≥8.5 kPa measured by FibroScan and CAP score measured by FibroScan ≥280 dB/m (unless the enrolling study site does not have the capability to measure CAP) during the Screening period.
7. Histologic confirmation of NASH: must have had a prior liver biopsy within 180 days before the Screening visit, or a new biopsy during the screening period, with fibrosis stage F2-F3 and a NAS of ≥4 with at least a score of 1 in each of the following NAS components:
    a. Steatosis (scored 0 to 3)
    b. Ballooning degeneration (scored 0 to 2)
    c. Lobular inflammation (scored 0 to 3)
8. AST >20 U/L.

<u>Exclusion Criteria</u>

1. History of harmful alcohol intake for a period of more than 3 consecutive months within 1 year prior to Screening in the judgement of the Investigator.
2. Active substance abuse, including inhaled or injected substances (cocaine and other illegal/banned substances; any opiate, amphetamine, or benzodiazepine for which the subject does not have an existing prescription) within 1 year prior to Screening (note that recreational cannabis/tetrahydrocannabinol use is permissible).
3. Patient-reported or medically documented gain or loss of >5% of body weight in the 6 months prior to Baseline (Day 1) or >10% of body weight in the 12 months prior to Screening.
4. Prior or planned (during the study period) bariatric surgery that may interfere with study drug absorption (e.g., roux-en-Y gastric bypass); gastroplasty and gastric reduction surgery are acceptable.
5. Type 1 diabetes mellitus by history.
6. Positive SARS-CoV-2 polymerase chain reaction (PCR) test within 30 days prior to the Baseline (Day 1) visit date or history of hospitalization for COVID-19 <6 months prior to the

Screening visit date. Note that previous COVID-19 infection alone is not exclusionary, and COVID-19 vaccination is allowed. Infection and/or vaccination must be documented as medical history and/or concomitant medication, respectively.

7. Known positivity for HIV infection or positive HIV antibody result at Screening.
8. Positive hepatitis B virus antigen (HBsAg) result at Screening.
9. Positive hepatitis C virus (HCV) RNA test at Screening; however, subjects with chronic HCV infection and liver disease who were treated with anti-HCV therapy and achieved a sustained virologic response at least 2 years prior to Screening are not prevented from study participation.
10. Uncontrolled T2DM, defined as HbA1c >9.5% at Screening.
11. Serum LDL-C concentration at Screening >190 mg/dL, and the subject has been taking an LDL-C–lowering treatment for ≥30 days prior to Screening.
12. ALT and/or AST result >5 × the upper limit of normal (ULN) at Screening. One repeat test may be allowed within 7 days of receipt of the result at the discretion of the Investigator.
13. Alkaline phosphatase (ALP) result ≥2 × ULN at Screening.
14. Total serum bilirubin concentration >1.3 mg/dL at Screening; subjects with a confirmed diagnosis of Gilbert's syndrome (ie, prior to Screening and whose total bilirubin result at Screening exceeds 1.3 mg/dL) may be eligible for study inclusion at the Investigator's discretion.
15. International normalized ratio (INR) result >1.3 at Screening.
16. Serum albumin concentration <3.5 g/dL at Screening.
17. Platelet count <140,000/μL at Screening.
18. Estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2, as determined using the Modification of Diet in Renal Disease Study (MDRD) equation, at Screening.
19. Presence of cirrhosis on liver histology (stage 4 fibrosis), according to the judgement of the central reader; and/or cross-sectional imaging evidence consistent with cirrhosis and/or portal hypertension (e.g., nodular liver contour; atrophy and hypertrophy of the right and left hepatic lobes respectively; splenomegaly; known presence or history of esophageal varices; and/or elastography evidence consistent with cirrhosis).
20. F0, F1, or F4 fibrosis, or inconclusive result, on liver histology.
21. Use of drugs historically associated with risk of development of NAFLD (e.g., amiodarone, methotrexate, systemic glucocorticoids [unless used at physiologic replacement doses for treatment of confirmed adrenal insufficiency], tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids [except for testosterone preparations used at physiologic replacement doses for treatment of documented/confirmed hypogonadism], valproic acid, and other known hepatotoxins) for more than 12 consecutive months at any time during the 5 years prior to the Screening visit (refer to Section 9.7, Concomitant Medications).
22. Use of glucagon-like peptide-1 (GLP-1) agonists or a sodium-glucose co-transporter-2 (SGLT2) inhibitor, unless on a stable daily dose for at least 6 months prior to the Screening visit date
    OR
    On a complex oral antidiabetic (OAD) regimen (3 or more OADs [except for a GLP-1 agonist or an SGLT2 inhibitor]), unless on stable doses for at least 3 months prior to the Screening visit date (refer to Section 9.7, Concomitant Medications).
23. Use of vitamin E supplementation at a daily dose >400 IU unless on a stable daily dose for at

least 6 months prior to the Screening visit (refer to Section 9.7, Concomitant Medications).

24. Use of strong concomitant cytochrome P450 (CYP) 3A4 inhibitors or inducers during the study (refer to Section 9.7, Concomitant Medications).
25. Known diagnosis of hereditary hemochromatosis.
26. Subjects with active or quiescent chronic liver disease of etiologies other than NASH (e.g., viral or autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, "autoimmune hepatitis-overlap" syndromes, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, alcohol-related liver disease, drug-induced liver disease, and/or infiltrative conditions [e.g., sarcoidosis]).
27. Current or historic clinically evident hepatic decompensation (e.g., ascites formation, variceal hemorrhage, hepatic encephalopathy).
28. Active, serious medical disease with likely life expectancy <2 years.
29. History of clinically significant dry eye (xerophthalmia) or other corneal abnormality, as determined by an ophthalmologist or optometrist during Screening.
30. Participation in an investigational study in the 30 days prior to randomization.
31. Participation in an investigational drug trial for subjects with NASH, T2DM, and/or weight reduction within 6 months of Screening; only if it can be confirmed the subject received placebo during the earlier study would it be possible for such a subject to be screened for this study sooner than 6 months before Screening.
32. Any subject who has sustained a clinically evident cardiovascular, cerebrovascular and/or peripheral vascular event (e.g., unstable angina, acute coronary syndrome, myocardial infarction, life-threatening tachy- and/or brady-dysrhythmia, stroke, transient ischemic attack [TIA], peripheral vascular disease) during the 12 months prior to the anticipated Baseline (Day 1) visit date.
33. Any contraindication to MRI (e.g., claustrophobia, metal implants).
34. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, compromise the well-being of the subject, or interfere with the study outcomes.

Investigational Product, Dosage and Mode of Administration:

TVB-2640 will be provided as 25-mg and 50-mg strength uncoated tablets. Study drug will be administered PO QD, with or without food. Study drug should be taken at approximately the same time each day in the evening.

Duration of Treatment:

The Treatment period for this study is 52 weeks in duration.

Reference Therapy, Dosage and Mode of Administration:

Placebo will be provided in 2 tablet sizes: one to match the TVB-2640 25-mg tablet and one to match the TVB-2640 50-mg tablet. Study drug will be administered PO QD, with or without food.

Criteria for Evaluation:

<u>Efficacy and Pharmacodynamics</u>

Liver histology with NAS and fibrosis score

Magnetic resonance imaging studies: MRI-PDFF (MRI-PDFF will not be performed at select sites)

Liver stiffness by FibroScan, including CAP and FAST scores

Digital pathology
Clinical laboratory tests:

- Lipid and metabolic panels, HbA1c, and lipoprotein analyses
- NASH and fibrosis noninvasive biomarkers (e.g., adiponectin and FGF-21)

Lipidomic biomarkers:

- Includes tripalmitin, ceramides, bile acids, diacylglycerols, and other classes of metabolites

Gut microbiome assessments (in a subset of subjects)
HepVita Nutritional Survey (in a subset of subjects)
Other Assessments
Genomics
Urine and blood samples for storage
[redacted]
Safety
AEs
Vital signs
Physical examinations
Eye examinations
12-lead ECGs
Safety laboratory assessments:

- Hematology
- Clinical chemistry
- Coagulation
- Urinalysis
- Pregnancy testing

Concomitant medications
Anthropometric assessments:

- Weight, height, and BMI
- Waist circumference
- Hip circumference
- Waist-hip ratio

Endpoints
Primary Efficacy (Responder) Endpoint
The proportion of subjects experiencing either of the following:

- Histological improvement at Week 52 in NAS (ie, ≥2 points improvement in NAS with ≥1 point improvement in ballooning or inflammation) and without worsening of fibrosis (by NASH CRN fibrosis score).

OR

- Resolution of steatohepatitis and no worsening of liver fibrosis (by NASH CRN fibrosis score). Resolution of steatohepatitis is defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis.

Secondary Efficacy and Pharmacodynamic Endpoints

- Proportion of MRI-PDFF ≥30% responders at Week 26, where an MRI-PDFF ≥30% responder is defined as a subject with ≥8% liver fat content at Baseline who achieves a relative reduction from Baseline in MRI-PDFF ≥30%.
- Proportion of MRI-PDFF ≥30% responders at Week 52.
- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN fibrosis score without worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis) at Week 52.
- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN score with no increase in any component of NAS at Week 52.
- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN score without increase of total NAS score at Week 52.
- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN score without any worsening of NASH (defined as no worsening of ballooning and lobular inflammation; a 1 grade change in steatosis may be acceptable) at Week 52.
- Proportion of subjects experiencing **both** of the following at Week 52:
    - Resolution of steatohepatitis on overall histopathological reading and no worsening of live fibrosis on NASH CRN fibrosis score. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis

  AND

    - Improvement in liver fibrosis greater than or equal to one state (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).
- Proportion of subjects experiencing **both** of the following at Week 52:
    - Histological improvement at Week 52 in nonalcoholic fatty liver disease (NAFLD) activity score (NAS) (ie, ≥2 points improvement in NAS with ≥1 point improvement in ballooning or inflammation) and without worsening of fibrosis (by NASH Clinical Research Network [CRN] fibrosis score)

  AND

    - Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).
- Proportion of subjects experiencing **both** of the following at Week 52:
    - Resolution of steatohepatitis and no worsening of liver fibrosis (by NASH CRN fibrosis score). Resolution of steatohepatitis is defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis.

AND

- Histological improvement at in NAS (≥2 points improvement in NAS).

- Proportion of subjects with histological improvement at Week 52 in NAS.
- MRI-PDFF percent change in liver fat and change from Baseline at Week 26.
- MRI-PDFF percent change in liver fat and change from Baseline at Week 52.
- Proportion of subjects with NASH resolution (defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis) at Week 52.
- Change from Baseline in ALT, AST, and GGT at Weeks 26 and 52 and at each study visit.
- Change from Baseline in LDL-C and other lipid levels at Weeks 26 and 52 and at each study visit.
- Change from Baseline in collagen/fibrous area and fibrosis score, assessed by digital pathology, at Week 52.
- Changes from Baseline in metabolic parameters, including fasting insulin, fasting glucose, HOMA-IR, adipo-IR, and HbA1c levels at Weeks 26 and 52 and at each study visit.
- Change from Baseline in FGF-21, adiponectin, and other NASH biomarker levels at Weeks 26 and 52 and at each study visit.
- Change from Baseline in FibroScan and CAP score results at Weeks 26 and 52.
- Change from Baseline in PRO-C3 and other fibrosis biomarkers at Weeks 4, 13, 26, and 52.
- Change from Baseline in ELF score at Weeks 26 and 52.
- Plasma concentrations of TVB-2640 at Weeks 1, 4, 13, 26, and 52.

<u>Exploratory Efficacy and Pharmacodynamic Endpoints</u>

- Proportion of MRI-PDFF ≥30% responders at Week 52 who have ≥17 U/L reduction in ALT.
- Change from Baseline in FAST score at Weeks 26 and 52.
- Change from Baseline in levels of select fibrosis biomarkers (e.g., TIMP-1) at Weeks 4, 13, 26, and 52.
- Change from Baseline in levels of lipidomic/metabolomic biomarkers (e.g., tripalmitin, ceramides, bile acids, diacylglycerols, and other classes of metabolites) at Weeks 4, 13, 26, and 52.
- Change from Baseline in HbA1c levels among subjects with T2DM at Weeks 13, 26, 39, and 52.
- Change from Baseline in FIB-4 at Weeks 4, 13, 26, and 52.
- Change from Baseline in zonal analyses of fibrosis, NAS, and individual NAS components as determined by digital pathology at Week 52.
- Correlation of changes in MRI-PDFF with changes in other endpoints.
- Presence or absence of SNPs relevant for NASH.
- Correlation of predictive signature with other endpoints
  - Correlation of lipids (e.g., tripalmitin) with other endpoints
  - Change from Baseline in gut microbiome analyses at Weeks 26 and 52 in substudy

subjects.

- Change from Baseline in HepVita Nutritional Survey at Weeks 26 and 52 in substudy subjects.

Safety Endpoints

- AEs throughout the study.
- ECGs at Weeks 26 and 52.
- Vital signs at each study visit.
- Physical examination findings at each study visit.
- Eye examination findings at each study visit.
- Hematology and coagulation results at each study visit.
- Liver aminotransferase levels at each study visit.
- Clinical chemistry results at each study visit.
- Urinalysis results at each study visit.
- Pregnancy test results throughout the study.
- Prior and concomitant medications throughout the study.
- Results of anthropometric measurements at Week 52.

Statistical Methods:

Analysis of the primary efficacy endpoint: The primary efficacy endpoint is the proportion of subjects experiencing either a histological improvement at Week 52 in NAS (ie, ≥2 points improvement in NAS with ≥1 point improvement in ballooning or inflammation) and without worsening of fibrosis (by NASH CRN fibrosis score), **OR** resolution of steatohepatitis and no worsening of liver fibrosis (by NASH CRN fibrosis score). The treatment groups will be compared based on the primary efficacy endpoint using a one-sided Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratifications T2DM status (yes or no), region (North America or not North America), and amount of fibrosis (F2 or F3) at the 0.05 significance level (where a higher responder proportion is a better outcome) and will be based on the Intention-to-Treat (ITT) population. The response Clopper-Pearson 90% and 95% confidence intervals (CI) will be derived for each treatment group.

A sensitivity analysis employing a logistic regression will be used to examine the robustness of the CMH results (see details described in the statistical section, below).

A subject who discontinues treatment prior to Week 42, does not provide a histological assessment on or after Week 42, or who otherwise has missing data will be considered a non-responder.

Further sensitivity analysis of the primary efficacy endpoint will employ multiple imputations for binary data. Pertinent details are included in the statistical analysis plan (SAP).

Analysis of the secondary efficacy and pharmacodynamics endpoints: The analysis of the secondary efficacy endpoints will be based on the ITT population. The imputation mechanism used in the analysis of the primary efficacy endpoint will also be adopted where applicable.

The analysis of the secondary efficacy endpoints of a categorical nature will be analyzed in a manner similar to the primary efficacy endpoint.

For the continuous secondary endpoints such as change from Baseline and percent change from Baseline, the Wilcoxon rank-sum test will be used to compare the treatment groups. For the continuous secondary endpoints, an analysis of covariance (ANCOVA) model will also be used with change from

Baseline (and percent change from Baseline) as the dependent variable; treatment group, T2DM status (yes or no), region (North America or not North America), and amount of fibrosis (F2 or F3) as factors; and Baseline as a covariate. Least-squares means and their differences will be estimated from the ANCOVA model and their corresponding 95% CI will be derived. Inferential statistics will be presented for both the ANCOVA model and the Wilcoxon test. For the continuous secondary endpoints with sufficient postbaseline frequency of measurements, a mixed model repeated measure (MMRM) model will also be employed.

Analysis of PK parameters: Planned PK parameters will be calculated for each subject with serial PK samples employing the standard linear trapezoidal convention using all available drug concentration measurements. Specifically, the following TVB-2640 PK parameters will be estimated (via noncompartmental methods): time to maximum concentration (T_{max}), maximum concentration (C_{max}), area under the concentration-time curve from time of dosing to the last measured concentration ($AUC_{0\text{-}last}$), area under the concentration-time curve from time of dosing extrapolated to infinity ($AUC_{0\text{-}\infty}$), and plasma elimination half-life ($t_{1/2}$). Standard descriptive statistics (mean, median, n, standard deviation, minimum, maximum, coefficient of variation) will be used to summarize the stated PK parameters along with the corresponding 90% CI whenever appropriate. All subject-level concentrations will be provided in a listing and the stated summary statistics presented in a tabular format. Graphical depiction of the concentration measurements by time profile will be presented. Sparse PK sample results will be analyzed using a population PK model.

Definition of analysis populations:

- Intention-to-Treat (ITT) population: Comprises all randomized subjects; this population will serve as the basis for all efficacy analyses. Subjects' data will be analyzed according to their randomized treatment assignment.
- Modified Intention-to-Treat (mITT): Comprises all subjects in the ITT population who have completed at least 42 weeks of treatment and have an evaluable posttreatment histological assessment.
- Interim Analysis Modified Intention-to-Treat (IAmITT): Comprises a subset of subjects in the ITT population with 8% >/= MRI-PDFF at screening or at baseline with at least 1 evaluable post-Baseline MRI-PDFF value, defined as an MRI-PDFF assessment obtained at least 22 weeks after the first dose of study drug.
- The Safety analysis set: Comprises all subjects who are randomized and received at least 1 dose (partial or complete) of study drug.
- PK Population: Comprises all subjects in the ITT population with available PK measurements.

Power considerations and sample size determination: The study estimated total sample size is approximately 162 randomized subjects (108 on TVB-2640 and 54 on placebo). The sample size was derived using the normal approximation to the binomial distribution, and the estimated power to detect a difference in the primary efficacy response of 20% (TVB-2640 40% and placebo 20% at Week 52) was at least 80% (one-sided test at the 0.05 significance level). A 2-to-1 randomization allocation was assumed (TVB-2640 to placebo). An anticipated dropout rate of 18.5% was also applied to estimate the final sample size (N=162).

Safety Analyses

Safety data will be evaluated for the Safety population on the basis of treatment-emergent adverse events (TEAEs), clinical laboratory assessments, vital signs, ECGs, weight, and physical examinations. Changes from Baseline in key clinical laboratory measurements, vital signs, physical examinations, and weight will be summarized by treatment group using standard descriptive statistics. TEAE incidence rates will be summarized using frequency and percentage for each treatment group and in total. TEAEs through 30 days after the last dose of study treatment will be summarized by MedDRA

(current version) system organ class, and preferred term. AEs will also be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (current version) grade, and by causality (attribution to study treatment, related/not related to investigational medicinal product). All safety data will be presented in data listings.

Interim Analysis

A single (secondary endpoint) efficacy interim analysis is planned when approximately 60 subjects with an MRI-PDFF value of ≥8% liver fat at Baseline have completed Week 26 or an Early Termination visit after Week 22. The purpose of the proposed interim analysis is to examine the TVB-2640 benefit over placebo based on a Week 26 secondary efficacy endpoint consisting of "proportion of MRI-PDFF ≥30% responders, where an MRI-PDFF ≥30% responder is defined as a subject with ≥8% liver fat content at Baseline who achieves a percent change (reduction) from Baseline in MRI-PDFF ≥30%". An interim analysis of the primary efficacy endpoint is not feasible since the primary endpoint is only evaluated at Week 52, and not Week 26. Therefore, a statistical penalty is not envisaged in conjunction with the Week 26 interim analysis of the above-stated secondary endpoint.

Interim safety summaries will accompany the interim analysis of the secondary efficacy endpoint.

Planned study committees: An independent data monitoring committee (IDMC) will be established by charter to provide independent review and assessment of study data and to monitor the overall study conduct in a systematic manner to safeguard the safety of study subjects. The interim analysis will be reviewed by the IDMC and will include select biomarkers and safety interim results to allow for a more complete examination of the totality of the data.

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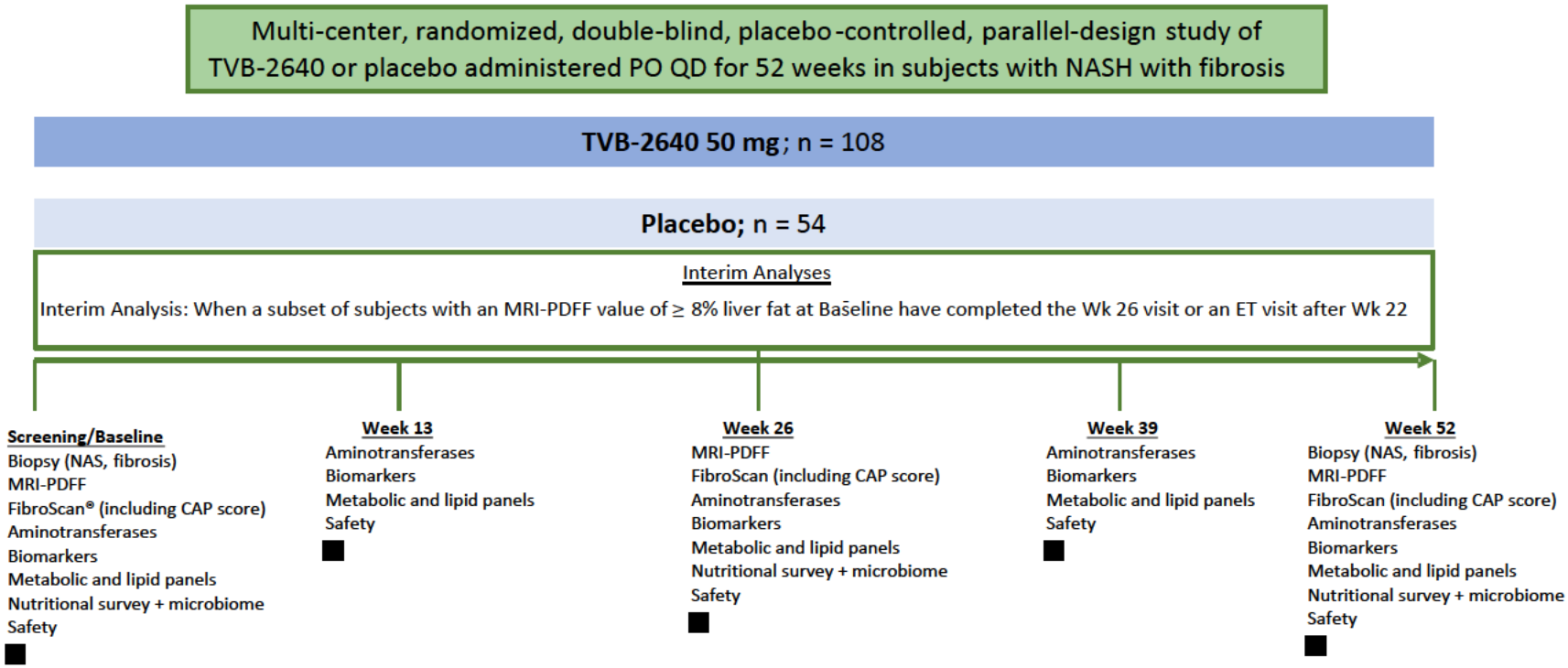
Figure 1: Study Design



Abbreviations: CAP = controlled attenuation parameter; MRI = magnetic resonance imaging: NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; PDFF = protein density fat fraction; [redacted] PO = orally; QD = once daily.

Table 2: Schedule of Assessments

Evaluation	[redacted]	Study Visit								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Screening/Baseline Assessments										
Informed consent	X									
Inclusion and exclusion criteria review	X	X								
Demographics	X									
Pregnancy test[b]	X[b]	X[b]								
eGFR	X									
Medical and social history[c]	X	X								
Alcohol breath test or blood alcohol test	X	X								
Urine drug screen[d]	X	X								
Histologic confirmation of NASH diagnosis, and either Stage 2 or Stage 3 fibrosis[e]	X									
Aminotransferases and INR	X	X								
Viral serology[f]	X									
Genomics pertaining to NASH [g]		X								
Height, body weight, BMI, waist and hip circumference, and waist-hip ratio[h]	X	X								
Safety Assessments										
12-lead ECG[i]	X	X[j]				X			X	X
Vital signs[k]	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X								X	X
Symptom-directed physical examination[l]		X	X	X	X	X	X	X		
Eye examination[m]	X[m]		X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Safety laboratory tests Hematology and coagulation[n]	X	X	X	X	X	X	X	X	X	X

Evaluation	[redacted]	[redacted]				[redacted]				
Liver aminotransferases[o]	X	X	X	X	X	X	X	X	X	X
Clinical chemistry[p]	X	X	X	X	X	X	X	X	X	X
Urinalysis[q]	X	X	X	X	X	X	X	X	X	X
Pregnancy testing[b]			X	X	X	X	X	X	X	X
Adverse events[gg]		Document all AEs occurring from the signing of the ICF through 28 days after the last dose								
Prior/concomitant medications[r]	X	Document medications as described in Section 9.7								
Efficacy and PD Assessments										
Liver histology/NAS/digital pathology[e,s]	X[e]							X[e]	X[e]	
MRI-PDFF[t]	X[t]					X[t]		X[t]	X[t]	
FibroScan, FAST score, and CAP score[u]	X					X		X	X	
Body weight	X	X	X	X	X	X	X	X	X	X
Waist and hip circumference and waist-hip ratio[h]	X	X						X	X	
Blood sample collection for: Lipid panel[v]	X	X	X	X	X	X	X	X	X	X
HbA1c	X	X			X	X	X	X	X	
Metabolic panel[w]		X	X	X	X	X	X	X	X	X
Fibrosis biomarkers[x]		X	X		X	X		X	X	
NASH inflammation and metabolic biomarkers[y]		X	X		X	X		X	X	
Alcohol biomarkers[z]		X				X		X	X	
Lipidomic biomarkers[aa]		X	X		X	X		X	X	
Lipoprotein analyses (subset of sites)[bb]		X				X		X	X	
Stool sample (subset of sites)		X				X		X	X	
Nutritional survey (subset of sites)		X				X		X	X	

Evaluation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]p
Urine sample for storage[cc]		X						X	X	
Whole blood sample for storage[cc]		X						X	X	
[redacted]										
[redacted]		[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]							
Study Drug Administration										
Randomization[ff]		X								
Dosing compliance (Diary)		X	X	X	X	X	X	X	X	
Study drug dispensation[gg]		X			X	X	X			
Study drug administration[gg]		QD PO from Day 1 through Week 52								
Study drug accountability[gg]					X	X	X	X	X	

Abbreviations: adipo-IR = adipose tissue insulin resistance index; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ApoB = apolipoprotein B; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; BUN = blood urea nitrogen; CAP = controlled attenuation parameter; CDT = carbohydrate-deficient transferrin; CK-18 = cytokeratin-18; COVID-19: coronavirus disease-19; CPK = creatine phosphokinase; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ELF = enhanced liver function (score); FAEE = fatty acid ethyl esters; FAST = FibroScan-AST; FGF-21 = fibroblast growth factor-21; FIB-4 = Fibrosis-4 score; FU = follow-up; GGT = gamma-glutamyltransferase; HA = hyaluronic acid; HbA1c = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL-C = high density lipoprotein cholesterol; HIV = human immunodeficiency virus; HOMA = homeostatic model assessment index; INR = international normalized ratio; IR = insulin resistance; LDL-C = low density lipoprotein cholesterol; Lp(a) = lipoprotein (a); MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; NAFLD: nonalcoholic fatty liver disease; NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; NEFA = nonesterified fatty acid; PCR = polymerase chain reaction; PD = pharmacodynamic; PDFF = proton density fat fraction; PEth = phosphatidylethanol; PIIINP = procollagen III amino-terminal peptide; [redacted] PO = orally; PRO-C3 = pro-peptide of type lll collagen; PT = prothrombin time; QD = once daily; RBC = red blood cell; RNA: ribonucleic acid; SARS-CoV-2: severe acute respiratory syndrome- coronavirus -2 TIMP-1 = tissue inhibitor of matrix metalloproteinase 1; vLDL = very low density lipoprotein cholesterol; WBC = white blood cell.

a. Baseline evaluations are to be performed predose, unless otherwise specified.
b. Serum β-hCG pregnancy testing is to be performed for female subjects of childbearing potential during Screening, and a urine pregnancy test is to be performed within 24 hours before the first dose on Day 1 (Baseline). Subjects with a positive serum pregnancy test result are not eligible for study participation. Serum pregnancy testing is to be repeated at the Week 56 Follow-up visit or at Early Termination (whichever takes place sooner), and during the study any time pregnancy is suspected. Female subjects of childbearing potential are required to perform urine home pregnancy tests monthly between study visits and the results should be recorded in a subject diary. A positive urine test should be followed by an unscheduled serum pregnancy test as soon as possible. Study drug is to be held in the event of a positive urine pregnancy test and permanently discontinued for any subject with a positive serum pregnancy test result.
c. A complete medical history is to be documented during Screening and updated at Baseline, prior to administration of the first study drug dose. A history of harmful alcohol intake for a period of more than 3 consecutive months within 1 year prior to Screening in the judgement of the Investigator is exclusionary.

d. Active substance abuse, including inhaled or injected substances (cocaine and other illegal/banned substances; any opiate, amphetamine, or benzodiazepine for which the subject does not have an existing prescription), within 1 year prior to Screening is exclusionary. However, recreational cannabis/tetrahydrocannabinol use is permissible.
e. To qualify for this study, liver histology results must be available before randomization (randomization is within 3 days of Baseline [Day 1]). If the subject terminates early from the study, the end of study biopsy is only required if the subject has completed at least 42 weeks of treatment. See Section 8.1, Criterion 7, and Section 8.2, Criterion 20 for detailed requirements for histology results.
f. Screening serologies include HIV RNA, HBsAg, anti-HCV antibody, HCV RNA (reflex testing, if HCV antibody result at Screening is positive), and SARS-CoV-2 PCR test. The SARS-CoV-2 PCR test may be performed locally and must be performed within 30 days before Baseline (Day 1), other viral serology tests should be performed by the central laboratory. Subjects with chronic HCV infection and liver disease who were treated with anti-HCV therapy and achieved a sustained virologic response at least 2 years prior to Screening are not prevented from study participation.
g. A blood sample for genomics pertaining to NASH will be collected at all sites unless forbidden by local regulations. If not collected at Baseline, this sample may be collected at any other time after the subject signs the separate consent for this sample. Provision of blood samples for genomic analysis is voluntary.
h. Also see further information regarding anthropometric measurements in Section 12.1.6.
i. Single 12-lead ECGs are to be performed at the times indicated and at any other time as clinically indicated. ECGs should be performed before any blood draws planned for the same time period.
j. On Day 1, a single 12-lead ECG should be performed up to 2 hours before and 4 hours (-1 hour/+ 2 hours) after the first study drug dose.
k. Vital signs include oral temperature, pulse, systolic/diastolic blood pressure, and respiration rate. Measurements are to be made after the subject has been resting in a supine position for a minimum of 5 minutes.
l. Abbreviated, symptom-directed physical examinations will include at a minimum, examination of focused liver signs (e.g., jaundice, spider angiomata, palmar erythema, hepatomegaly, splenomegaly, asterixis), skin, and extremities, and any other areas needed to address any complaints or concerns verbalized by the subject. If hand-foot symptoms/signs present at this visit or previous hand-foot symptoms/signs increases in severity to a Grade 2 or above, a dermatologist consult should be considered for further evaluation and treatment recommendations.
m. Baseline eye examinations may be performed at any time during the Screening period. Eye exams at Week 4, Week 8, Week 13, Week 26, Week 39, Week 52, Week 56 and/or Early Termination are required only if eye-related signs or symptoms are reported by the subject or observed by the investigator. If a subject experiences a treatment-emergent eye abnormality, an eye examination inclusive of slit lamp and near and far visual acuity testing should be performed by a qualified ophthalmologist or optometrist within 24 to 48 hours of event onset or on the next business day after symptom onset to evaluate the abnormality.
n. Hematology and coagulation parameters include hemoglobin, MCV, MCHC, hematocrit, platelet count, RBC count, WBC count with differential, ANC, and PT, aPTT, INR, and fibrinogen. See also Table 5.
o. Liver aminotransferases include AST and ALT. Liver aminotransferases collected as part of the clinical chemistry panel for safety are also applicable for efficacy assessments.
p. Fasting clinical chemistries include chloride, carbon dioxide, sodium, potassium, glucose, BUN, calcium, magnesium, creatinine, albumin, ALT, AST, ALP, GGT, total bilirubin, indirect and direct bilirubin, and total protein. CPK (total and fractionated) is to be reported at Screening and at Baseline. See also Table 5.
q. Urinalysis includes specific gravity, pH, blood, glucose, protein, ketones, and microscopic examination of sediment, if present. See also Table 5.
r. Subject contact to reliably assess medication use between visits is encouraged around Week 10, Week 17, Week 23, Week 30, Week 34, Week 43, and Week 47. See Section 9.7 for a list of accepted and excluded concomitant medications. If a subject receives a vaccine, including the COVID-19 vaccine, details regarding that vaccine should be recorded as a concomitant medication(s), including manufacturer, dose, and dates of each injection. Any vaccine-related reactions should be recorded as described in Section 12.2.
s. The same biopsy samples will be used for histology analysis by the central study pathologist and by digital pathology.
t. Subjects will have an MRI-PDFF performed at each indicated timepoint unless it presents a logistical or physical hardship to the subject. MRI-PDFF will not be performed at select sites. The Baseline MRI-PDFF is to be performed during Screening or at Baseline before study drug dosing on Day 1. MRI-PDFF is not required at Early Termination if a subject has completed less than 22 weeks of study treatment.
u. CAP and FAST scores will be measured each time a FibroScan is performed (unless the enrolling study site does not have the capability to measure CAP).
v. Fasting lipid panel includes LDL-C, vLDL, HDL-C, non–HDL-C, total cholesterol, triglycerides, ApoB, and Lp(a) particles.
w. Fasting metabolic panel includes insulin and NEFA. HOMA-IR and adipo-IR are to be calculated from fasting insulin, fasting glucose (see footnote p), and fasting NEFA, as applicable. An analysis of bile acid will also be performed at Baseline, Week 26, Week 52, and/or at Early Termination.

x. Fibrosis biomarkers include ELF (TIMP-1, PIIINP, and HA), PRO-C3, FIB-4, and potentially other markers.
y. NASH biomarkers include CK-18, adiponectin, FGF-21, and other chemokines/cytokines relevant to NASH.
z. Alcohol biomarkers will include PEth and may also include: GGT, MCV, ALT/AST, CDT, and FAEE.
aa. Blood samples for lipidomic biomarkers will be collected in all subjects and analysis will include tripalmitin, ceramides, bile acids, diacylglycerols, and other classes of metabolites.
bb. The lipoprotein substudy will be conducted in approximately 30 or more subjects. Provision of blood samples for the lipoprotein substudy is voluntary.
cc. Additional spot urine and blood samples will be collected at specified time points and stored for potential future analyses for biomarkers relevant to NAFLD/NASH. These samples will not be used for genetic analysis or for creation of cell lines. Providing spot urine and blood samples for storage is voluntary.
dd. [redacted].
gg. In the event a subject is unable to complete the end of treatment MRI-PDFF and/or liver biopsy within the protocol-specified window (Week 52 +/- one week), extended dosing is permitted to maintain continuous dosing up to the time both assessments are completed, to a maximum total of 56 weeks of dosing. In this instance, the Follow-up visit at Week 56 for posttreatment safety and efficacy assessments is to be adjusted to occur four weeks after the last dose (+/- one week).

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
ACC	Acetyl-CoA carboxylase
adipo-IR	Adipose tissue insulin resistance index
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoB	Apolipoprotein B
APRI	AST to platelets ratio index
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from time of dosing extrapolated to infinity
AUC_{0-last}	Area under the concentration-time curve from time of dosing to the last measured concentration
β-hCG	Beta-human chorionic gonadotropin
BMI	Body mass index
CAP	Controlled attenuation parameter
CK-18	Cytokeratin-18
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CoA	Coenzyme A
CRN	Clinical Research Network
CRO	Clinical research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DILI	Drug-induced liver injury
DNL	*de novo* lipogenesis
DPP-4	Dipeptidyl peptidase 4
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture

Abbreviation or Specialist Term	Explanation
eGFR	Estimated glomerular filtration rate
ELF	Enhanced liver function
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FASN	Fatty acid synthase
FAST	FibroScan-AST
FDA	US Food and Drug Administration
FGF-21	Fibroblast growth factor 21
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP	Good laboratory practices
GLP-1	Glucagon-like peptide-1
HA	Hyaluronic acid
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment of insulin resistance
IAmITT	Interim analysis modified Intention-to-Treat
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intention-to-Treat
IUD	Intrauterine device
IWRS	Interactive Web-based Response System
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
LS	Least-squares

Abbreviation or Specialist Term	Explanation
MDRD	Modification of Diet in Renal Disease Study
MedDRA	Medical Dictionary for Regulatory Activities
MICE	Multiple Imputations by Chained Equations
mITT	Modified Intention-to-Treat
MMRM	Mixed model repeated measure
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging–proton density fat fraction
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Nonalcoholic steatohepatitis
NCI	National Cancer Institute
NEFA	Non-esterified fatty acid
NMR	Nuclear magnetic resonance
OAD	Oral antidiabetic
PIIINP	Procollagen III amino-terminal peptide
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PEth	Phosphatidylethanol
PK	Pharmacokinetic
PO	Orally
PPE	Palmar-plantar erythrodysesthesia
PRO-C3	N-terminal type III collagen propeptide
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SGLT2	Sodium-glucose co-transporter-2
SHG	Second harmonic generation
SNP	Single-nucleotide polymorphisms
$T_{½}$	Plasma elimination half-life
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack

Abbreviation or Specialist Term	Explanation
TIMP-1	Tissue inhibitor of metalloproteinase-1
T_{last}	Time of the last measurable concentration
T_{max}	Time to C_{max}
TZD	Thiazolidinediones
ULN	Upper limit of normal
US	United States
vLDL	Very low density lipoprotein cholesterol

5. INTRODUCTION

5.1. Nonalcoholic Fatty Liver Disease

Fatty acid synthase (FASN) is a key enzyme in the de novo lipogenesis (DNL) pathway and catalyzes the biosynthesis of palmitate from acetyl-coenzyme A (CoA) and malonyl-CoA substrates, which can then undergo further modifications into other fatty acids and complex lipids. Because FASN catalyzes the last step in the fatty acid biosynthetic pathway, it is believed to be a determinant of the maximal liver capacity to synthesize fatty acids by DNL (Postic, 2008).

Dysregulation of FASN activity is found in a number of different disease states, including cancer (Buckley, 2017) and metabolic diseases (e.g., obesity, type 2 diabetes mellitus [T2DM]) (Menendez, 2009).

Nonalcoholic fatty liver disease (NAFLD) ranges from simple steatosis to the more progressive nonalcoholic steatohepatitis (NASH) characterized by hepatocyte necrosis, chronic inflammation, and resultant fibrosis formation. Patients with NASH are at increased risk of death due to advanced liver disease, including cirrhosis and hepatocellular carcinoma, as well as cardiovascular disease. Risk factors of developing NAFLD include T2DM (Cusi, 2016), obesity, and metabolic syndrome, all characterized by an imbalance in energy utilization and storage (Grundy, 2005). This imbalance may lead to dysregulated metabolic pathways and inflammatory responses that drive further changes leading to liver damage and comorbid conditions. NASH is the most rapidly increasing indication for liver transplantation in the United States (US) (Younossi, 2020).

Normal responses to ingesting carbohydrate in meals include a transient increase in hepatic DNL, a FASN-dependent pathway, followed by a return to baseline levels upon fasting. In patients with NAFLD, however, hepatic DNL is increased (Donnelly, 2005; Lambert, 2014), and FASN gene expression has been shown to be elevated in liver histology specimens from patients with NAFLD (Kohjima, 2007; Mitsuyoshi, 2009), contributing to elevated liver stores of triglycerides and saturated fatty acid species, which in turn may contribute to liver inflammation (Wei, 2006), tissue damage, and fibrosis formation.

There are currently no drugs licensed for the treatment of NASH in the US, Europe, or China. Inhibiting lipogenesis, with a FASN inhibitor for example, may be a viable clinical strategy to address NASH. Pharmacological inhibition of FASN with TVB-3664, a chemical surrogate of TVB-2640, improved hepatic steatosis, inflammation, and fibrosis in a diet-induced mouse model of NASH (Duke, 2017). Moreover, studies in patients with NASH have shown that inhibition of DNL with the acetyl-CoA carboxylase (ACC) inhibitors firsocostat (Stiede, 2017) and PF-05221304 results in a significant reduction of intrahepatic fat and surrogate markers of fibrosis and cell death, albeit with problematic increases of plasma triglyceride levels as a direct consequence of ACC inhibition (Sanyal, 2017; Kim, 2018). Further studies are needed, however, to evaluate the full spectrum of treatment effects elicited by these drugs and management of their side effects.

5.2. TVB-2640

Sagimet Biosciences has developed an oral (PO), once-daily (QD) FASN inhibitor, TVB-2640. This drug has been evaluated in >300 humans to date, including patients with NASH, patients with solid tumors, and healthy adults, some of whom had characteristics of the metabolic syndrome. The safety, pharmacokinetic (PK), and pharmacodynamic (PD) parameters of TVB-2640 have been measured.

[redacted]

Safety data are available from 129 subjects with NASH who have been enrolled in the US and China in Study CLIN-005 (FASCINATE-1). In the US, subjects received 25 mg TVB-2640, 50 mg TVB-2640, or placebo PO, QD for approximately 12 weeks. A total of 68 subjects were treated with TVB-2640. Overall, 62 (63%) subjects experienced at least 1 treatment-emergent adverse event (TEAE), all of which were assessed by the Investigator as mild, with the exception of 1 case each of Grade 2 urinary tract infection and Grade 2 increased appetite at 25 mg and Grade 2 dyspnea at 50 mg, all of which resolved without dose adjustment. No on-treatment serious adverse events (SAEs) occurred in either TVB-2640 dose group. Overall, the most common TEAEs among TVB-2640-treated subjects were headache (6 subjects; 9%) and peripheral edema, rash, and upper respiratory tract infection (4 subjects each; 6%). Two (3%) subjects discontinued TVB-2640 due to a TEAE: 1 subject due to mild eye allergy (after 1 day of dosing) and the other due to mild conjunctivitis; both of these events occurred in the 25-mg dose group.

Among the 30 subjects enrolled in China, 21 were treated with TVB-2640 50 mg and 9 were treated with placebo for 12 weeks. Seventeen (81.0%) patients experienced at least 1 TEAE, all of which were reported as Grade 2 or less, with the exception of 2 cases of Grade 3 hypertriglyceridemia, both of which were deemed as unrelated to TVB-2640. All TEAEs resolved without dose adjustment. No on-treatment SAEs occurred. Skin and subcutaneous tissue disorders were the most common type of TEAEs. Overall, the most common TEAEs among TVB-2640-treated patients were dry eye (8 patients), skin exfoliation (7 patients), and palmar-plantar erythrodysesthesia syndrome (PPE) and upper respiratory tract infection (each 3 patients).

[redacted]

TVB-2640 reduced hepatic DNL in subjects with features of metabolic syndrome (Syed-Abdul, 2020). Reduction of DNL was dose dependent. The lowest dose tested, 50 mg, exhibited a

significant and meaningful decrease of DNL. Results from the Phase 2a clinical study CLIN-005 demonstrated that QD, PO administration of TVB-2640 for 12 weeks in both the 25-mg and 50-mg cohorts decreased hepatic liver fat in a dose-dependent manner and improved other noninvasive markers of fibrosis, inflammation, and metabolism in subjects with NASH.

The data summarized above support further investigation of TVB-2640 as a novel therapy for patients with NASH. Therefore, the present study will be a Phase 2b, double-blind, parallel-group clinical study to evaluate the safety, efficacy, and PK of 50 mg TVB-2640 compared with matching placebo in approximately 162 patients with NASH over a 12-month Treatment period.

[redacted] Accordingly, female subjects of childbearing potential must use 2 forms of birth control, one being a barrier method (ie, condoms, diaphragm, nonhormonal intrauterine device [IUD]) throughout the study and for at least 3 months after the final study drug dose. Hormonal contraception (stable ≥3 months) and hormonal IUDs are permitted if used with a secondary barrier birth control method (e.g., condoms).

Refer to the Investigator's Brochure for more detailed information regarding TVB-2640.

6. TRIAL OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objectives

- To evaluate the effect of TVB-2640 50 mg PO QD compared with matching placebo in noncirrhotic subjects with NASH and F2-F3 fibrosis by either:
    - Histological improvement at Week 52 in NAFLD activity score (NAS) (ie, ≥2 points improvement in NAS with ≥1 point improvement in ballooning or inflammation) and without worsening of fibrosis (by NASH Clinical Research Network [CRN] fibrosis score)

    OR

    - Resolution of steatohepatitis and no worsening of liver fibrosis (by NASH CRN fibrosis score). Resolution of steatohepatitis is defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis.
- To evaluate the safety and tolerability of TVB-2640 50 mg PO QD in subjects with confirmed NASH and liver fibrosis.

6.1.2. Secondary Objectives

- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on the proportion of subjects with ≥8% liver fat content at Baseline who achieve a ≥30% relative reduction in liver fat content as assessed by magnetic resonance imaging–proton density fat fraction (MRI-PDFF) at Week 26.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on the proportion of subjects with ≥8% liver fat content at Baseline who achieve a ≥30% relative reduction in liver fat content as assessed by MRI-PDFF at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on fibrosis as assessed by ≥1 stage of fibrosis improvement (by NASH CRN score) without worsening of steatohepatitis (no increase in NAS for ballooning, inflammation, or steatosis) at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on fibrosis as assessed by ≥1 stage of fibrosis improvement by NASH CRN score without worsening of NAS (defined as no increase in any component of NAS) at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on fibrosis as assessed by ≥1 stage of fibrosis improvement by NASH CRN score without increasing of total NAS scores at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on fibrosis as assessed by ≥1 stage of fibrosis improvement by NASH CRN score without any worsening of NASH (no worsening of ballooning and lobular inflammation, a 1 grade change in steatosis may be acceptable) at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo the proportion

of subjects experiencing **both** of the following at Week 52:

- Resolution of steatohepatitis on overall histopathological reading and no worsening of liver fibrosis on NASH CRN fibrosis score. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis.

AND

- Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).

- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on the proportion of subjects experiencing **both** of the following at Week 52:
  - Histological improvement at Week 52 in NAFLD NAS (ie, ≥2 points improvement in NAS with ≥1 point improvement in ballooning or inflammation) and without worsening of fibrosis (by NASH CRN fibrosis score)

  AND

  - Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on the proportion of subjects experiencing **both** of the following at Week 52:
  - Resolution of steatohepatitis and no worsening of liver fibrosis (by NASH CRN fibrosis score). Resolution of steatohepatitis is defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis.

  AND

  - Histological improvement at in NAS (≥2 points improvement in NAS).
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on histological improvement at Week 52 in NAS.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on liver fat content as assessed by MRI-PDFF at Week 26.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on liver fat content as assessed by MRI-PDFF at Week 52.
- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on NASH resolution (defined as absence of fatty liver or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis) at Week 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on change from Baseline at 26 and 52 weeks in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT).
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on the change from Baseline at 26 and 52 weeks in low-density lipoprotein cholesterol (LDL-C) and other lipid levels.

- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on the change from Baseline at 52 weeks in the amount of collagen/fibrous area and fibrosis score, assessed by digital pathology.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on the change from Baseline at 26 and 52 weeks in fasting insulin, fasting glucose, homeostatic model assessment of insulin resistance (HOMA-IR), adipose tissue insulin resistance (adipo-IR), and glycosylated hemoglobin (HbA1c) levels.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on the change from Baseline at 26 and 52 weeks in fibroblast growth factor 21 (FGF-21), adiponectin, and other NASH biomarker levels.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on change from Baseline at 26 and 52 weeks in FibroScan® and controlled attenuation parameter (CAP) score.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on N-terminal type III collagen propeptide (PRO-C3) levels and other fibrosis biomarkers on change from Baseline at Weeks 4, 13, 26, and 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on change from Baseline at 26 and 52 weeks in enhanced liver function (ELF) score.
- [redacted]

6.1.3. Exploratory Objectives

- To evaluate the effect of TVB-2640 50 mg QD compared with matching placebo on the proportion of subjects with ≥8% liver fat content at Baseline who achieve a ≥30% relative reduction in liver fat content as assessed by MRI-PDFF **AND** achieve ≥17 U/L reduction in ALT at Week 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on FibroScan-AST (FAST) score at Weeks 26 and 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on select fibrosis biomarkers (including at least tissue inhibitor of metalloproteinase-1 [TIMP-1]) at Weeks 4, 13, 26, and 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on lipidomic biomarkers (including tripalmitin, ceramides, bile acids, diacylglycerols, and other classes of metabolites) at Weeks 4, 13, 26, and 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on glycosylated hemoglobin (HbA1c) levels among subjects with T2DM at Weeks 13, 26, 39, and 52.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on Fibrosis 4 score (FIB-4) at Weeks 4, 13, 26, and 52.

- To use digital pathology to perform zonal analysis of fibrosis at Week 52.
    - To use digital pathology to evaluate the concurrence of fibrosis with components of the NAS score.
    - To use digital pathology to evaluate the NAS components.
- To correlate changes in MRI-PDFF with changes in, or baseline levels of, serum biomarkers and explore predictive markers of response.
- To explore the relationship between changes in, or Baseline levels of, serum biomarkers and histology results, and explore predictive markers of response.
- To explore the relationship between MRI-PDFF results and histology results.
- To correlate the presence of relevant single-nucleotide polymorphisms (SNPs) or other genes relevant to NAFLD or NASH with clinical and histopathologic response.
- To determine the effect of TVB-2640 50 mg QD compared with matching placebo on gut microbiome change from Baseline to Weeks 26 and 52 in a subset of subjects.
- To explore the relationship between nutrition, as measured by the HepVita Nutritional Survey, and clinical, histopathological, and biomarker changes in NASH at Weeks 26 and 52 in a subset of subjects.

6.2. Endpoints

6.2.1. Primary Efficacy (Responder) Endpoint

The proportion of subjects experiencing either of the following:

- Histological improvement at Week 52 in NAS (ie, ≥2 points improvement in NAS with ≥1 point improvement in ballooning or inflammation) and without worsening of fibrosis (by NASH CRN fibrosis score)

  OR

- Resolution of steatohepatitis and no worsening of liver fibrosis (by NASH CRN fibrosis score). Resolution of steatohepatitis is defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis.

6.2.2. Secondary Efficacy and Pharmacodynamic Endpoints

- Proportion of MRI-PDFF ≥30% responders at Week 26, where an MRI-PDFF ≥30% responder is defined as a subject with ≥8% liver fat content at Baseline who achieves a relative reduction from Baseline in MRI-PDFF ≥30%.
- Proportion of MRI-PDFF ≥30% responders at Week 52.
- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN fibrosis score without worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis) at Week 52.

- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN score with no increase in any component of NAS at Week 52.
- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN score without increase of total NAS score at Week 52.
- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN score without any worsening of NASH (defined as no worsening of ballooning and lobular inflammation; a 1 grade change in steatosis may be acceptable) at Week 52.
- Proportion of subjects experiencing **both** of the following at Week 52:
    - Resolution of steatohepatitis on overall histopathological reading and no worsening of live fibrosis on NASH CRN fibrosis score. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis

    AND

    - Improvement in liver fibrosis greater than or equal to one state (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).
- Proportion of subjects experiencing **both** of the following at Week 52:
    - Histological improvement at Week 52 in nonalcoholic fatty liver disease (NAFLD) activity score (NAS) (ie, ≥2 points improvement in NAS with ≥1 point improvement in ballooning or inflammation) and without worsening of fibrosis (by NASH Clinical Research Network [CRN] fibrosis score)

    AND

    - Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).
- Proportion of subjects experiencing **both** of the following at Week 52:
    - Resolution of steatohepatitis and no worsening of liver fibrosis (by NASH CRN fibrosis score). Resolution of steatohepatitis is defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis.

    AND

    - Histological improvement at in NAS (≥2 points improvement in NAS).
- Proportion of subjects with histological improvement at Week 52 in NAS.
- MRI-PDFF percent change in liver fat and change from Baseline at Week 26.
- MRI-PDFF percent change in liver fat and change from Baseline at Week 52.
- Proportion of subjects with NASH resolution (defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis) at 52 weeks.

- Change from Baseline in ALT, AST, and GGT at Weeks 26 and 52 and at each study visit.
- Change from Baseline in LDL-C and other lipid levels at Weeks 26 and 52 and at each study visit.
- Change from Baseline in collagen/fibrous area and fibrosis score, assessed by digital pathology, at Week 52.
- Changes from Baseline in metabolic parameters, including fasting insulin, fasting glucose, HOMA-IR, adipo-IR, and HbA1c levels at Weeks 26 and 52 and at each study visit.
- Change from Baseline in FGF-21, adiponectin, and other NASH biomarker levels at Weeks 26 and 52 and at each study visit.
- Change from Baseline in FibroScan and CAP score results at Weeks 26 and 52.
- Change from Baseline in PRO-C3 and other fibrosis biomarkers at Weeks 4, 13, 26, and 52.
- Change from Baseline in ELF score at Weeks 26 and 52.
- Plasma concentrations of TVB-2640 at Weeks 1, 4, 13, 26, and 52.

6.2.3. Exploratory Efficacy and Pharmacodynamic Endpoints

- Proportion of MRI-PDFF ≥30% responders at Week 52 who have ≥17 U/L reduction in ALT.
- Change from Baseline in FAST score at Weeks 26 and 52.
- Change from Baseline in levels of select fibrosis biomarkers (e.g., TIMP-1) at Weeks 4, 13, 26, and 52.
- Change from Baseline in levels of lipidomic/metabolomic biomarkers (e.g., tripalmitin, ceramides, bile acids, diacylglycerols, and other classes of metabolites) at Weeks 4, 13, 26, and 52.
- Change from Baseline in HbA1c levels among subjects with T2DM at Weeks 13, 26, 39, and 52.
- Change from Baseline in FIB-4 at Weeks 4, 13, 26, and 52.
- Change from Baseline in zonal analyses of fibrosis as determined by digital pathology at Week 52.
- Correlation of changes in MRI-PDFF with changes in other endpoints.
- Presence or absence of SNPs relevant for NASH.
- Correlation of predictive signature with other endpoints.
- Correlation of lipids (e.g. tripalmitin) with other endpoints.

- Change from Baseline in gut microbiome analyses at Weeks 26 and 52 in a substudy of subjects.
- Change from Baseline in HepVita Nutritional Survey at Weeks 26 and 52 in a substudy of subjects.

6.2.4. Safety Endpoints

- Adverse events (AEs) throughout the study.
- Electrocardiograms (ECGs) at Weeks 26 and 52.
- Vital signs at each study visit.
- Physical examination findings at each study visit.
- Eye examination findings at each study visit.
- Hematology and coagulation results at each study visit.
- Liver aminotransferase levels at each study visit.
- Clinical chemistry results at each study visit.
- Urinalysis results at each study visit.
- Pregnancy test results throughout the study.
- Prior and concomitant medications throughout the study.
- Results of anthropometric measurements at Week 52.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-design study to evaluate the safety and efficacy of TVB-2640 compared with matching placebo in subjects with NASH who are aged ≥18 years at Screening. Histological eligibility will be determined during the Screening period or prior to Screening but within 180 days of the Screening visit in 1 of 2 ways:

- If an 'eligible' and adequate (this refers to the quality and quantity of remaining tissue) liver histology specimen, in the judgement of the central pathologist, exists from the time period within 180 days before the subject's Screening visit, the subject may participate so long as other eligibility criteria are satisfied.
- If no liver histology specimen exists from the period within 180 days of the Screening visit, the subject must undergo liver biopsy during the Screening period.

Approximately 162 unique subjects with liver fibrosis stage F2-F3 will be enrolled and randomized to achieve a 2:1 ratio with approximately 108 subjects on TVB-2640 50 mg and 54 subjects on placebo. Dynamic allocation is used for the randomization, stratified by 3 factors: T2DM status (yes or no), region (North America or not North America), and amount of fibrosis (F2 or F3).

Subjects will be screened for study eligibility within 90 days before randomization (randomization is within 3 days of Baseline [Day 1]). Subjects who are determined to be eligible for the study based on Screening assessments are to be randomized into the study within 3 days before Baseline (ie, Day 1, the first day of study drug administration). Subjects who are randomized are considered to be enrolled in the study.

Subjects will receive TVB-2640 or matching placebo PO QD for 52 weeks, with the first dose administered on Day 1. During the 52-week Treatment period, subjects are to attend study center visits at Weeks 4, 8, 13, 26, 39, and 52. After completion of the 52-week Treatment period, subjects are to attend a Follow-up visit at Week 56 for posttreatment safety and efficacy assessments.

In the event a subject is unable to complete the end of treatment MRI-PDFF and/or liver biopsy within the protocol-specified window (Week 52 +/- one week), extended dosing is permitted to maintain continuous dosing up to the time both assessments are completed, to a maximum total of 56 weeks of dosing. In this instance, the Follow-up visit at Week 56 for post treatment safety and efficacy assessments is to be adjusted to occur four weeks after the last dose (+/- one week).

In the instance of a dose hold due to an AE or SAE, the decision to resume study drug will require consultation with the Investigator, the CRO's Medical Monitor, and the Sponsor's Chief Medical Officer.

Improvement of NAS and improvement of fibrosis score will be evaluated by comparison of Baseline and Week 52 liver histology specimens. Subjects will also undergo MRI-PDFF prior to the start of treatment, at Week 26, and at Week 52 or Early Termination unless it presents a logistical or physical hardship to the subject. MRI-PDFF is not required at Early Termination if a

subject has completed less than 22 weeks of study treatment. Other efficacy and PD assessments include FibroScan with CAP, and measurement of liver aminotransferases, lipid parameters, and other noninvasive biomarkers of NASH and liver fibrosis throughout the study.

During the study, safety will be assessed by vital signs, 12-lead ECGs, physical examinations including eye examinations, and clinical laboratory testing. Subjects will be evaluated for AEs and concomitant medication use throughout the study.

[redacted].

An independent data monitoring committee (IDMC) will be established by charter to provide independent review and assessment of study data and to monitor the overall study conduct in a systematic manner to safeguard the safety of study subjects. The IDMC will be tasked with making recommendations to the Sponsor to continue, amend, or stop the study based on these assessments.

A secondary endpoint efficacy interim analysis (IA) is planned when approximately 60 subjects with an MRI-PDFF value of ≥8% liver fat at Baseline have completed Week 26 or an Early Termination visit after Week 22. The purpose of the proposed interim analysis is to examine the TVB-2640 benefit over placebo based on a Week 26 secondary efficacy endpoint consisting of "proportion of MRI-PDFF ≥30% responders at Week 26, where an MRI-PDFF ≥30% responder is defined as a subject with ≥8% liver fat content at Baseline who achieves a percent change (reduction) from Baseline in MRI-PDFF ≥30%."

Interim summaries of safety and selected biomarker data will accompany the interim efficacy analysis of the secondary efficacy endpoint.

The study design is summarized in **Error! Reference source not found.**, and the Schedule of Assessments is provided in Figure 1: Study Design

Abbreviations: CAP = controlled attenuation parameter; MRI = magnetic resonance imaging: NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; PDFF = protein density fat fraction; [redacted] PO = orally; QD = once daily.

Table 2.

7.2. Stopping Rules

Enrollment of new subjects may be suspended in the event of any of the following:

- ≥1 subject experiences a Grade 5 TEAE (ie, TEAE with a fatal outcome)
- ≥2 subjects experience the same Grade 4 TEAE

In such cases, the Sponsor's Chief Medical Officer and the clinical research organization's (CRO's) Medical Monitor will review blinded data to determine if the IDMC needs to be convened to review the unblinded data to determine the relationship of the TEAE(s) to TVB-2640. The IDMC will make a recommendation to the Sponsor regarding whether to continue, amend, or stop the study.

7.3. Dose Adjustment Criteria

Dose modification will be allowed for subjects who experience an on-target AE considered to be treatment related that would otherwise lead to study or treatment discontinuation. The decision to reduce the dose of study drug will require consultation with the Investigator, the CRO's Medical Monitor, and the Sponsor's Chief Medical Officer. To preserve the study blind, the total number of combined tablets of study drug and matching placebo will remain the same. The subject's study drug assignment will NOT be unblinded. Dose modification is not allowed for subjects who have any of the TEAEs described in Section 8.3 that require permanent discontinuation. Additional details are provided in the Pharmacy Manual.

Dose interruptions may also be allowed (see also Appendix A and Section 8.3).

In the instance of a dose hold due to an AE or SAE, the decision to resume study drug will require consultation with the Investigator, the CRO's Medical Monitor, and the Sponsor's Chief Medical Officer.

7.4. Independent Data Monitoring Committee

An IDMC will be established to provide independent review and assessment of study data and to monitor the overall study conduct in a systematic manner in order to safeguard the safety of study subjects. The IDMC will be tasked with making recommendations to the Sponsor to continue, amend, or stop the study based on these assessments.

The members of the IDMC will be independent of the Sponsor and the study team, including the CRO. The IDMC will consist of at least 3 independent individuals, including 1 biostatistician and 2 physicians with expertise in NAFLD. In addition, an independent, nonvoting statistician who is not a member of the IDMC or a member of the study team will serve as a liaison between the Sponsor and the IDMC and will provide periodic outputs of safety data for IDMC review. The specific procedures for interactions between the IDMC and non-IDMC individuals will be defined in the IDMC charter.

IDMC meetings will consist of open and closed sessions. Closed sessions will be attended only by IDMC members and the independent statistician. Study team personnel, including the Sponsor and the CRO, will be restricted to the open sessions.

A single (secondary endpoint) efficacy interim analysis is planned when approximately 60 subjects with an MRI-PDFF value of ≥8% liver fat at Baseline have completed Week 26 or an Early Termination visit after Week 22. The purpose of the proposed interim analysis is to examine the TVB-2640 benefit over placebo based on a Week 26 secondary efficacy endpoint consisting of "proportion of MRI-PDFF ≥30% responders at Week 26, where an MRI-PDFF ≥30% responder is defined as a subject with ≥8% liver fat content at Baseline who achieves a percent change (reduction) from Baseline in MRI-PDFF ≥30%."

Interim safety summaries will accompany the interim efficacy analysis of the secondary efficacy endpoint.

The IDMC will also meet any time that the stopping rules outlined in Section 7.2 are met. Additional scheduled and ad hoc meetings may take place as required, and rules for these meetings will be defined in the IDMC charter.

The Sponsor will establish a charter document explaining the working procedures and responsibilities of the IDMC. All deliberations and decisions of the board will be appropriately documented.

7.5. Criteria for Study Termination by the Sponsor

The Sponsor reserves the right to terminate the study or a particular study center at any time. If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then study termination can occur only after appropriate consultation between the Sponsor and Investigators. Conditions that may warrant study or study center termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure of the Investigator to enter subjects at an acceptable rate
- Insufficient adherence to the protocol requirements
- A decision on the part of the Sponsor to suspend or discontinue development of study drug

Should the study be closed prematurely, all study materials (study drug, etc) must be returned to the Sponsor or designee (or disposed of as directed by the Sponsor or designee).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Unless otherwise specified, repeat testing for laboratory and clinical Screening assessments may be performed in consultation with the Medical Monitor.

8.1. Subject Inclusion Criteria

Subjects meeting all of the following criteria are eligible for enrollment into the study.

1. Must be willing and able to participate in the study and provide written informed consent.
2. Male and female adults ≥18 years of age on the date that written informed consent to take part in the study is provided.
3. Body mass index (BMI) ≥23 kg/m^2 for Asians and ≥25 kg/m^2 for other races.
4. Female subjects must be either:
   a. Not of childbearing potential (ie, surgically [bilateral oophorectomy, hysterectomy, or tubal ligation] or naturally sterile [>12 consecutive months without menses]).
   OR
   b. Female subjects of childbearing potential must have a negative serum pregnancy (beta-human chorionic gonadotropin [β-HCG]) test during Screening, a negative urine pregnancy test within 24 hours before the first dose of study drug on Day 1, and must agree to perform urine home pregnancy tests monthly between study visits. Female subjects of childbearing potential must not be breastfeeding, not plan to become pregnant during the study, and must use 2 forms of birth control, one being a barrier method (ie, condoms, diaphragm, IUD) throughout the study and for at least 3 months after the final study drug dose. Hormonal contraception (stable ≥3 months) and hormonal IUDs are permitted if used with a secondary barrier birth control method (e.g., condoms).
5. Male subjects who have sexual intercourse with a female partner of childbearing potential from the first dose of study drug until 3 months after completion of study drug intake must be either surgically sterile (confirmed by documented azoospermia >90 days after the procedure) OR agree to use a condom with spermicide. All male subjects must agree not to donate sperm from the first dose of study drug until 3 months after completion of study drug intake.
6. Must have liver stiffness measurement ≥8.5 kPa measured by FibroScan and CAP score measured by FibroScan ≥280 dB/m (unless the enrolling study site does not have the capability to measure CAP) during the Screening period.
7. Histologic confirmation of NASH: must have had a prior liver biopsy within 180 days before the Screening visit, or a new biopsy during the screening period, with fibrosis stage F2-F3 and a NAS of ≥4 with at least a score of 1 in each of the following NAS components:
   a. Steatosis (scored 0 to 3)
   b. Ballooning degeneration (scored 0 to 2)
   c. Lobular inflammation (scored 0 to 3)

8. AST >20 U/L.

8.2. Subject Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for enrollment into the study.

1. History of harmful alcohol intake for a period of more than 3 consecutive months within 1 year prior to Screening in the judgement of the Investigator.
2. Active substance abuse, including inhaled or injected substances (cocaine and other illegal/banned substances; any opiate, amphetamine, or benzodiazepine for which the subject does not have an existing prescription), within 1 year prior to Screening (note that recreational cannabis/tetrahydrocannabinol use is permissible).
3. Patient-reported or medically documented gain or loss of >5% of body weight in the 6 months prior to Baseline (Day 1) or >10% of body weight in the 12 months prior to Screening.
4. Prior or planned (during the study period) bariatric surgery that may interfere with study drug absorption (e.g., roux-en-Y gastric bypass); gastroplasty and gastric reduction surgery are acceptable.
5. Type 1 diabetes mellitus by history.
6. Positive SARS-CoV-2 polymerase chain reaction (PCR) test within 30 days prior to the Baseline (Day 1) visit date or history of hospitalization for COVID-19 <6 months prior to the Screening visit date. Note that previous COVID-19 infection alone is not exclusionary, and COVID-19 vaccination is allowed. Infection and/or vaccination must be documented as medical history and/or concomitant medication, respectively.
7. Known positivity for HIV infection or positive HIV antibody result at Screening.
8. Positive hepatitis B virus antigen (HBsAg) result at Screening.
9. Positive hepatitis C virus (HCV) RNA test at Screening; however, subjects with chronic HCV infection and liver disease who were treated with anti-HCV therapy and achieved a sustained virologic response at least 2 years prior to Screening are not prevented from study participation.
10. Uncontrolled T2DM, defined as HbA1c >9.5% at Screening.
11. Serum LDL-C concentration at Screening >190 mg/dL, and the subject has been taking LDL-C–lowering treatment for ≥30 days prior to Screening.
12. ALT and/or AST result >5 × the upper limit of normal (ULN) at Screening. One repeat test may be allowed within 7 days of receipt of the result at the discretion of the Investigator.
13. Alkaline phosphatase (ALP) result ≥2 × ULN at Screening.
14. Total serum bilirubin concentration >1.3 mg/dL at Screening; subjects with a confirmed diagnosis of Gilbert's syndrome (ie, prior to Screening and whose total bilirubin result at Screening exceeds 1.3 mg/dL) may be eligible for study inclusion at the Investigator's discretion.

15. International normalized ratio (INR) result >1.3 at Screening.
16. Serum albumin concentration <3.5 g/dL at Screening.
17. Platelet count <140,000/μL at Screening.
18. Estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2, as determined using the Modification of Diet in Renal Disease Study (MDRD) equation, at Screening.
19. Presence of cirrhosis on liver histology (stage 4 fibrosis), according to the judgement of the central reader; and/or cross-sectional imaging evidence consistent with cirrhosis and/or portal hypertension (e.g., nodular liver contour; atrophy and hypertrophy of the right and left hepatic lobes, respectively; splenomegaly; known presence or history of esophageal varices; and/or elastography evidence consistent with cirrhosis).
20. F0, F1, or F4 fibrosis, or inconclusive result, on liver histology.
21. Use of drugs historically associated with risk of development of NAFLD (e.g., amiodarone, methotrexate, systemic glucocorticoids [unless used at physiologic replacement doses for treatment of confirmed adrenal insufficiency], tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids [except for testosterone preparations used at physiologic replacement doses for treatment of documented/confirmed hypogonadism], valproic acid, and other known hepatotoxins) for more than 12 consecutive months at any time during the 5 years prior to the Screening visit.
22. Use of glucagon-like peptide-1 (GLP-1) agonists or a sodium-glucose co-transporter-2 (SGLT2) inhibitor, unless on a stable daily dose for at least 6 months prior to the Screening visit date
    OR
    On a complex oral antidiabetic (OAD) regimen (3 or more OADs [except for a GLP-1 agonist or an SGLT2 inhibitor]), unless on stable doses for at least 3 months prior to the Screening visit date (refer to Section 9.7, Concomitant Medications).
23. Use of vitamin E supplementation at a daily dose >400 IU unless on a stable daily dose for at least 6 months prior to the Screening visit (refer to Section 9.7, Concomitant Medications).
24. Use of strong concomitant cytochrome P450 (CYP) 3A4 inhibitors or inducers during the study (refer to Section 9.7, Concomitant Medications).
25. Known diagnosis of hereditary hemochromatosis.
26. Subjects with active or quiescent chronic liver disease of etiologies other than NASH (e.g., viral or autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, “autoimmune hepatitis-overlap” syndromes, hemochromatosis, Wilson’s disease, alpha-1 antitrypsin deficiency, alcohol-related liver disease, drug-induced liver disease, and/or infiltrative conditions [e.g., sarcoidosis]).
27. Current or historic clinically evident hepatic decompensation event (e.g., ascites formation, variceal hemorrhage, hepatic encephalopathy).
28. Active, serious medical disease with likely life expectancy <2 years.

29. History of clinically significant dry eye (xerophthalmia) or other corneal abnormality, as determined by an ophthalmologist or optometrist during Screening.
30. Participation in an investigational study in the 30 days prior to randomization.
31. Participation in an investigational drug trial for subjects with NASH, T2DM, and/or weight reduction within 6 months of Screening; only if it can be confirmed the subject received placebo during the earlier study would it be possible for such a subject to be screened for this study sooner than 6 months before Screening.
32. Any subject who has sustained a clinically evident cardiovascular, cerebrovascular, and/or peripheral vascular event (e.g., unstable angina, acute coronary syndrome, myocardial infarction, life threatening tachy- and/or brady-dysrhythmia, stroke, transient ischemic attack [TIA], peripheral vascular disease) during the 12 months prior to anticipated Baseline (Day 1) visit date.
33. Any contraindication to MRI (e.g., claustrophobia, metal implants).
34. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, compromise the well-being of the subject, or interfere with the study outcomes.

8.3. Subject Withdrawal Criteria

Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. Study drug must be permanently discontinued and the subject withdrawn from the study for any of the following TEAEs, with the subject managed as indicated:

- **Palmar-plantar Erythrodysesthesia (PPE):** For mild to moderate symptoms of PPE (e.g., redness, pain, or scaling of hands or feet), study drug should be interrupted and symptomatic measures, including hand cream such as "Udder Cream," instituted immediately. Study drug may be resumed after resolution of symptoms; study drug should be discontinued permanently if PPE Grade ≥2 recurs after study drug is resumed. Study drug should also be permanently discontinued at the first sign of significant/severe, redness, pain, or scaling of hands or feet, and symptomatic measures instituted immediately.
- **Dyspnea or suspected pneumonitis:** Study drug should be permanently discontinued for subjects with shortness of breath or other respiratory symptoms that are otherwise unexplained. An unscheduled SARS-CoV-2 test should be done if a subject develops dyspnea or pneumonitis. The subject is to be carefully monitored for improvement. In the event that symptoms worsen or present as more than mild intensity, immediate referral to a qualified pulmonologist for definitive diagnosis and treatment should be undertaken.
- **Visual symptoms (including keratitis):** Study drug should be permanently discontinued at the first sign of significant redness (erythema), pain, or dryness affecting one or both eyes. Symptomatic measures, including moisturizing eye drops, should be instituted. In the event that symptoms worsen or present as more than mild, immediate referral to a qualified ophthalmologist or optometrist should be undertaken.

- **Suspected drug-induced liver injury (DILI):** Study drug intake should be managed according to the different laboratory and clinical circumstances itemized in Appendix A for subjects with suspected DILI.

Refer to the Study Manual for additional details regarding the assessment and management of these events.

Furthermore, the Investigator also has the right to withdraw subjects from the study for any of the following reasons:

- Progression of underlying disease that, in the opinion of the Investigator, precludes further study treatment.
- Occurrence of any other unacceptable AE.
- Study drug interruption for any reason for >15 days.
- Subject requires use of a prohibited concomitant medication or therapy.
- General or specific changes in the subject's condition unacceptable for further treatment within the study parameters, in the judgment of the Investigator.
- Noncompliance.
- Lost to follow-up.
- Subject withdrawal of consent.
- Sponsor request.

At the time of study withdrawal, all study procedures outlined for the Early Termination visit should be completed (Figure 1: Study Design

Abbreviations: CAP = controlled attenuation parameter; MRI = magnetic resonance imaging: NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; PDFF = protein density fat fraction; [redacted] PO = orally; QD = once daily.

Table 2). The primary reason for a subject's withdrawal from the study is to be recorded in the electronic case report form (eCRF) together with explanatory comment where required. If the subject is not on site when the decision to withdraw the subject from the study is confirmed, the subject should return to the clinic to undergo the Early Termination visit as soon as possible thereafter.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

9.1.1. TVB-2640

TVB-2640 is a small-molecule, orally-bioavailable, reversible inhibitor of the human FASN enzyme. TVB-2640 has a molecular formula of $C_{27}H_{29}N_5O$ and a molecular weight of 440.

TVB-2640 immediate-release formulation will be supplied for PO QD administration as 25- and 50-mg strength uncoated tablets.

9.1.2. Placebo

Placebo tablets that conform to the appearance, shape, and size of the TVB-2640 25-mg and 50-mg strength tablets will be used during this study.

9.2. Study Drug Packaging and Labeling

TVB-2640 will be packaged in bulk, screw-top plastic bottles containing 100 tablets.

TVB-2640 will be labeled in accordance with applicable regulatory requirements. Study drug labels will not bear any statement that is false or misleading in any manner or represents that the study drug is safe or effective for the purposes for which it is being investigated.

9.3. Study Drug Storage

TVB-2640 drug product and placebo should be stored in a secure, limited-access storage area at room temperature. Further study drug storage conditions and requirements will be provided in the study's Pharmacy Manual.

9.4. Study Drug Accountability

The US Food and Drug Administration (FDA) and other applicable regulatory authorities require accounting of all investigational drug received by each study center. Records of drug disposition required include the date received by the center, date administered, quantity administered, and the subject to whom study drug was administered. The Investigator is responsible for the accountability of all used and unused study drug containers and unused study drug.

Study drug (and placebo) will be provided to the investigational site. Site personnel will acknowledge receipt of the study drug using interactive response technology (IRT) to confirm the shipment condition and content. If a damaged shipment is received and/or a temperature excursion has been incurred, site personnel will notify the Sponsor/CRO and follow the guidelines according to the current version of the study's Pharmacy Manual.

The designated personnel will maintain accurate records of the study drug throughout the clinical study, including the inventory delivered to the study center, the use by each subject, the reconciliation of all delivered study drug, and the return of unused study drug as specified in the current version of the Pharmacy Manual.

The study monitor should check the study supplies at each study center at any time during the study. It is the responsibility of the study monitor to ensure that the Investigator (or designee) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided to site staff. Details will be provided in the Pharmacy Manual.

A full drug accountability log will be maintained at the study center at all times. The study monitor will arrange collection of any unused study drug. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

9.5. Study Drug Dose and Administration

All subjects will receive study drug PO QD for 52 weeks or until the final on-study investigation (MRI-PDFF and/or liver biopsy). The first dose of study drug should be taken at the study site under supervision of study staff.

In the event a subject is unable to complete the end of treatment MRI-PDFF and/or liver biopsy within the protocol-specified window (Week 52 +/- one week), extended dosing is permitted to maintain continuous dosing up to the time both assessments are completed, to a maximum total of 56 weeks of dosing. In this instance, the Follow-up visit at Week 56 for posttreatment safety and efficacy assessments is to be adjusted to occur four weeks after the last dose (+/- one week).

In the instance of a dose hold due to an AE or SAE, the decision to resume study drug will require consultation with the Investigator, the CRO's Medical Monitor, and the Sponsor's Chief Medical Officer.

Each QD dose of study drug is to be taken at the same time of day in the evening with or without food, with each dose separated by approximately 24 hours (±4 hours).

Subjects will receive one of the following each day, based on their blinded treatment assignment:

- **Placebo:** one placebo tablet matching the 50-mg TVB-2640 tablet and one placebo tablet matching the 25-mg TVB-2640 tablet
- **TVB-2640 50 mg:** one 50-mg TVB-2640 tablet and one placebo tablet matching the 25-mg TVB-2640 tablet

If a dose adjustment for an individual subject is approved as described in Section 7.3, the subject will continue to receive 2 tablets QD as follows to preserve the study blind (see the Pharmacy Manual for additional details):

- **Dose adjustment from TVB-2640 50 mg to TVB-2640 25 mg:** one 25-mg TVB-2640 tablet and one placebo tablet matching the 50-mg TVB-2640 tablet
- **Dose adjustment for those randomized to placebo:** there will be no change in the size or number of placebo tablets. To maintain the blind, the subject will be provided with new study drug bottles

9.6. Treatment Assignment, Randomization, Blinding, and Unblinding

This will be a double-blind, randomized study. Subjects will be centrally assigned to randomized study treatment using an Interactive Web-based Response System (IWRS). Study medication will be dispensed at the study visits summarized in the Schedule of Assessments (Figure 1: Study Design

Abbreviations: CAP = controlled attenuation parameter; MRI = magnetic resonance imaging: NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; PDFF = protein density fat fraction; [redacted] PO = orally; QD = once daily.

Table 2). Returned study drug should not be redispensed.

All subjects, Investigators, the Sponsor, and the CRO will be blinded to the treatment assignment of each individual subject. Members of the IDMC and the IDMC's independent statistician will be unblinded to treatment assignment as needed. In addition, specific vendors whose role in study conduct requires them to be unblinded (e.g., personnel operationally associated with the IWRS) may also be unblinded.

Subjects will be randomized to achieve a 2:1 ratio with approximately 108 subjects on TVB-2640 50 mg and approximately 54 subjects on placebo. Dynamic allocation will be used for the randomization, stratified by 3 factors: T2DM status (yes or no), region (North America or not North America), and amount of fibrosis (F2 or F3).

In the event that emergency unblinding is required for a given subject because of AEs or concerns for the subject's safety or well-being, the Investigator may request a code from the CRO in order to break the randomization code for the subject via the IWRS, by which system the unblinding will be captured. The unblinding and its cause will also be documented on the eCRF.

9.7. Concomitant Medications

All concomitant medications taken from 28 days before the first dose through 28 days after the last dose should be recorded in the appropriate eCRF, including dose adjustments. In addition, concomitant medications that are required to be stable within the 3, 6, or 12 months prior to the study must be recorded from the medication start date, as listed in Section 9.7.1.

9.7.1. Excluded Medications

The following medications and treatments are prohibited during study participation.

- Any investigational agent or device other than TVB-2640.
- Strong inhibitors or inducers of CYP3A4. (Refer to the following for examples: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.)
    - Drugs historically associated with risk of development of NAFLD (e.g., amiodarone, methotrexate, systemic glucocorticoids [unless used at physiologic replacement doses for treatment of confirmed adrenal insufficiency], tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids [except for testosterone preparations used at physiologic replacement doses for treatment of documented/confirmed hypogonadism], valproic acid, and other known hepatotoxins) for more than 12 consecutive months at any time during the 5 years prior to the Screening visit date.
        - Short courses of systemic glucocorticoids may be allowed to treat acute illnesses.
    - GLP-1 agonist (e.g., semaglutide), SGLT2 inhibitor (e.g., empagliflozin, canagliflozin), vitamin E at a daily dose >400 IU, and/or thiazolidinediones (TZD) (e.g., pioglitazone) unless on a stable daily dose for at least 6 months prior to the Screening visit date. Subjects who provide a historical Screening liver biopsy specimen to determine study eligibility should have been on a stable dose of these medications for at least 12 months prior to the Baseline [Day 1] visit date.
    - Vitamin E at a daily dose >400 IU, and/or thiazolidinediones (TZD) (e.g., pioglitazone) should not be initiated after the Screening liver biopsy is performed.
    - A complex OAD regimen (3 or more OADs [except for a GLP-1 agonist or a SGLT2 inhibitor]e.g.), unless:
        - on stable doses for at least 3 months prior to the Screening visit date and/or
        - used for uncontrolled diabetes management that is not responsive to optimized doses of other classes of anti-diabetic medications during the double-blind Treatment period.

- Insulin dose adjustment >10% (increase or decrease). (Subjects receiving insulin at Baseline [Day 1] who require a >10% dose adjustment for the management of T2DM are to be discontinued from the study.)
- Introduction of a GLP-1 agonist for weight loss during the double-blind Treatment period is prohibited.
- GLP-1 agonists, and SGLT2 inhibitors required for diabetes management that is not responsive to optimized doses of other classes of anti-diabetic medications during the double-blind Treatment period may be initiated after discussion with the Medical Monitor and with Sponsor approval. Though usage of GLP-1 agonists, and SGLT2 inhibitors do not pose safety risks to study subjects, these drugs may lead to weight loss and could potentially confound the study results.

Subjects requiring such treatment during study participation are to be discontinued.

9.7.2. Permitted Medications

Medications and treatments other than those specified in Section 9.7.1 are permitted during the study. Subjects should be closely monitored, and treatment is to be instituted for disease-related symptoms, as appropriate.

If a subject receives a vaccine, including the COVID-19 vaccine, details regarding that vaccine should be recorded as a concomitant medication(s), including manufacturer, dose, and dates of each injection. Any vaccine-related reactions should be recorded as described in Section 12.2.

9.8. Treatment Compliance

The verification of daily dosing of the study drug will be performed through the completion of a daily diary by all subjects. Subjects should be instructed to bring their study drug diary and study drug containers to each study visit for compliance assessment. The treatment compliance of individual subjects will be monitored using the electronic data capture (EDC) system, by review of the study drug diary, and by counting returned clinical trial materials. Subject contact to reliably assess medication use between visits is also encouraged around Week 10, Week 17, Week 23, Week 30, Week 34, Week 43, and Week 47.

10. SCREENING/BASELINE ASSESSMENTS

Screening and Baseline (Day 1) assessments will be conducted in accordance with the time points indicated in the Schedule of Assessments (Figure 1: Study Design

Abbreviations: CAP = controlled attenuation parameter; MRI = magnetic resonance imaging: NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; PDFF = protein density fat fraction; [redacted] PO = orally; QD = once daily.

Table 2). Note that most Screening assessments may be performed within 90 days of Day 1; however, the Screening SARS-CoV-2 PCR test must be performed no more than 30 days before Day 1, and a Screening urine pregnancy test must be performed within 24 hours of dosing on Day 1 (as indicated).

All subjects must provide written informed consent, as described in Section 14.4, before the performance of any study-related procedures.

10.1. Demographics

Subject demographics, including age, sex, race, and ethnicity, are to be documented during Screening.

10.2. Medical and Social History

A complete medical history is to be documented during Screening and updated at Baseline, prior to administration of the first study drug dose.

The medical history also is to include NASH-related history, including the date of diagnosis, and, as available, NAS, AST to platelets ratio index (APRI), NAFLD fibrosis score, as well as abbreviated weight history, family history (subjects and their first degree relatives [parents, full siblings, and children]; particularly of obesity and liver disease), past medical/surgical events and illness history (including diabetes mellitus, gestational diabetes mellitus, systemic hypertension, lipodystrophy, polycystic ovarian syndrome, and any history of Gilbert's disease) and other associated comorbid conditions including previously diagnosed lipid and metabolic disease-related conditions (hypercholesterolemia, hypertriglyceridemia, diabetes mellitus), and all diagnoses related to previous liver disease as well as other diagnoses of major organ systems including cardiac disease, renal disease, endocrine disease, hypertension, gout or other arthropathies, disturbances of vision, peripheral neuropathy, myopathy, pancreatitis, and cholelithiasis.

History of previous COVID-19 infection or vaccination against COVID-19 should also be documented.

Social history, including weekly alcohol consumption, daily tobacco use, and daily caffeinated coffee intake, will also be documented.

10.3. Viral Serology

Screening serologies include HIV RNA, HBsAg, anti- HCV antibody, HCV RNA (reflex testing, if HCV antibody result at Screening is positive), and SARS-CoV-2 (the virus that causes COVID-19) PCR test. The SARS-CoV-2 PCR test may be performed locally; other tests should be performed by the central laboratory.

Subjects with chronic HCV infection and liver disease who were treated with anti-HCV therapy and achieved a sustained virologic response at least 2 years prior to the Screening visit date are not prevented from study participation (see Section 8.2).

10.4. Pregnancy Testing

For female subjects of childbearing potential, a serum beta-human chorionic gonadotropin (β-hCG) pregnancy test will be performed during Screening, and a urine pregnancy test is to be performed within 24 hours before the first dose on Day 1 (Baseline). Subjects with a positive serum pregnancy test result are not eligible for study participation. Serum pregnancy testing is to be repeated at the Week 56 Follow-up visit or at Early Termination (whichever takes place sooner), and during the study any time pregnancy is suspected. Female subjects of childbearing potential are required to perform urine home pregnancy tests monthly between study visits and the results should be recorded in a subject diary. A positive urine test should be followed by an unscheduled serum pregnancy test as soon as possible. Study drug is to be held in the event of a positive urine pregnancy test and permanently discontinued for any subject with a positive serum pregnancy test result. See Section 12.2.6 for details regarding management of any pregnancies during the study.

Female subjects not of childbearing potential must have such documentation included as part of their medical history, ie, surgically [bilateral oophorectomy, hysterectomy, or tubal ligation] or naturally sterile [>12 consecutive months without menses]).

10.5. Alcohol and Urine Drug Screening

At Screening and Baseline, subjects will undergo an alcohol breath test or blood alcohol test and a urine screening test for drugs of abuse. Active substance abuse, including inhaled or injected substances (cocaine and other illegal/banned substances; any opiate, amphetamine, or benzodiazepine for which the subject does not have an existing prescription), within 1 year prior to Screening is exclusionary. However, recreational cannabis/tetrahydrocannabinol use is permissible.

Details regarding the collection, storage, shipment, and analysis of laboratory samples will be provided in the Laboratory Manual.

10.6. Other Screening/Baseline Assessments

Other Screening/Baseline assessments are described in sections below, including the following:

- Information regarding eGFR, aminotransferases, and INR is provided in Section 12.1.5.
- Information regarding histologic confirmation of NASH diagnosis is provided in Section 11.1.1.
- Information regarding genomics pertaining to NASH with fibrosis is provided in Section 11.2.1.
- Information regarding anthropometric measurements (height, body weight, BMI, waist and hip circumference, and waist-hip ratio) is provided in Section 12.1.6.
- Information regarding FibroScan, CAP score, and FAST score is provided in Section 11.1.3.

11. EFFICACY, PHARMACODYNAMIC [redacted] ASSESSMENTS

Efficacy, PD, [redacted] assessments will be conducted in accordance with the time points indicated in the Schedule of Assessments (Figure 1: Study Design

Abbreviations: CAP = controlled attenuation parameter; MRI = magnetic resonance imaging: NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; PDFF = protein density fat fraction; [redacted] PO = orally; QD = once daily.

Table 2).

11.1. Efficacy and Pharmacodynamic Assessments

11.1.1. Liver Biopsy, Fibrosis Staging, and Histological Measurement of Nonalcoholic Fatty Liver Disease Activity Score

Liver biopsy with NAS and fibrosis staging will be required. If a clinically evident complication occurs at the time of and/or following liver biopsy, study drug intake may continue or be interrupted at the discretion of the supervising physician.

The NAS is a widely used histological grading system for NAFLD. The NAS was developed by the NASH CRN (Kleiner, 2005) as a tool to measure changes in NAFLD during therapeutic

trials. NAS components are presented in Table 3. The total NAS represents the sum of scores for steatosis, lobular inflammation, and ballooning, and ranges from 0 to 8.

Table 3: NAS Components and Scoring

Item	Score	Extent	Definition and Comment
Steatosis	0	<5%	Refers to amount of surface area involved by steatosis as evaluated on low to medium power.
	1	5%-33%	
	2	>33%-66%	
	3	>66%	
Lobular Inflammation	0	No foci	Acidophil bodies are not included in this assessment, nor is portal inflammation.
	1	<2 foci/200×	
	2	2-4 foci/200×	
	3	>4 foci/200×	
Hepatocyte ballooning	0	None	"Few" means rare but definite ballooned hepatocytes as well as cases that are diagnostically borderline. Most cases with prominent ballooning also had Mallory's hyaline, but Mallory's hyaline is not scored separately for the NAS.
	1	Few balloon cells	
	2	Many cells/ prominent ballooning	

Abbreviations: NAS = Nonalcoholic Fatty Liver Disease Activity Score.
Adapted from The Transplant Pathology Internet Services (TPIS) Histological Scoring System for Nonalcoholic Fatty Liver Disease web page. 2020. Available at: https://tpis.upmc.com/changebody.cfm?url=/tpis/schema/NAFLD2006.jsp

The NASH CRN fibrosis score is determined separately from the NAS according to the scale presented in Table 4.

Table 4: NASH CRN Fibrosis Scoring

Item	Score	Extent	Definition and Comment
Fibrosis	0	None	
	1	Perisinusoidal or periportal	
	1A	Mild, zone 3, perisinusoidal	"delicate" fibrosis
	1B	Moderate, zone 3, perisinusoidal	"dense" fibrosis
	1C	Portal/periportal	This category is included to accommodate cases with portal and/or periportal fibrosis without accompanying pericellular/ perisinusoidal fibrosis
	2	Perisinusoidal and portal/periportal	
	3	Bridging fibrosis	
	4	Cirrhosis	

Abbreviations: NASH CRN = Nonalcoholic Steatohepatitis Clinical Research Network.

11.1.2. Magnetic Resonance Imaging Studies

All imaging studies will be interpreted centrally by a trained image analyst. The analyst will be blinded to the subject's treatment group allocation and will not have access to the subject's clinical and biochemical data. The results of the central imaging interpretation will be used in the analysis of imaging data.

For incidental findings, a radiology assessment of images will also be performed by qualified medical personnel at any imaging site according to clinical routine. Personnel interpreting imaging will also be blinded to the subject's treatment group allocation, and clinical and biochemical data. The assessment will be reported to the Investigator at the referring site, who will review and file the assessment in the subject´s source documents. The subjects will be invited for follow up if there are clinically significant incidental findings, and findings will be evaluated as potential AEs. The incidental finding will not be part of the central imaging.

11.1.2.1. Proton-density Liver Fat Fraction by Magnetic Resonance Imaging

MRI-PDFF is a noninvasive, quantitative, and accurate measure of liver fat content to assess treatment response in early-phase NASH studies (Caussy 2018). Subjects who are randomized will have repeat liver fat content measurements performed in accordance with the time points indicated in the Schedule of Assessments (Figure 1: Study Design

Abbreviations: CAP = controlled attenuation parameter; MRI = magnetic resonance imaging: NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; PDFF = protein density fat fraction; [redacted] PO = orally; QD = once daily.

Table 2). Scans may be repeated if an inconclusive result occurs (e.g., if there is excessive subject movement during the scan). MRI-PDFF will not be performed at selected sites. MRI-PDFF is optional if it presents a logistical or physical hardship to the subject. In addition, MRI-PDFF is not required at Early Termination if a subject has completed less than 22 weeks of study treatment.

11.1.3. Liver Stiffness and Liver Steatosis by FibroScan and Controlled Attenuation Parameter

Subjects will be required to fast for 3 hours before a FibroScan is performed; however, normal volumes of water are allowed.

FibroScan is a specialized ultrasound of the liver, which measures stiffness by transient elastography, a surrogate of liver fibrosis, in units of kPa. Normal results for FibroScan are generally considered to be lower than 6 or 7 kPa. The degree of liver stiffness and with it, fibrosis, will be assessed using FibroScan.

Vibration-controlled transient elastography with controlled attenuation parameter (CAP) is a technology based on the principle of the ultrasonic attenuation of transient elastography depending on the viscosity (fat content) of the liver and the distance of propagation of the ultrasonic signals into the liver, providing a useful method for the quantitative detection of liver fat content. CAP is measured by a FibroScan device in decibels per meter (dB/m) and reflects the decrease in the amplitude of ultrasound signal in the liver. Therefore, a higher CAP is reflective

of a higher degree of steatosis (Zenovia, 2021). A CAP score will be calculated at each time a FibroScan is performed unless the enrolling site does not have the capability to measure CAP.

A FAST score will also be calculated each time FibroScan, CAP, and AST are performed. The FAST score is a FibroScan-based composite score that combines the results of the FibroScan liver stiffness measurement, CAP, and AST (Newsome, 2020).

11.1.4. Digital Pathology

Digital pathology is a novel technology using imaging techniques to objectively and quantitatively assess liver tissue biopsy samples. These optical imaging modalities can be used to accurately stage fibrosis in biopsy specimens, as well as to analyze other histological components of NASH.

11.1.5. Clinical Laboratory Tests

Refer to the Laboratory Manual for details regarding clinical efficacy/pharmacodynamic laboratory sample collection, processing, storage, and shipment.

11.1.5.1. Lipid and Metabolic Panel, Glycosylated Hemoglobin, and Lipoprotein Particle Size

A fasting blood sample for lipid and metabolic panels as well as HbA1c is to be collected. Subjects are to fast overnight for at least 9 hours prior to collection of the fasting sample (water is permissible).

The following parameters are to be determined:

- **Lipid Panel:** LDL-C, vLDL (very low density lipoprotein cholesterol), high density lipoprotein cholesterol (HDL-C), non–HDL-C, total cholesterol, triglycerides, apolipoprotein B (ApoB), and lipoprotein (a) (Lp[a]) particles.
- **Metabolic Panel:** Insulin and non-esterified fatty acid (NEFA). Homeostatic model assessment insulin resistance (HOMA-IR) and adipose tissue insulin resistance index (adipo-IR) are to be calculated from fasting insulin, fasting glucose (see Section 12.1.5), and fasting NEFA, as applicable. An analysis of bile acid will also be performed at Baseline, Week 26, Week 52, and/or at Early Termination.
- **HbA1c**
- **Lipoprotein Particle Size Analysis** by nuclear magnetic resonance (NMR) will be performed for a subset of subjects.

11.1.5.2. NASH/Fibrosis Markers

A blood sample for NASH/fibrosis markers, including cytokeratin-18 (CK-18), ELF (comprising TIMP-1, procollagen III amino-terminal peptide [PIIINP], hyaluronic acid [HA]), PRO-C3, FGF-21, FIB-4, and potentially other markers of fibrosis is to be collected. Instructions regarding the calculation of indices are provided in the Operations Manual.

11.1.5.3. Adiponectin

A blood sample for determination of adiponectin, an insulin-regulating adipose tissue cytokine, is to be collected. Adiponectin concentration in blood samples will be determined using enzyme-linked immunosorbent assay (ELISA).

11.1.6. Alcohol Biomarkers

A sample of whole blood for determination of phosphatidylethanol (PEth) and other biomarkers of alcohol consumption will be collected.

11.1.7. Lipidomic Biomarkers

A blood sample for determination of lipidomic biomarkers including tripalmitin, ceramides, bile acids, diacylglycerols, and other classes of metabolites will be collected. Tripalmitin levels will be analyzed to provide a surrogate readout of palmitate and an indicator of FASN pathway activity. Broad lipidomic profiling will be conducted by mass spectrometry coupled to ultra-high performance liquid chromatography.

11.1.8. Lipoprotein Analyses Substudy

A fasting blood sample for lipoprotein analyses will be collected in a subset of approximately 30 or more participants. Provision of blood samples for the lipoprotein analyses substudy is voluntary.

11.1.9. Metabolic and Microbiome Substudy

A metabolic and microbiome substudy will be performed at a subset of sites.

Stool samples will be collected from participating subjects and used for exploratory analyses of gut microbiome composition during the study. Those subjects will also complete the HepVita Nutritional Survey. This nutritional survey tool uses scientifically validated dietary analysis software that provides the equivalent of 90 days of nutrition tracking in a survey that requires approximately 30 minutes to complete (HepVita web site, 2021).

Provision of stool samples and completion of the nutritional survey for the metabolic and microbiome substudy is voluntary.

11.2. Other Assessments

11.2.1. Genomics

A blood sample for genomics pertaining to NASH will be collected at Baseline, or at any other time after the subject signs the separate consent for this sample, at all sites unless forbidden by local regulations. Subjects will be asked to provide separate written informed consent for the collection of such samples. Genomic analysis will investigate only the presence of SNPs associated with NASH, T2DM, or related diseases. Broad genome analysis will not be performed. The laboratory platform to be used will depend upon advances in the genomic signature of NASH and new developments.

Provision of blood samples for genomic analysis is voluntary.

11.2.2. Sample Collection for Storage

Blood and spot urine samples for storage will be collected. These samples will be stored for the duration of the TVB-2640 clinical development program and used for analysis of additional pharmacodynamic biomarkers relevant to NAFLD and/or NASH when such biomarkers are identified and/or relevant assays are developed.

These samples will not be used for genetic analysis or creation of cell lines. The biomarker assessments performed may include tests to determine the level of certain proteins, RNA, or other disease-related molecules and whether they change after TVB-2640 treatment.

The samples will be coded and de-identified, in the same way all other study samples are coded and de-identified. Every study subject has a unique study number that will be used to track the samples. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

The Sponsor and/or its designee and applicable regulatory authorities will have access to the samples/data if they are ever used for future research.

Provision of blood and spot urine samples for storage is voluntary.

[redacted]

[redacted]

12. ASSESSMENT OF SAFETY

Safety assessments will be conducted in accordance with the time points indicated in the Schedule of Assessments (Figure 1: Study Design

Abbreviations: CAP = controlled attenuation parameter; MRI = magnetic resonance imaging: NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; PDFF = protein density fat fraction; [redacted] PO = orally; QD = once daily.

Table 2).

12.1. Safety Parameters

12.1.1. Vital Signs

Vital signs, including oral temperature, pulse (bpm), systolic and diastolic blood pressure (mm Hg), and respiration rate (breaths/minute), are to be measured and documented in the eCRF. Measurements are to be made after the subject has been resting in a supine position for a minimum of 5 minutes.

12.1.2. Physical Examination and Height

A complete physical examination will be conducted for all subjects at Screening and at the Follow-up visit or Early Termination visit, whichever takes place sooner. The complete physical

examination must include general appearance, and careful examination head/ears/eyes/nose/throat, lungs/chest, heart, abdomen, lymph nodes, musculoskeletal, extremities, skin, and neurological systems. Liver signs (e.g., jaundice, spider angiomata, palmar erythema, hepatomegaly, splenomegaly, asterixis) also are to be assessed.

During Screening, the physical examination is to include measurement of height (cm).

Symptom-directed physical examinations, including assessment of focused liver signs (e.g., jaundice, spider angiomata, palmar erythema, hepatomegaly, splenomegaly, asterixis), skin, and extremities, will be conducted to address any complaints or concerns verbalized by the subject at all other study visits.

If hand-foot symptoms/signs present during the study, or previous hand/foot symptoms/signs increase in severity to a Grade 2 or above, a dermatologist consult should be considered for further evaluation and treatment recommendations.

Any abnormal physical examination finding which, in the Investigator's judgement, is of clinical significance, is to be documented as an AE.

Medical photographic images may be requested to document certain AEs such as hand-foot symptoms/signs or hair thinning. Complete anonymity is impossible, but the minimum possible area of the body should be photographed. Eyes should only be included when absolutely essential. Recognizable tattoos and birthmarks should be avoided in the frame. Identifiable jewelry and name tags should be kept out of the frames. A separate consent will be completed by the subject before any photographs are taken.

12.1.3. Electrocardiograms

Single 12-lead ECGs are to be performed for all subjects.

On Day 1, ECGs are to be performed up to 2 hours before and 4 hours (-1 hour/+ 2 hours) after the first study drug dose [redacted]

For calculated ECG parameters, the following web site should be used:
https://www.mdcalc.com/corrected-qt-interval-qtc#next-steps

12.1.4. Eye Examinations

Eye examinations are to be performed for all subjects by a qualified ophthalmologist or optometrist.

Near and far visual acuity is to be assessed by an ophthalmologist or optometrist using standard measures (e.g., Early Treatment Diabetic Retinopathy Study or similar) in each eye. If the subject wears corrective lenses (e.g., glasses), then visual acuity is to be checked first with corrective lenses and then without correction. A best-corrected examination is not required.

A slit lamp examination (biomicroscopy), including examination of the eyelids, conjunctiva, cornea, anterior chamber, iris, and lens, is to be performed after completion of visual acuity testing for the determination of corneal health.

Eye exams at Week 4, Week 8, Week 13, Week 26, Week 39, Week 52, Week 56 and/or Early Termination are required only if eye-related signs or symptoms are reported by the subject or observed by the investigator.

If a subject experiences a treatment-emergent eye abnormality, an ophthalmologic examination should be performed by a qualified ophthalmologist or optometrist within 24 to 48 hours or on the next business day after symptom onset to evaluate the abnormality.

12.1.5. Safety Laboratory Assessments

Blood and urine samples are to be collected for hematology, clinical chemistry, and urinalysis. The safety laboratory parameters to be measured are presented in Table 5.

Table 5: Safety Laboratory Parameters

Hematology	
Hematocrit	Platelet count
Hemoglobin	White blood cell count with differential
Red blood cell count	Absolute neutrophil count
MCV	MCHC
Coagulation Studies	
Prothrombin time	Fibrinogen
INR	aPTT
Chemistry (Fasting)	
Chloride	Carbon dioxide
Sodium	Potassium
Blood urea nitrogen	Calcium
Creatinine	Magnesium
Albumin	Glucose
Total protein	Alkaline phosphatase
AST*	ALT*
GGT	eGFR (Screening only)
Total, indirect, and direct bilirubin	
Creatine phosphokinase (total and fractionated) (Screening and Baseline only)	
Urinalysis	
Specific gravity	Protein
pH	Ketones
Blood	Microscopic examination of sediment
Glucose	
Other	
Serum or urine β-hCG[ǂ]	

*AST and ALT collected as part of the clinical chemistry panel are also applicable for efficacy assessments.

ǂ Serum β-HCG pregnancy testing is to be performed for female subjects of childbearing potential during Screening, and a urine pregnancy test is to be performed within 24 hours before the first dose on Day 1 (Baseline). Subjects with a positive serum pregnancy test result are not eligible for study participation. Serum pregnancy testing is to be repeated at the Week 56 Follow-up visit or at Early Termination (whichever takes place sooner), and during the study any time pregnancy is suspected. Female subjects of childbearing potential are required to perform urine home pregnancy tests monthly between study visits and the results should be recorded in a subject diary. A positive urine test should be followed by an unscheduled serum pregnancy test as soon as possible. Study drug is to be held in the event of a positive urine pregnancy test and permanently discontinued for any subject with a positive serum pregnancy test result.

Abbreviations: β-HCG = beta human chorionic gonadotropin; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyltransferase; INR = international normalized ratio; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume.

Liver enzyme tests determined as part of the clinical chemistry panel will also be used for the assessment of efficacy endpoints.

Clinical laboratory evaluations are to be repeated as necessary during treatment at a schedule determined by the Investigator, based on the subject's clinical status.

Laboratory abnormalities that are considered by the Investigator to be clinically significant for a particular subject are to be reported as an AE.

Information regarding alcohol and urine drug screening is provided in Section 10.5.

12.1.6. Anthropometric Assessments

Anthropometric assessments are to be performed, including:

- Weight (without shoes or heavy clothing) (kg), with calculation of BMI using Screening height and weight.
- Waist circumference at umbilicus (cm)
- Hip circumference (cm)
- Waist-hip ratio

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

AEs also include the following:

- Complications that occur as a result of a protocol-mandated procedure (e.g., venipuncture, biopsy).
- Any pre-existing condition that increases in severity, or changes in nature during the study or as a consequence of the study treatment.
- Complications and termination of pregnancy (see Section 12.2.6 for additional information).
- Any symptom (e.g., myalgia, fever), physical examination finding, or clinical syndrome (e.g., coryzal illness) that occurs as a result of infection and/or following COVID-19 vaccination and is believed by the Investigator to be linked to the viral infection or immunization. (Further details for EDC update are contained within the EDC completion guidelines.)

An unexpected AE is any event for which the nature or severity is not consistent with the information in the current Investigator's Brochure.

All AEs that occur from Screening (i.e., after the informed consent form [ICF] is signed) through 28 days after the last dose of study drug, whether or not they are related to the study drug, are to be reported in the eCRF.

12.2.1.2. Serious Adverse Event

An AE or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it:

- Results in death.
- Is life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned). Additional exclusions to SAE reporting include hospitalizations for:

Elective procedures that are planned at the time of signing the informed consent.

Social/administrative reasons in the absence of an AE.

Expected deterioration caused by progression of the underlying disease.

- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 28 days following the cessation of treatment, whether or not they are related to the study drug, must be recorded on EDC or paper forms (if applicable) provided by Sagimet Biosciences, or designee.

12.2.2. Adverse Event Assessment

12.2.2.1. Intensity

The intensity of each AE is to be assessed by the Investigator according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (see https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf). If the AE is not included in the NCI CTCAE, then the Investigator is to determine the intensity of the AE according to the following criteria:

Mild (Grade 1):	AE that disappears or is easily tolerated on continuation of study drug.
Moderate (Grade 2):	AE sufficiently discomforting to cause interference with usual work activities.
Severe (Grade 3):	AE that is incapacitating, with inability to work or perform daily activities.
Life-Threatening (Grade 4):	AE that is *potentially* life-threatening.[1]
Death (Grade 5):	Death related to AE.

12.2.2.2. Relationship to Study Drug

The causal relationship of each AE to study drug will be determined by the Investigator according to best medical judgment, as follows:

Definitely related:	This category applies when, after careful medical consideration, there is almost no consideration of other causation.
Probably related:	There is a clinically plausible time sequence between onset of the AE and study drug administration. The AE is unlikely to be caused by a concurrent and/or underlying illness, other drugs, or procedures. If applicable, the AE follows a clinically consistent resolution pattern upon withdrawal of study drug.
Possibly related:	There is a clinically plausible time sequence between onset of the AE and study drug administration, but the AE could also have been caused by the concurrent and/or underlying illness, other drugs, or procedures. Information regarding study drug withdrawal may be lacking or unclear. “Possible” should be used when study drug administration is one of several biologically plausible causes of the AE.

1. If a life-threatening (Grade 4) adverse event is *immediately* life-threatening, the event is, by definition, serious and is to be reported as described in Section 12.2.4.

Unlikely related: The AE is most likely due to a non-study drug-related cause. However, association with the study drug cannot be completely ruled out.

Unrelated: Another cause of the AE is most plausible, and a clinically plausible temporal sequence is inconsistent with the onset of the AE and study drug administration and/or a causal relationship is considered biologically implausible.

If the relationship between the AE/SAE and study drug is determined to be "possible", "probable", or "definite", the event will be considered to be treatment-related for the purposes of expedited regulatory reporting and safety analyses.

12.2.2.3. Seriousness

AEs that meet the criteria specified in Section 12.2.1.2 are to be considered serious.

12.2.3. Recording Adverse Events

Each subject must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each physical examination, observations on the part of study personnel, and spontaneous reports from subjects.

All AEs (serious and non-serious) spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be documented in the subject's source documents and recorded in the eCRF. Any clinically relevant (as determined by the Investigator) deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded in the subject's source documents and in the eCRF.

Information about AEs will be collected from Screening (i.e., after the ICF is signed) through 28 days after the last dose of study drug. The AE term should be recorded in standard medical terminology when possible. Also, when possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For each AE, the Investigator will evaluate and report the onset date, resolution date, intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

12.2.4. Reporting Serious Adverse Events

All SAEs (related and unrelated) occurring from Screening through 28 days after the last study drug dose are to be reported within 24 hours of first awareness on the part of site staff. Any suspected case of pneumonitis considered an adverse events of special interest, should be reported in the same manner as an SAE.

The Investigator must report all SAEs within 24 hours of discovery via the EDC system, which will trigger email notifications to the Syneos Health, Medical Monitor/Safety team. In the event the EDC system is not available, then SAE reports must be emailed [redacted]:

[redacted]

Alternatively, a pdf copy of the SAE report form may be faxed [redacted]

The Investigator must complete and electronically sign and date the SAE pages of the eCRF and verify the accuracy of the information recorded on the SAE pages with the corresponding source documents.

Additional follow-up information, if required or available, should be submitted within the EDC system within 1 business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

Sagimet Biosciences is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of all SAEs that occur at his or her study center. Investigators will also be notified of all unexpected, serious, drug-related events (i.e., all 7- or 15-Day Safety Reports) that occur during the clinical study. Each study center is responsible for notifying its IRB/IEC of these additional SAEs.

Any incident diagnosis of cancer that occurs in a subject taking part in the study, from the time written informed consent is provided until study completion/exit, must be reported as an SAE ('medically important') within 24 hours of first awareness on the part of site staff.

12.2.5. Follow-Up of Adverse Events

The Investigator must continue to follow all treatment-emergent SAEs and non-serious AEs considered to be at least possibly related to study drug either until resolution or the event is clearly determined to be stable or due to a subject's stable or chronic condition or inter-current illness(es). This follow-up may extend after the end of the study.

12.2.6. Pregnancy

Pregnancies occurring in a female subject while the subject is receiving study drug or within 1 month after the subject's last dose of study drug, or in a female partner of a male subject while the subject is receiving study drug or within 3 months after the subject's last dose of study drug will not be considered serious, but are to be reported using the same procedures as for SAEs described in Section 12.2.1.2.

Study drug is to be held in the event of a positive urine pregnancy test and permanently discontinued for any subject with a positive serum pregnancy test result. The subject should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the subject/subject's partner until completion of the pregnancy and must notify the Medical Monitor of the outcome within 5 days. The Investigator will provide this information as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), then the Investigator should report it as such. Furthermore, all neonatal deaths that occur within 28 days of birth should be reported, without

regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the study drug should also be reported.

12.2.7. Overdose of TVB-2640

Signs and symptoms of an overdose should be reported as AEs. Overdoses will not be considered SAEs unless the outcome of the overdose meets seriousness criteria (see Section 12.2.1.2).

12.2.8. Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis and only in the event of an emergency. The Investigator or other physician in attendance in such an emergency must contact the Medical Monitor as soon as possible to discuss the circumstances of the emergency.

The CRO's Medical Monitor, in conjunction with the Investigator, will decide whether the subject should continue to participate in the study. All protocol deviations and reasons for such deviations must be documented in the subject's source records.

13. STATISTICAL CONSIDERATIONS

13.1. Statistical General Considerations

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-design study to evaluate the safety and efficacy of TVB-2640 compared with matching placebo in subjects with NASH.

For "change from Baseline" and "percent change from Baseline" calculations, "Baseline" refers to the last measurement obtained prior to the first administration of study drug. Study Day 1 is the first day of study treatment (TVB-2640 50 mg or placebo). Demographic data (including age, race, ethnicity, sex, height, and weight), medical history, prior treatments, pretreatment clinical characteristics, and other baseline characteristics will be summarized by treatment group and overall.

Descriptive statistics will be displayed by treatment group for all subjects with liver fibrosis stage F2-F3, for all subjects with liver fibrosis stage F1-F3, and for all subjects, as appropriate, to provide an overview of the study results. As appropriate, descriptive statistics will also be displayed by treatment group and by enrollment group. For categorical parameters, the number and percentage of subjects in each category will be presented in data summaries. The denominators for percentages will be based on the number of subjects (n) appropriate for analysis. Continuous variables will generally be summarized based on the following: n, mean, standard deviation, median, minimum, maximum, and standard error of the mean. Categorical data will be summarized using frequency tabulations (number and percentage of subjects).

Demographics and Baseline characteristics (medical histories, physical examinations, and concomitant medications) will be summarized using descriptive statistics for continuous variables and frequency distributions for discrete variables. Study subjects who discontinue the study along with reasons for discontinuation will be summarized and listed. Confidence intervals with be at the 90% and 95% levels. All statistical analyses will be performed using SAS v9.4.

13.2. Efficacy Analysis

13.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects experiencing either a histological improvement at Week 52 in NAS (i.e., ≥2-point improvement in NAS with 1-point improvement in ballooning or inflammation) and without worsening of fibrosis score (by NASH CRN fibrosis score), **OR** resolution of steatohepatitis and no worsening of liver fibrosis (by NASH CRN fibrosis score). Resolution of steatohepatitis is defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis.

Subjects will be eligible for analysis of the primary efficacy endpoint if they have completed at least 42 weeks of treatment and have a posttreatment biopsy.

The principal analysis of the primary efficacy endpoint will be based on the Intention-to-Treat (ITT) analysis set (Section 13.4.2). The treatment groups will be compared based on the primary efficacy endpoint using a one-sided Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratifications T2DM status (yes or no), region (North America or not North

America), and amount of fibrosis (F2 or F3) at the 0.05 significance level (where a higher responder proportion is a better outcome). A Clopper-Pearson 90% and 95% CI will be derived, and the odds ratio (with its 90% and 95% CI, using the control group as a reference group) will be produced to assess the treatment effect magnitude.

Evaluation of the robustness of the principal analysis of the primary efficacy endpoint will be carried out using a logistic regression with response as a dependent variable; treatment group, randomization stratification factors (T2DM status [yes or no], region [North America or not North America], and amount of fibrosis [F2 or F3]) as independent factors; and age as a baseline covariate. Other baseline covariates and other adjustment factors will be prespecified in the statistical analysis plan (SAP). The analysis of the primary efficacy endpoint will be repeated for the modified Intention-to-Treat (mITT) population (Section 13.4.2) to ascertain any changes in the conclusion of the principal analysis findings.

Subgroup analyses of the primary efficacy endpoint will be performed to assess whether the treatment effect is concordant among subgroups. The planned subgroup analyses are based on age category (<40 years, 40 to <65 years, and ≥65 years) and race (White, Black, Asian, and other).

A subject who discontinues treatment prior to Week 42, does not provide a histological assessment on or after Week 42, or who otherwise has missing data will be considered a non-responder.

Further sensitivity analysis of the primary efficacy endpoint will employ multiple imputations for binary data. Pertinent details are included in the SAP.

13.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are:

- Proportion of MRI-PDFF ≥30% responders at Week 26, where an MRI-PDFF ≥30% responder is defined as a subject with ≥8% liver fat content at Baseline who achieves a percent change (relative reduction) from Baseline in MRI-PDFF ≥30%. Treatment groups will be compared based on this secondary efficacy endpoint using an analysis similar to the primary efficacy endpoint.
- Proportion of MRI-PDFF ≥30% responders at Week 52. Treatment groups will be compared based on this secondary efficacy endpoint using an analysis similar to the primary efficacy endpoint.
- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN fibrosis score without worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis) at 52 weeks. Treatment groups will be compared based on this secondary efficacy endpoint using an analysis similar to the primary efficacy endpoint.
- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN score with no increase in any component of NAS at Week 52. Treatment groups will be compared based on this secondary efficacy endpoint using an analysis similar to the primary efficacy endpoint.

- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN score without increase of total NAS score at Week 52. Treatment groups will be compared based on this secondary efficacy endpoint using an analysis similar to the primary efficacy endpoint.
- Proportion of subjects with improvement in liver fibrosis ≥1 stage by NASH CRN score without any worsening of NASH (defined as no worsening of ballooning and lobular inflammation; a 1 grade change in steatosis may be acceptable) at Week 52. Treatment groups will be compared based on this secondary efficacy endpoint using an analysis similar to the primary efficacy endpoint.
- Proportion of subjects experiencing **both** of the following at Week 52:
    - Resolution of steatohepatitis on overall histopathological reading and no worsening of live fibrosis on NASH CRN fibrosis score. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis

    AND

    - Improvement in liver fibrosis greater than or equal to one state (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).

    Treatment groups will be compared based on this secondary efficacy endpoint using an analysis similar to the primary efficacy endpoint.
- Proportion of subjects experiencing **both** of the following at Week 52:
    - Histological improvement at Week 52 in nonalcoholic fatty liver disease (NAFLD) activity score (NAS) (i.e., ≥2 points improvement in NAS with ≥1 point improvement in ballooning or inflammation) and without worsening of fibrosis (by NASH Clinical Research Network [CRN] fibrosis score)

    AND

    - Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).

    Treatment groups will be compared based on this secondary efficacy endpoint using an analysis similar to the primary efficacy endpoint.
- Proportion of subjects experiencing **both** of the following at Week 52:
    - Resolution of steatohepatitis and no worsening of liver fibrosis (by NASH CRN fibrosis score). Resolution of steatohepatitis is defined as absence of fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS of 0 or 1 for inflammation, 0 for ballooning, and any value for steatosis.

    AND

    - Histological improvement at in NAS (≥2 points improvement in NAS).

    Treatment groups will be compared based on this secondary efficacy endpoint using

an analysis similar to the primary efficacy endpoint.

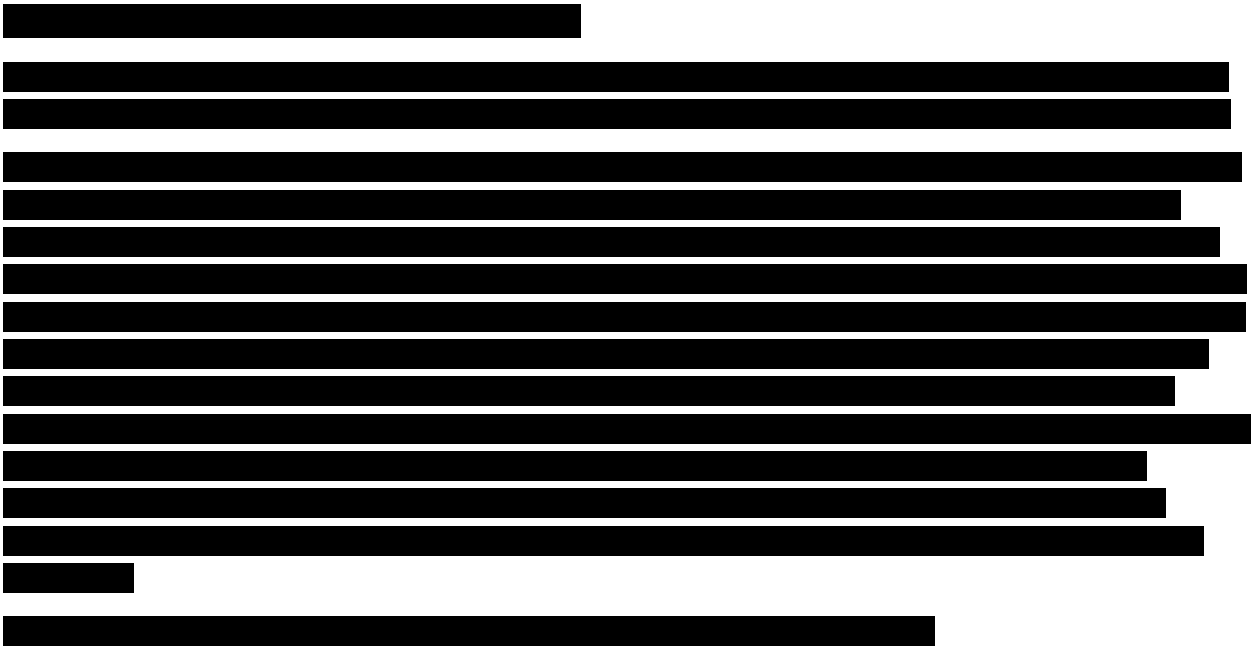
- Proportion of subjects with histological improvement at Week 52 in NAS. Treatment groups will be compared based on this secondary efficacy endpoint using an analysis similar to the primary efficacy endpoint.
- MRI-PDFF percent change and change from Baseline at Week 26. This secondary efficacy endpoint will be compared between treatment groups using a one-sided Wilcoxon rank-sum test. An analysis of covariance (ANCOVA) model will also be used with percent change and change from baseline as the dependent variable; treatment group, T2DM status (yes, no), region (North America, not North America), and amount of fibrosis (F2, F3) as factors; and Baseline as a covariate. Least-squares (LS) means and their differences will be estimated from the ANCOVA model and their corresponding 95% CI will be derived. Inferential statistics will be presented for both the ANCOVA model and the Wilcoxon test. For the continuous secondary endpoints with sufficient postbaseline frequency of measurements, a mixed model repeated measure (MMRM) model will also be employed.
- MRI-PDFF percent change and change from Baseline at Week 52. This secondary endpoint will be analyzed similarly to MRI-PDFF percent change and change from Baseline at Week 26, as described above.
- Proportion of subjects with NASH resolution at 52 weeks. Treatment groups will be compared based on this secondary efficacy endpoint using an analysis similar to the primary efficacy endpoint.
- Change from Baseline in ALT, AST, and GGT at Weeks 26 and 52 and at each study visit. This secondary endpoint will be analyzed similarly to MRI-PDFF percent change and change from Baseline at Week 26, as described above.
- Change from Baseline in LDL-C and other lipid levels at Weeks 26 and 52 and at each study visit. This secondary endpoint will be analyzed similarly to MRI-PDFF percent change and change from Baseline at Week 26, as described above.
- Change from Baseline in collagen/fibrous area and fibrosis score, assessed by digital pathology, at Week 52. This secondary endpoint will be analyzed similarly to MRI-PDFF percent change and change from Baseline at Week 26, as described above.
- Changes from Baseline in metabolic parameters, including fasting insulin, fasting glucose, HOMA-IR, adipo-IR, and HbA1c levels at Weeks 26 and 52 and at each study visit. This secondary endpoint will be analyzed similarly to MRI-PDFF percent change and change from Baseline at Week 26, as described above.
- Change from Baseline in FGF-21, adiponectin, and other NASH biomarker levels at Weeks 26 and 52 and at each study visit. This secondary endpoint will be analyzed similarly to MRI-PDFF percent change and change from Baseline at Week 26, as described above.
- Change from Baseline in FibroScan and CAP score results at Weeks 26 and 52. This secondary endpoint will be analyzed similarly to MRI-PDFF percent change and change from Baseline at Week 26, as described above.

- Change from Baseline in PRO-C3 and other fibrosis biomarkers at Weeks 4, 13, 26, and 52. This secondary endpoint will be analyzed similarly to MRI-PDFF percent change and change from Baseline at Week 26, as described above.
- Change from Baseline in ELF score at Weeks 26 and 52. This secondary endpoint will be analyzed similarly to MRI-PDFF percent change and change from Baseline at Week 26, as described above.

The analysis of the primary and secondary endpoints will be carried out for the ITT analysis set and repeated for the mITT analysis set.

13.2.3. Exploratory Endpoints

Exploratory endpoints will be summarized primarily with descriptive statistics. Select endpoints may be evaluated with statistical tests and/or CIs. Further details on exploratory analyses will be provided in the SAP.



13.3. Safety Analysis

Safety data will be evaluated for the Safety population (Section 13.4.2) on the basis of TEAEs, clinical laboratory assessments, vital signs, ECGs, weight, and physical examinations. Changes from Baseline in key clinical laboratory measurements, vital signs, physical examinations, and weight will be summarized by treatment group using standard descriptive statistics. A TEAE is defined as an AE that was not present prior to treatment with study drug but appeared following treatment or was present at treatment initiation but worsened during treatment. All AEs will be coded by preferred term using the Medical Dictionary for Regulatory Activities (MedDRA; current version) and NCI CTCAE (current version) grading.

TEAE incidence rates will be summarized using frequency and percentage for each treatment group and in total. TEAEs through 30 days after the last dose of study treatment will be

summarized by MedDRA (current version) system organ class and preferred term. AEs will also be summarized by NCI CTCAE grade and by causality (attribution to study treatment, related/not related to investigational medicinal product). Grades 3 and 4 AEs, SAEs, and AEs resulting in dose modification or treatment discontinuation will be summarized by preferred terms. Investigational medicinal product compliance and tolerability ratings will be summarized descriptively for each treatment group.

All safety data will be presented in data listings.

13.4. Statistical and Analytical Methods

13.4.1 Hypothesis Testing

The study primary hypothesis is the (statistical) one-sided superiority of a TVB-2640 50-mg dose over placebo based on the primary efficacy endpoint at the 0.05 significance level, where a higher responder proportion is a better outcome. The statistical analysis (one-sided) test (CMH) of the primary hypothesis is declared if $p<0.05$.

Mathematically, the null and alternative hypotheses for the primary efficacy endpoint are stated as:

Ho: $p_T \leq p_p$

Ha: $p_T > p_p$

Here, p_T is the proportion of responders in the TVB-2640 50-mg treatment group and p_p is the proportion of responders in the placebo treatment group.

Both one-sided and two-sided 0.05 significance level tests will be used for the secondary efficacy endpoints. For each endpoint, the SAP will specify whether the test of significance is one- or two-sided along with the expected direction of effect.

13.4.2 Analysis Sets

13.4.2.1 Intention-to-Treat Population

The principal analysis of the primary and secondary efficacy endpoints will be based on the Intention-to-Treat (ITT) population, which comprises all randomized subjects; this population will serve as the basis for all efficacy analyses. Subjects' data will be analyzed according to their randomized treatment assignment.

13.4.2.2 Modified Intention-to-Treat Populations

Modified Intention-to-Treat (mITT): Comprises all subjects in the ITT population who have completed at least 42 weeks of treatment and have an evaluable posttreatment histological assessment. Interim Analyses Modified Intention-to-Treat Population

Modified Intention-to-treat (IAmITT): Comprises a subset of subjects in the ITT population with 8% >/= MRI-PDFF at screening or at baseline with at least 1 evaluable post-Baseline MRI-PDFF value, defined as an MRI-PDFF assessment obtained at least 22 weeks after the first dose of study drug.

13.4.2.3 Safety Population

The Safety population will consist of all randomized subjects who received at least 1 dose (partial or complete) of study drug. This population will be used for all summaries of subject accountability, demographic and baseline data, and safety information, including AE incidence, clinical laboratory data, ECG data, and vital signs data. Subjects' data will be summarized according to the treatment they received.

13.4.2.4 Pharmacokinetic Population

The PK population will comprise all ITT subjects with available PK measurements.

13.5. Power Considerations and Sample Size Determination

The study is powered to test the one-sided (statistical) superiority hypothesis stipulating that a TVB-2640 50-mg dose provides better benefit than placebo based on the primary efficacy endpoint. The study estimated total sample size is approximately 162 randomized subjects (108 on TVB-2640 and 54 on placebo). The sample size was derived using the normal approximation to the binomial distribution, and the estimated power to detect a difference in the primary efficacy response of 20% (TVB-2640 40% and placebo 20% at Week 52) was at least 80% (one-sided test at the 0.05 significance level). A 2-to-1 randomization allocation was assumed (TVB-2640 to placebo), and an anticipated dropout rate of 18.5% was also applied to estimate the final total sample size (N=162).

13.6. Interim Analysis

A single (secondary endpoint) efficacy interim analysis is planned when approximately 60 subjects with an MRI-PDFF value of ≥8% liver fat at Baseline have completed Week 26 or an Early Termination visit after Week 22. The purpose of the proposed interim analysis is to examine the TVB-2640 benefit over placebo based on a Week 26 secondary efficacy endpoint consisting of "proportion of MRI-PDFF ≥30% responders, where an MRI-PDFF ≥30% responder is defined as a subject with ≥8% liver fat content at Baseline who achieves a percent change (reduction) from Baseline in MRI-PDFF ≥30%."

Interim safety summaries will accompany the interim analyses of the secondary efficacy endpoint.

An interim analysis of the primary efficacy endpoint is not feasible since the primary endpoint is only evaluated at Week 52, and not Week 26. Therefore, a statistical penalty is not envisaged in conjunction with the Week 26 interim analysis of the above-stated secondary endpoint. Interim summaries of safety and selected biomarker data will accompany the interim efficacy analysis of the secondary efficacy endpoint.

13.7. Planned Study Committees

An independent data monitoring committee (IDMC) will be established by charter to provide independent review and assessment of study data and to monitor the overall study conduct in a systematic manner to safeguard the safety of study subjects. Periodic meetings will occur as outlined in the IDMC charter. An interim analysis, which will be reviewed by the IDMC, will be performed when approximately 60 subjects with an MRI-PDFF value of ≥8% liver fat at

Baseline have completed the Week 26 visit or an Early Termination Visit after Week 22. The IDMC will be provided with selected biomarker and safety interim results to allow for a more complete examination of the totality of the data. Upon review of the interim analysis findings, the IDMC may communicate with the Sponsor by making recommendations to the Sponsor to continue, amend, or stop the study based on these interim analysis results. The Sponsor will maintain its blind to any individual treatment assignments.

14. ETHICS

14.1. Good Clinical Practice Compliance

The 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 and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6.

The Investigator also must undertake to perform the study in accordance with ICH GCP Guideline E6 and applicable regulatory requirements and guidelines.

ICH GCP Guideline E6 is available at:
https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

14.2. Institutional Review Board or Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at study centers where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

The final study protocol, including the final version of the informed consent form, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. Written IRB/IEC approval must be received by Sagimet Biosciences or designee before a site can enroll any subject into the study.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol (and other amended study documents) must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulations require. The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sagimet Biosciences will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

To ensure compliance with GCP and all applicable regulatory requirements, Sagimet Biosciences or designee may conduct a quality assurance audit. Please see Section 15.6 for more details regarding the audit process.

14.3. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP, and applicable regulatory requirements.

14.4. Written Informed Consent

The Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of taking part in the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. This process should be recorded in the subject's source documentation.

The subject's signed and dated informed consent must be obtained before conducting any study procedures. Documentation of the consenting process must be recorded in the subject's source documents.

A separate signature documenting informed consent will be required for subjects who provide a blood sample for research regarding genomics pertaining to NASH with fibrosis (Section 11.2.1).

If medical photographs are requested to document an AE (Section 12.1.2), a separate signature documenting informed consent will be required before any photographs are taken.

The Investigator(s) must maintain the original, signed informed consent form(s). A copy of the signed informed consent form must be given to the subject, and this must be documented in the subject's source documents.

14.5. Subject Confidentiality

In order to maintain subject privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15. ADMINISTRATIVE REQUIREMENTS

15.1. Study Monitoring

Monitoring and auditing procedures developed by the Sponsor or designee will be followed, in order to comply with GCP guidelines.

Before a study center can enter a subject into the study, a representative of Sagimet Biosciences or designee will visit the study center to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sagimet Biosciences or its representatives. This will be documented in a Clinical Study Agreement between Sagimet Biosciences and the Investigator.

During the study, a monitor from Sagimet Biosciences or designee will have regular contacts with the study center, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol that data are being accurately recorded in the source documents and eCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Sagimet Biosciences.
- Confirm AEs and SAEs have been properly documented in the eCRFs and confirm any SAEs have been forwarded to the Sponsor or designee, and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.2. Case Report Form Completion

The Sponsor or designee will provide the study centers with eCRFs for each subject.

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a subject is seen for an

examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must electronically sign and date the Investigator's Statement at the end of the eCRF to endorse the recorded data.

15.3. Computerized Systems/Medical Records as Source Data

All study data recorded on source documents are to be transcribed into the eCRFs.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site.

All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based EDC system maintained by Syneos Health. Access to the EDC system is available only to authorized users via the study's internet website, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through use of the EDC system.

eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

15.4. Source Documents

Source documents are considered to be 'all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study'. The Investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IRB/IEC, and regulatory inspections.

The Investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained where necessary.

15.5. Retention of Records

The Investigator will maintain all study records according to ICH GCP and applicable regulatory requirement(s). Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, and at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s).

If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept that responsibility. The Sponsor must be notified immediately by telephone or e-mail and the notification confirmed in writing if a custodial change occurs.

15.6. Audits and Inspections

Authorized representatives of Sagimet Biosciences or designee, a regulatory authority, or IRB/IEC may visit the study center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP, and any applicable regulatory requirements.

The Investigator should contact Sagimet Biosciences or designee immediately if contacted by a regulatory agency about an inspection.

15.7. [redacted]

[redacted]

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APPENDIX A. ALGORITHM FOR EVALUATING SUBJECTS FOR POTENTIAL DRUG-INDUCED LIVER INJURY

During the study, aminotransferase elevations are to be managed as follows:

1. Isolated aminotransferase elevation (i.e., total bilirubin - normal):

ALT or AST	Event during the study	Action
Baseline ALT and AST within normal range	Increase ≥5 × ULN	Repeat liver profile (AST, ALT, bilirubin) and PT/INR within 2 to 3 business days from the date results are received for review. Monitor the subject as per "close observation" definition* in the DILI guidance.
ALT or AST above normal range at Baseline	Increase ≥3 × Baseline result, but no liver related symptoms (e.g., anorexia, nausea, vomiting, right upper quadrant pain, pruritus, cholestasis)	
ALT or AST above normal range at Baseline	Increase ≥3x Baseline result, and subject experiences liver- related symptoms (e.g., anorexia, nausea, vomiting, right upper quadrant pain, pruritus, cholestasis)	Interrupt study drug for at least 15 days. Initiate potential DILI evaluation for alternative etiologies, and repeat liver profile and PT/INR within 2 to 3 business days from the date results are received for review, and place subject under "close observation" as defined in the DILI guidance.

Abbreviations: ALP = alkaline phosphatase: ALT = alanine aminotransferase; AST = aspartate aminotransferase: DILI = drug-induced liver injury; GGT = gamma-glutamyltransferase; INR = international normalized ratio; PT = prothrombin time; ULN = upper limit of normal.
*Close observation as defined in the FDA DILI guidance (i.e., laboratory testing and physical examination 2 to 3 times per week. Study drug is to be restarted only if a firm alternative etiology is "identified" and the liver tests return to 'baseline' levels).

Note the following:

The 'baseline' result for any laboratory parameter is the average of the Screening visit result, the Day 1 visit result and any unscheduled visit that occurred during the Screening period.'

Study drug interruption refers to cessation of study drug intake, but with the possibility that intake may re-start at a later date if certain requirements described in this appendix are confirmed.

Conversely, study drug discontinuation refers to cessation of study drug intake and without the possibility that intake may restart at a later date. However, such a subject should remain in the study, continue to undergo 'close observation' where required, and other scheduled study assessments.

If a subject sustains a liver test elevation but remains eligible to continue study drug intake in parallel with 'close observation', and 'close observation' is not possible then study drug intake should be interrupted until it is possible for the subject to undergo further assessment.

Close observation as defined in the FDA DILI guidance i.e., laboratory testing and physical examination 2 to 3 times per week. Study drug is to be restarted only if a firm alternative etiology is "identified" and the liver tests return to 'baseline' levels.

2. Elevation of aminotransferase and total bilirubin or cholestatic liver test markers:

Analyte	Event during the study	Action
TB + AST or ALT	↑ TB >2 mg/dL and ↑ ALT or ALT ≥3 × Baseline or 5 × ULN (whichever comes first)	Interrupt study drug for at least 15 days. Initiate potential DILI evaluation for alternative etiologies. Repeat liver profile and PT/INR within 2 to 3 business days from the date results are received for review, and place subject under "close observation" as defined in the DILI guidance. Study drug can be re-started only if a firm competing etiology is identified and the liver tests return to Baseline levels.
TB, ALP, or GGT	↑ TB >2 mg/dL and ALP or GGT ↑ >2 × ULN	
TB OR INR + symptoms (regardless of any magnitude AST/ALT elevation)	Elevation ↑ TB >2 mg/dL OR INR ≥1.5 and Indicators of immunological reaction (i.e., rash or >5% eosinophilia), or appearance of liver-related symptoms, e.g., anorexia, nausea, vomiting, right upper quadrant pain, pruritus, cholestasis.	Permanently discontinue study drug. Initiate potential DILI evaluation for alternative etiologies. Repeat liver profile and PT/INR within 2 to 3 business days from the date results were received for review, and place subject under "close observation" as defined in the DILI guidance.

Abbreviations: ALP = alkaline phosphatase: ALT = alanine aminotransferase; AST = aspartate aminotransferase: DILI = drug-induced liver injury; GGT = gamma-glutamyltransferase; INR = international normalized ratio; PT = prothrombin time; TB = total bilirubin; ULN = upper limit of normal.

Note the following:

If a subject lives in a remote area, they can be tested using a local ('non-central') laboratory, with the results communicated to the Investigator promptly.

For subjects with Gilbert's syndrome, a doubling of direct bilirubin concentration instead of total bilirubin concentration should be used for close monitoring and TVB-2640 discontinuation.

If either of the following criteria are met, study drug must be discontinued and the subject must be followed until the clinical and laboratory abnormalities stabilize or normalize:

- In the presence of total bilirubin elevation (>2 × ULN or >1.5 × Baseline level); with any degree of aminotransferase elevation; AND if there is appearance of symptoms i.e., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- If any total bilirubin, ALT, or AST elevation above the subject's Baseline result recurs following rechallenge with study drug.