A Pilot Study to Treat Adults with Non-Alcoholic Steatohepatitis with Oral Idebenone

Study Protocol and Statistical Analysis Plan

NCT04669158

September 15, 2021

6. PROTOCOL

Title: A Pilot Study to treat adults with Non-Alcoholic Steatohepatitis with oral Idebenone

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Study Product: Idebenone (2-(10-hydroxydecyl)-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione)

Protocol Date: January 7, 2021
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IND Number: [redacted]

Protocol Synopsis

Protocol Title	A Pilot Study to treat adults with Non-Alcoholic Steatohepatitis with oral Idebenone
Product	Idebenone (2-(10-hydroxydecyl)-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione)
Objective	To evaluate the safety and tolerability of oral idebenone in adults with non-alcoholic steatohepatitis (NASH)
Secondary Objective(s)	To explore the efficacy of oral idebenone in NASH patients, a) by assessing serum liver chemistries, and b) improvement in liver stiffness as assessed by MRE.
Study Design	Randomized, Double-blinded, prospective pilot study
Study Population	Adults of 18 years of age or older diagnosed with NASH Clinical Research Network NAFLD activity score (NAS) (NAS score >4, and/or fibrosis stage 1-3)
Number of Participants	45, 1:2 randomization
Duration of Participation	~18 months Screening period: 1-4 weeks; Treatment period: 48 weeks; Post treatment monitoring period; 12 weeks (to monitor for adverse events and liver tests)
Study Center	Stanford Medical Center, and affiliated hepatology clinics.
Dose Schedule	Idebenone, initially 200mg by mouth (P.O.) once a day for 2 weeks, then 200 mg twice a day for 2 weeks, then 3 times per day for the remainder of the study. If we observe no toxicity, we will continue with these doses for the treatment period.
Reference Therapy	The drug will be tested against placebo, that follows the same dosing/schedule, as above.
Biomarkers Schedule	Hepatic enzymes, CBC, serum metabolic panel: at 0, 2, 4, 6, 12, 24, 36, and 48 weeks during treatment period and at 4, and 12 weeks after the last dose Serum idebenone metabolite studies at 4, 24 and 48 weeks. Magnetic resonance elastography (MRE): at the time of enrollment, and at the time of completion at 48 weeks. FIB4 to assess fibrosis at 24w. (serum test) Serum peripheral mononuclear blood cells (PMBCs) at the 24 and 48 week blood draw will be collected to study target engagement.
Statistical Methodology	The study has sufficient sample size to provide preliminary safety profile and secondary outcome measures. This is based on the two group t-test for fold change assuming log-normal distribution (unequal n's) to detect 1.5 kPa decrease in stiffness in the treatment group at the 0.05 level (2-sided) with 83% power.

Estimated start: April 2021
Estimated finish: December 2022 (includes 6 months observation period post study).

6.1. Study Protocol

BACKGROUND

Nonalcoholic Steatohepatitis (NASH): NAFLD is characterized by the accumulation of fat droplets (steatosis) in the liver and is highly prevalent in the USA (24%) (1). Steatosis when accompanied by inflammation and fibrosis can lead to NASH, the more progressive form of the disease, that eventually culminates in cirrhosis and/or hepatocellular carcinoma (2). The rate of NASH doubled between 2005 and 2010, and soon NASH will be the most common cause of liver transplantation in the USA and worldwide (3). Currently, there is no FDA-approved medical therapy for NASH. Obesity and type 2 diabetes mellitus (T2DM) are associated with more advanced stages of the disease and faster progression (4). Increased production of reactive oxidant species (ROS) is an early feature of NASH and is directly linked to fibrogenesis (5). Of the ROS-generating enzymes in the liver, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs) emerged as major sources, and are implicated in the production of high levels of ROS during fibrogenesis (6-8).

NADPH oxidase (NOX) and Src homology 2 domain containing collagen-related proteins (Shc): NOX family proteins transfer electrons donated by NADPH across biological membranes to form superoxide (O^{-}_{2}) (9). Our group has previously shown that NADPH oxidases (NOXs) are central sources of ROS in the liver (4). Hepatocytes, hepatic stellate cells (HSC) and macrophages express the phagocytic NOX2 ($gp91^{phox}$) (22). During activation of NOX2, the regulatory subunit $p47^{phox}$ coordinates membrane translocation of the other subunits, assembling the active oxidase, and catalyzing the formation of superoxide (10). Our group has identified for the first time that Src homology 2 domain containing collagen-related proteins (Shc) are able to bind to and activate NOX2, resulting in an oxidative burst (11). Shc is encoded by SHC1 gene and has three isoforms, p46Shc, p52Shc and p66Shc (12). The association between p52 Shc and NOX2 provides a strong rationale for targeted treatment with idebenone that inhibits Shc and its association with NOX2, therefore preventing oxidative bursts. (The results have been discussed in detail in this IND, section. 3.4).

Idebenone: Idebenone was originally developed in 1985 Takeda Company Ltd. as a potent antioxidant for the treatment of Alzheimer's disease (13). Idebenone has been approved in Europe for the treatment of Leber's hereditary optic neuropathy (LHON), an inherited disease characterized by progressive loss of sight in children and adolescence of 12 years and older (EMA/452944/2015, EMEA/H/C/003834).
Idebenone's anti-oxidant activity is linked to regulating NAD(P)H:quinone oxidoreductase-1 (NQO1). Additionally, it can induce generation of adenosine triphosphate (ATP) in the mitochondria by cytoplasmic-mitochondrial electron transfer to complex III, and reduce liver free fatty acids (FFAs) by acting as peroxisome proliferator-activated receptor alpha (PPAR-α) agonist, which in turn induces free fatty acid (FFA) β-oxidation. Our group has proven its ability to inhibit p52Shc, and this mechanism is the target of this application. Through inhibition of p52Shc, as described above, idebenone inhibits the activation of NOX2, and therefore reduces oxidative stress in the liver. This in turn reduces inflammation and fibrosis in patients with NASH. Idebenone also improves insulin signaling and lipid peroxidation in mouse livers

(Pharmacology is discussed in detail in the PD/PK section of this IND application) (11, 14).

Idebenone has been extensively studied as a potential therapeutic agent for neurological diseases, including Alzheimer's disease, Huntington's disease, Friedrich's ataxia (FRDA) and multi-infarct dementia. In these clinical trials, different doses and regimens were employed, and in all of them idebenone was found to be safe and well tolerated. In phase I trials and dose escalation trials, no dose-limiting toxicity was observed up to the maximum dose tested (75 mg/kg) (18). In a double-blinded, placebo-controlled trial in patients with Huntington's disease, 100 patients were randomized to receive 90mg idebenone or placebo three times every day for 12 months. Ninety-one patients completed the study, and none of the patients left the trial due to adverse events attributed to idebenone (19). Data from the phase 2 and 3 clinical trials for Alzheimer's disease, in which patients received 120mg, 240mg, or 360mg idebenone three times per day for up to 2 years, suggest a benign toxicity profile (20). The most frequently cited adverse effects that occurred in the idebenone group were gastrointestinal symptoms such as anorexia, nausea and diarrhea.
Idebenone demonstrated rapid absorption in the species tested (rat, mouse and dog). After a single dose, 91% was found to be absorbed in rats and 62% in dogs, with t-max occurring within 1 hour. However, due to a high first pass metabolism, less than 1% of parent idebenone reaches the systemic circulation. The terminal half-lives of total radioactivity in the plasma of rats and dogs after oral administration of [14C] idebenone were 4.5 and 15.4 hrs, respectively. As idebenone has high first pass metabolism rate we opted for lower doses that are likely to have local hepatic effects. Also, this will further diminish the possibility of systemic affects.

HYPOTHESIS

The overarching hypothesis is that idebenone is a well-tolerated and safe treatment in patients with NASH. This Phase 1/2a study will provide the safety and tolerability data necessary to further advance the development of this therapeutic strategy. We will collect serum biomarker and liver stiffness data that will help in gauging its efficacy.

STUDY OBJECTIVES

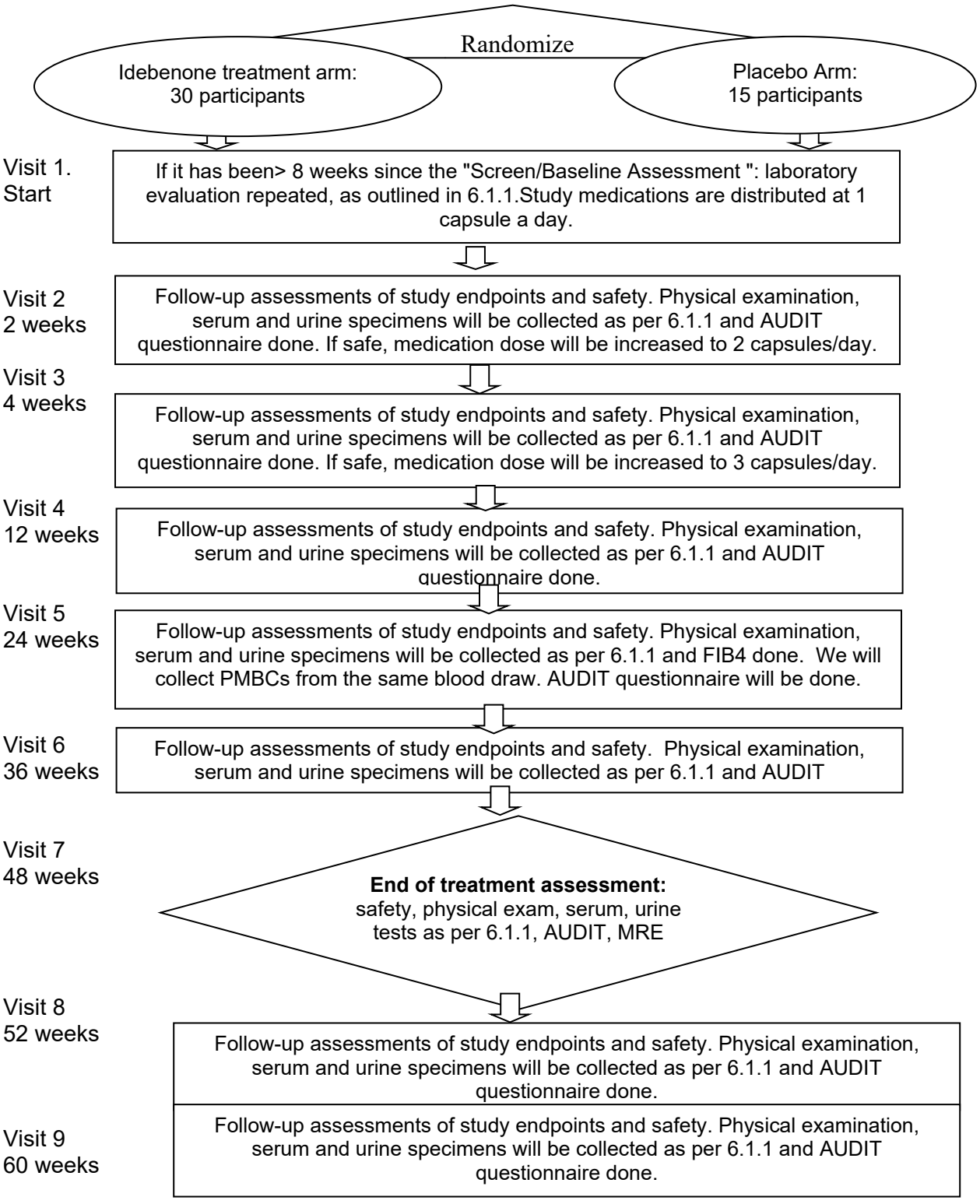
Primary objective: To assess the safety and efficacy of idebenone in adults with NASH.
Secondary objectives: To evaluate changes in biomarkers of disease progression and liver stiffness in adults treated with Idebenone for 48 weeks compared to placebo:

- Serum aminotransferases, and GGT levels
- Fasting markers of insulin resistance (HOMA)
- Lipid profile (triglycerides, HDL, LDL)
- Liver stiffness, using MRE. Will include MR-PDFF as well, to evaluate steatosis.
- Idebenone Metabolites in NASH patients

Protocol Design Schema

Prior to Enrollment

Total number of participants-45: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain full history, document. Obtain laboratory tests, and MRE as outlined in detail in Section 6.1.1.


Randomize
Idebenone treatment arm:
30 participants
Placebo Arm:
15 participants
Visit 1.
Start
If it has been> 8 weeks since the "Screen/Baseline Assessment ": laboratory evaluation repeated, as outlined in 6.1.1.Study medications are distributed at 1 capsule a day.
Visit 2
2 weeks
Follow-up assessments of study endpoints and safety. Physical examination, serum and urine specimens will be collected as per 6.1.1 and AUDIT questionnaire done. If safe, medication dose will be increased to 2 capsules/day.
Visit 3
4 weeks
Follow-up assessments of study endpoints and safety. Physical examination, serum and urine specimens will be collected as per 6.1.1 and AUDIT questionnaire done. If safe, medication dose will be increased to 3 capsules/day.
Visit 4
12 weeks
Follow-up assessments of study endpoints and safety. Physical examination, serum and urine specimens will be collected as per 6.1.1 and AUDIT questionnaire done.
Visit 5
24 weeks
Follow-up assessments of study endpoints and safety. Physical examination, serum and urine specimens will be collected as per 6.1.1 and FIB4 done. We will collect PMBCs from the same blood draw. AUDIT questionnaire will be done.
Visit 6
36 weeks
Follow-up assessments of study endpoints and safety. Physical examination, serum and urine specimens will be collected as per 6.1.1 and AUDIT
Visit 7
48 weeks
End of treatment assessment:
safety, physical exam, serum, urine tests as per 6.1.1, AUDIT, MRE
Visit 8
52 weeks
Follow-up assessments of study endpoints and safety. Physical examination, serum and urine specimens will be collected as per 6.1.1 and AUDIT questionnaire done.
Visit 9
60 weeks
Follow-up assessments of study endpoints and safety. Physical examination, serum and urine specimens will be collected as per 6.1.1 and AUDIT questionnaire done.

Study Design:

This is a prospective phase 1/2a, randomized, double-blinded, placebo-controlled, single center study of safety and efficacy of oral idebenone in adults 18 years of age or older with non-alcoholic steatohepatitis (NASH). Following IRB approval and written informed consent, 45 participants will be enrolled in the study and randomized at a 1:2 ratio on REDCap data capturing software. Participants will be randomized to two groups and receive the following capsules: placebo, idebenone at escalating doses of 200mg by mouth (P.O.) once a day for 2 weeks, then 200 mg twice a day for 2 weeks, then 3 times per day for the remainder of the study (up to 48 weeks). Monitoring and safety evaluation will continue for 12 weeks after the final dose.

Study Population, Subject Selection, and Withdrawal

Male or non-pregnant female patients ≥ 18 years of age with non-alcoholic steatohepatitis and who meet all the eligibility criteria will be enrolled and randomized to 2 arms (placebo, and idebenone). There will be a total of 45 patients enrolled in the study, with 1:2 randomization (15 placebo, 30 patients on idebenone). Inclusion and exclusion will be evaluated and confirmed with the PI, or other clinicians on the delegation (DOA) log.

Inclusion Criteria:

1) Male or non-pregnant/ non-lactating women ≥ 18 years of age
2) Diagnosis of NASH: NASH Clinical Research Network (CRN) NAFLD activity score (NAS) of 4 or greater with a score of 1 for each of the following (steatosis scored 0-3, lobular inflammation scored 0-3, ballooning scored 0-2) on biopsies:
    - Steatosis
    - Lobular inflammation
    - Hepatocyte ballooning
3) Fibrosis F1-3, on liver biopsy or MRE or Fibroscan; within 6 months of enrollment, with MELD<10
4) Women of childbearing potential must agree to at least two methods of contraception, and males must agree to practice birth control during the study and up to 30 days after the last dose of idebenone.
5) Will not participate in any other clinical trial for the duration of the study
6) Will not consume alcohol for the duration of the study
7) If on vitamin E or pioglitazone prior to the study, will have been on stable therapies for 6-12 months prior to enrolment

Exclusion Criteria:

1) Presence of any other form of liver disease, including viral hepatitis, autoimmune hepatitis, alcoholic liver disease, genetic causes of chronic liver disease)
2) ALT>300 U/l
3) Total serum bilirubin ≥ to 1.3 mg/dL (Gilbert's Syndrome patients excepted)
4) International Normalized Ratio (INR) ≥ 1.3
5) MELD>10
6) Serum creatinine >2.0mg/dl and/or GFR < 50 ml/min/1.73m^2
7) Known alcohol abuse or alcohol use disorder (AUDIT profile and/or pos. urine ethylglucuronide):

- >20 g/day for women
- >30 g/day for men

8) Active substance abuse
9) Any medical condition that prevents MRE, MR-PDFF
10) Platelet count ≤150,000//mm^3
11) Cirrhosis
12) Hemoglobin <11 g/dl in females or <12 g/dl in males
13) Presence/history of HCC
14) History of liver transplantation
15) History of bariatric surgery
16) History of inflammatory bowel disease
17) History of cardiovascular disease, long QT syndrome.
18) Subjects who have participated in investigational drug trials and took any investigational drugs within 60 days prior to the first dose of idebenone.
19) Any concerns regarding being able to consent or compliance by enrolling physician

Recruitment and Screening:

Potential subjects will be identified by the investigators at hepatology clinics at Stanford University. A member of the research team (clinical research coordinator) will initiate the consenting process for those who meet eligibility criteria. Consenting will be done by the investigator or sub-investigator medical licensed doctors.

Early Withdrawal and Replacement:

Participants who do not adhere to protocol requirements (early drop-out, non-adherence or other non-safety related issue) will be removed from the study and replaced. Participants who are removed for drug-related severe adverse events or meet exclusion criteria during the study will not be replaced. Patients who progress to cirrhosis during the 48 weeks of the study will be taken off of the treatment protocol (Idebenone or placebo) and replaced. However, we will continue to follow outcomes for these patients throughout the course of the study. During consenting process, participants will be informed about their right to withdraw from the study at any time. The investigators will schedule an Early Termination and Follow-up Visits.

Data Collection and Early Withdrawal Visits:

Even though subjects may be withdrawn prematurely from the study, follow-up safety data will be collected during the follow-up period.

- Physical exam: Vital signs (blood pressure, pulse, O2 saturation on RA),
- Laboratory Tests: CBC with differential, INR, ALT, AST, Alkaline phosphatase, Total bilirubin, Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, Albumin, Total cholesterol.

Other Permitted Treatments

Participants may continue standard therapy including other treatment for other co-morbidities e.g. T2DM. All participants will receive the study drug in addition to the other drugs for standard of care, and will be asked to maintain the same doses of medications if clinically stable and warranted.

STUDY DRUG

Treatment Regimen

Idebenone capsules will be given at 200 mg by mouth (P.O.) once a day for 2 weeks, then 200 mg twice a day for 2 weeks, then 3 times per day for the remainder of the study. If we observe no toxicity, we will continue with these doses for the treatment period. The dosing of the placebo will follow the same time course. Capsules will be taken preferably with food for 48 weeks, as absorption and bioavailability are improved with food intake. Clinical visits have been added 2 weeks after each dose increase to assess for adverse reactions and clinical assessment (at 2weeks, 4weeks, and 6 weeks post-initial dose). Dose de-escalation e.g. from the 200 mg three times a day to 200 mg two times a day dosing will be permitted if side effects e.g. gastrointestinal symptoms are noted. Once de-escalated subjects will continue on that dose for the remainder of time.

Adherence to the Study Protocol and Medication

Participant's compliance will be monitored by follow-up phone calls performed by qualified research personnel. These follow-ups will be done every 2 weeks for the first 24 weeks and every 4 weeks for the rest of the study (except when the times and follow-up phone calls fall on the same day as follow-up visits).

Rationale for Dose Selection

The currently approved dose for idebenone in Europe is 300 mg three times a day. Since idebenone is extensively metabolized in the liver, local therapeutic levels could be reached at a lower dosing. Therefore, we will study idebenone at a maximum dose of 200 mg three times a day. Idebenone has an excellent safety profile that has been studied in multiple trials at dosages up to 2250 mg a day.

Rationale for study length:

Our rationale is treating patients for 48 weeks is that we are looking at fibrosis as an outcome, and shorter time frames, e.g. 24 weeks are insufficient to address this. Most clinical trials addressing NASH fibrosis are at least of 48 weeks duration. While other outcomes, e.g. necroinflammation is possible to assess after shorter duration of treatment (e.g. 24 weeks), fibrosis has not showed a significant signal only after 24 weeks of treatment. Nevertheless, we will assess fibrosis by FIB4 at 24 weeks.

Receiving, Storage, Dispensing and Returning of Study Drug

The study drug will be provided by HBC Health Solutions in ready-to-use form, and will be stored at Stanford's investigational clinical pharmacy. The placebo was manufactured and provided by Bravado Pharmaceuticals. Upon receipt of the of the study drug, an inventory will be performed, and a receipt log will be filled out and signed by the person accepting the shipment. Designated study staff will count and verify all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or placebo) will be documented in the study files. Labeling and dispensing will be performed at Stanford's investigational clinical pharmacy.

Idebenone (and placebo) capsules will be stored at controlled room temperature (15C-30°C) protected from light and humidity, and will be continuously recorded in the temperature log.

6.1.1. STUDY PROCEDURE

Participants will be recruited from Stanford Hospital Liver Clinics. Research coordinators will primarily evaluate patients with NASH for eligibility. Patients who received a liver biopsy as per standard of care in the previous 6 months, will be informed and those who are willing to participate in the study will be consented by the investigators. After consenting, participants will be randomized.

Screen/Baseline assessment (t= -1 to -6 weeks)

Prior to enrollment each participant will undergo medical screen and be introduced to study procedures. This will be performed concurrently with the patient's clinic visit. If the patient qualifies, the following assessment will be done:

- Prior to any study-related protocols, informed consent is obtained
- Procedures as per standard medical care:
    - Full medical history
    - Complete physical examination including height/weight, waist and hip circumference, blood pressure, heart rate, O_2 saturation
    - Baseline laboratory tests: CBC with differential, Liver tests: ALT, AST, Total bilirubin, Alkaline phosphatase, GGT; Comprehensive metabolic panel (fasting): Sodium, Potassium, Bicarbonate, Creatinine, BUN, Ca++, Phosphate, Albumin Glucose, Insulin, Glycosylated hemoglobin, HOMA-IR, ANA, anti-smooth muscle antibody, AMA, ceruloplasmin, α1-antitrypsin, ferritin; Lipid panel (fasting): Total cholesterol, LDL, HDL, Triglyceride; Coagulation studies: PT, INR
    - Calculation of MELD score
- Additional studies as part of the protocol:
    - serum pregnancy test
    - AUDIT screen and urinary ethylglucuronide
    - MRE imaging will be obtained and will be used to analyze shear stiffness at different areas. Cross-sectional images will represent the stiffness generated from wave propagation data and analysis. Co-localized regions of interests will be established to allow detection of longitudinal changes. We will also include PDFF mode to assess steatosis.

Main Treatment Period (t=0)

After it has been determined that the participant satisfies all eligibility criteria based on assessments at the Screen/Baseline Visit, the participant will be enrolled. The participant will receive study drug by one of two options: 1) The patient will return to Stanford Clinic to pick up study drug or 2) the study drug will be mailed to participant. The patient will be instructed to start the study drug or placebo, and the day that the study medication is started will be t = 0.

Participants will be encouraged to take the medication with food, as bioavailability and absorption are improved with food intake. The treatment period should start within 6 weeks from study enrollment. If it has been> 8 weeks since the "Screen/Baseline Assessment Visit", any changes in health should be re-assessed and laboratory evaluation repeated (CBC with differential, Na+, K+, Cl-, CO2, glucose, serum creatinine, BUN, Ca++, Phosphorus, total bilirubin, AST, ALT, GGT, Alkaline phosphatase, total bilirubin, albumin,).

Interim Clinic Visits During Treatment Period

At these visits the following will occur:

Visit at 2 weeks (+/- 4 days):

- Monitor for adverse events and assess adherence to the study medication.
- Physical examination including height/weight, waist and hip circumference, blood pressure, heart rate, O_2 saturation
    - Laboratory tests: CBC with differential, Liver tests: ALT, AST, Total bilirubin, Alkaline phosphatase, GGT; Comprehensive metabolic panel (fasting): Sodium, Potassium, Bicarbonate, Creatinine, BUN, Ca++, Phosphate, Albumin Glucose, Coagulation studies: PT, INR
    - Calculation of MELD score
    - AUDIT screen and urinary ethylglucuronide

Visit at 4 weeks (+/- 4 days) :

- Monitor for adverse events and assess adherence to the study medication.
- Physical examination including height/weight, waist and hip circumference, blood pressure, heart rate, O_2 saturation
    - Laboratory tests: CBC with differential, Liver tests: ALT, AST, Total bilirubin, Alkaline phosphatase, GGT; Comprehensive metabolic panel (fasting): Sodium, Potassium, Bicarbonate, Creatinine, BUN, Ca++, Phosphate, Albumin Glucose, Coagulation studies: PT, INR
    - Calculation of MELD score
    - Serum Idebenone Metabolite Studies (5 cc blood per patient)AUDIT screen and urinary ethylglucuronide

Visit at 6 weeks (+/- 4 days):

- Monitor for adverse events and assess adherence to the study medication.
- Physical examination including height/weight, waist and hip circumference, blood pressure, heart rate, O_2 saturation
    - Laboratory tests: CBC with differential, Liver tests: ALT, AST, Total bilirubin, Alkaline phosphatase, GGT; Comprehensive metabolic panel (fasting): Sodium, Potassium, Bicarbonate, Creatinine, BUN, Ca++, Phosphate, Albumin Glucose, Coagulation studies: PT, INR
    - Calculation of MELD score
    - AUDIT screen and urinary ethylglucuronide

Visit at 12 weeks(+/- 7 days):

- Monitor for adverse events and assess adherence to the study medication.
- Physical examination including height/weight, waist and hip circumference, blood pressure, heart rate, O_2 saturation
    - Laboratory tests: CBC with differential, Liver tests: ALT, AST, Total bilirubin, Alkaline phosphatase, GGT; Comprehensive metabolic panel (fasting): Sodium, Potassium, Bicarbonate, Creatinine, BUN, Ca++, Phosphate, Albumin Glucose, Insulin, Glycosylated hemoglobin, HOMA-IR, Coagulation studies: PT, INR
    - Lipid screen
    - Calculation of MELD score
    - AUDIT screen and urinary ethylglucuronide

Visit at 24 weeks(+/- 7 days):

- Monitor for adverse events and assess adherence to the study medication.
- Physical examination including height/weight, waist and hip circumference, blood pressure, heart rate, O_2 saturation
    - Laboratory tests: CBC with differential, Liver tests: ALT, AST, Total bilirubin, Alkaline phosphatase, GGT; Comprehensive metabolic panel (fasting): Sodium, Potassium, Bicarbonate, Creatinine, BUN, Ca++, Phosphate, Albumin Glucose, Insulin, Glycosylated hemoglobin, HOMA-IR, Coagulation studies: PT, INR
    - Calculation of MELD score
    - Collect PMBCs from peripheral blood draw, as above (5 cc blood/patient) to assess target engagement (decrease in Shc phosphorylation).
    - Idebenone Metabolite Studies (serum)
    - FIB-4 measurement for Interim analysis of fibrosis
    - AUDIT screen and urinary ethylglucuronide

Visit at 36 weeks(+/- 7 days):

- Monitor for adverse events and assess adherence to the study medication.
- Physical examination including height/weight, waist and hip circumference, blood pressure, heart rate, O_2 saturation
    - Laboratory tests: CBC with differential, Liver tests: ALT, AST, Total bilirubin, Alkaline phosphatase, GGT; Comprehensive metabolic panel (fasting): Sodium, Potassium, Bicarbonate, Creatinine, BUN, Ca++, Phosphate, Albumin Glucose, Insulin, Glycosylated hemoglobin, HOMA-IR, Coagulation studies: PT, INR
    - Calculation of MELD score
    - AUDIT screen and urinary ethylglucuronide

Visit at 48 weeks(+/- 7 days):

- Monitor for adverse events and assess adherence to the study medication.

- Physical examination including height/weight, waist and hip circumference, blood pressure, heart rate, O_2 saturation
    - Laboratory tests: CBC with differential, Liver tests: ALT, AST, Total bilirubin, Alkaline phosphatase, GGT; Comprehensive metabolic panel (fasting): Sodium, Potassium, Bicarbonate, Creatinine, BUN, Ca++, Phosphate, Albumin Glucose, Insulin, Glycosylated hemoglobin, HOMA-IR, Coagulation studies: PT, INR, lipid screen
    - Calculation of MELD score
    - Collect PMBCs from peripheral blood draw, as above (5 cc blood/patient) to assess target engagement (decrease in Shc phosphorylation).
    - Idebenone Metabolite Studies (serum)
    - MRE imaging will be obtained and will be used to analyze shear stiffness at different areas, following treatment. PDFF mode to assess steatosis.
    - AUDIT screen and urinary ethylglucuronide
    -

Telephone Contact During Treatment Period Follow-up telephone contact is done every 2 weeks (+/- 7 days) for the first 24 weeks and every 4 weeks(+/- 7 days) for the rest of the study. Study personnel will document any AEs, changes in health, study drug adherence, protocol deviations, etc. based on the phone call. The timing of telephone contact can occur within ± 7 days of scheduled time period.

Unscheduled Visits
Unscheduled visits will take place for an unexpected pregnancy or any complication or AE/SAE that requires an extra visit. These visits will be documented in the source document and the unscheduled visit case report form.

Dose De-escalation During Treatment Period
For participants receiving idebenone 200 mg po three times per day, dose de-escalation to 200 mg po two times per day, and then 200 mg daily for gastrointestinal side effects (e.g. diarrhea, bloating, abdominal discomfort) will be allowed. Once de-escalated, the participant will continue on this dose for the remainder of the treatment period.

Clinic Visits Post-Treatment (4 and 12 weeks post treatment)*
As part of routine clinical care the patient will be seen in clinic at approximately at 4 and 12 weeks after completing treatment. Timing can occur ± 1 month of scheduled time period to accommodate participant schedule. At these visits the following will occur:

- Monitor for adverse events and assess adherence to the study medication.
- Physical examination including height/weight, waist and hip circumference, blood pressure, heart rate, O_2 saturation
    - Laboratory tests: CBC with differential, Liver tests: ALT, AST, Total bilirubin, Alkaline phosphatase, GGT; Comprehensive metabolic panel (fasting): Sodium, Potassium, Bicarbonate, Creatinine, BUN, Ca++, Phosphate, Albumin Glucose, , Glycosylated hemoglobin, HOMA-IR, Coagulation studies: PT, INR

- Calculation of MELD score

*A clinic visit at Stanford is preferred, however, for participants who live out of the Bay Area, the visit may occur via telehealth/telephone contact. In this case, standard of care blood laboratories may be performed at a local clinical laboratory. Blood and imaging procedures that are only part of study protocol will not be performed.

For the serum metabolite studies: patients will take their morning dose of study medication with food. 1.5 hrs. later blood draw (5cc) in a Heparin tube will be performed in conjunction with the SOC labs. Un-identified (coded) serum and PMBC samples (pellets, previously processed by the PI's lab) will be sent to UC Davis by the PI to our collaborator (Dr. Cortopassi) who will perform idebenone metabolite assessment, and Shc target engagement studies on PMBCs.

Table of Treatment Events

Procedures	Screening weeks -6 to -1 *	Enrollment/Base-line*	**Study Visit 2** 2w	**Study Visit 3**: 4w	**Study Visit 3**: 6w	**Study Visit 4**: 12w	**Study Visit 5**: 24w	**Study Visit 6:** 36w	**Study Visit 7**: 48 weeks	**Study Visit 8**: 52 weeks	**Final Study Visit** 9: 60w
Informed consent	X										
Demographics	X										
Medical history	X										
Randomization		X									
Administer study intervention		X	X	X	X				X		
Concomitant medication review	X	→	→	→	→	→	→	→	→	→	→
Physical exam (including height and weight)		X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X
Height		X							X		
Weight		X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X
serum chemistry [a]	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [b]	X										
HbA1c	X		X		X	X	X	X	X	X	X
Autoimmune panel, ANA, ASMA, AMA	X										
ceruloplasmin	X										
Alpha 1 AT	X										
Ferritin	X										
Lipid panel	X					X			X		
Coag. Studies, PT, INR	X		X	X	X	X	X	X	X	X	X
Urine ethylgluc.	X		X	X	X	X	X	X	X		
AUDIT screen	X		X	X	X	X	X	X	X		

Procedures	Screening weeks -6 to -1 *	Enrollment/Base-line*	**Study Visit 2** 2w	**Study Visit 3**: 4w	**Study Visit 3**: 6w	**Study Visit 4**: 12w	**Study Visit 5**: 24w	**Study Visit 6:** 36w	**Study Visit 7**: 48 weeks	**Study Visit 8**: 52 weeks	**Final Study Visit** 9: 60w
Adverse event review and evaluation	X		→								
MRE	X^{Ω}								X^{Ω}		
Idebenone serum metabolites				X			X		X		
FIB-4							X		X		
Periph. Blood PBMC							X		X		
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X	X

*These procedures can occur on the same day of enrollment/baseline visit. Review of previous clinic labs as part of screening. If labs were done >8w, repeat labs on the day of enrollment.

Ω MRE can occur +/-4 weeks from scheduled visit, to allow patient flexibility

ENDPOINTS

Primary Endpoint

Safety and tolerability: assess the number of adverse events and the number of participants with adverse events by severity, causality, and type.

Secondary Endpoints

To evaluate changes in biomarkers of disease progression and liver stiffness in adults treated with idebenone for 48 weeks compared to placebo:

- Serum aminotransferases, and GGT levels
- Fasting markers of insulin resistance (HOMA, adipo-IR index)
- Lipid profile (triglycerides, HDL, LDL)
- Liver stiffness, using MRE. Will include MR-PDFF as well, to evaluate steatosis.
- Assess target engagement (PMBC Shc phosphorylation)
- Evaluate surrogate markers (FIB 4).
- Idebenone metabolite studies

STATISTICAL CONSIDERATIONS

Sample Size

The selection of 15 participants for the placebo group and 30 participants for the idebenone group was based on clinical judgment and past experience with observing potential treatment response. This number takes into account potential attrition, and a 15-20% placebo effect that has been previously observed in NASH studies. The study has sufficient sample size to provide preliminary safety profile and secondary outcome

measures. This is based on the two group t-test for fold change assuming log-normal distribution (unequal n's) to detect 1.5 kPa decrease in stiffness in the treatment group at the 0.05 level (2-sided) with 83% power.

Statistical Methodology
Descriptive statistics such as the number of observations, mean, median, standard deviation, minimum, and maximum will be presented for continuous variables. Other descriptive statistics such as counts, proportions, and/or percentages will be presented to summarize discrete variables. A 95% confidence level will be used for confidence intervals.

Demographics and Baseline Characteristics
The number of participants who either completed the study or were discontinued early from the study will be summarized. Demographic and baseline characteristics will also be summarized by dose group. These variables include race, age, gender, and selected clinical variables recorded prior to initiation of study drug. Study drug administration will be summarized in terms of number of days of dosing and reasons for final discontinuation of the study drug.

Safety and Clinical Laboratory Analyses
Adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Prior and concomitant medications will be summarized by World Health Organization (WHO) drug class.
Summary statistics for changes from baseline will be presented for laboratory values, such as hematology and serum chemistry data, and physical examination results. Continuous laboratory measurements will be described at each visit using descriptive statistics; observed values and changes from baseline will be summarized.

Analyses of Secondary Outcomes
Summary statistics for changes from baseline will be presented for the various secondary endpoints. Continuous measurements will be described at each visit using descriptive statistics; observed values and changes from baseline will be summarized.

Data Monitoring
Data entry, database management, and data quality assurance will be led by the study coordinator. Interim data analysis will occur after 5 participants have completed the study, and then final data analysis at completion of study.

RISK and DISCOMFORTS
1. Idebenone: Idebenone is currently not FDA approved for use in the United States. However, clinical experience suggests that idebenone is safe and well-tolerated oral medication. The safety of oral idebenone as high as 360 mg three times a day for up to 2 years has been demonstrated in humans. On the ClinicalTrials.gov site there have been 31 trials with idebenone, mostly for neurodegenerative disorders. Of these, there are ongoing trials for Phase 3 studies in Duchenne's muscular dystrophy (SIDEROS, NCT03603288) at sites within the US, as well as a single study for early Parkinson's (NCT04152655). In Europe, Idebenone has been authorized in the EU

since 8 September 2015 (EMEA/H/C/003834) for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON). According to the summary of risk assessment (https://www.ema.europa.eu/en/documents/rmp-summary/raxone-epar-risk-management-plan-summary_en.pdf), there were no reports on SAEs with idebenone. The most common reported side effects with Idebenone are nasopharyngitis, cough and mild to moderate diarrhea (affecting up to 1 in 10 people). Changes in blood test results, e.g. low level of white blood cells, or low level of red blood cells, or low level of platelets may occur however these are very rare and are classified as “unknown frequency” based on prior studies.
Chromaturia: The metabolites of idebenone are colored and may cause chromaturia, i.e. a reddish-brown discoloration of the urine. This effect is harmless, not associated with hematuria, and does not require any change in dose or discontinuation of treatment. Caution should be exercised to ensure that the chromaturia does not mask changes of urine color due to other reasons (e.g. renal or blood disorders).

2. Venipuncture: The risks of venipuncture include temporary discomfort, pain, and anxiety from the needle stick, bruising, and, rarely, infection. To minimize risk, all blood draws will follow hospital/clinical procedures and be drawn by experienced phlebotomists will be used for blood.

3. MR elastogram: MRE is an FDA approved noninvasive test used to assess liver stiffness (measured in kPa) as a measure of liver fibrosis. During the exam a special pad is placed on the abdomen, over the gown. It applies low-frequency vibrations that pass through the liver. The MRI system generates images of the waves passing through the liver and processes the information to create cross-sectional images that show the stiffness of tissue. During measurement, participants may feel a slight vibration on the skin. All precautions will be followed as per standard of care in terms of MRI use.

4. Privacy: Participation in research may involve a loss of privacy, but information about participants will be handled as confidentially as possible and in compliance with HIPPA regulations. Patient names and medical record numbers will be recorded for study management purposes. This information will not be included in the hard copy data case report forms or the electronic database used for data analysis, and will be maintained in a locked file in a lockable office. It will not be disclosed to others.
Study data will be identified by a unique study code for each patient. Hard copy study data will be maintained in a separate locked research file in a lockable office. The electronic data set, which will be identified by the unique study codes, will be keyed into a computer that is password protected and encrypted. Access to study data will be limited to research personnel who have completed protocol specific training.

SAFETY MONITORING AND ADVERSE EVENTS

Adverse Events Definition

An adverse event (AE) is any untoward or unfavorable medical occurrence in humans which occurs during the participant's participation of a clinical study, whether or not it is considered drug-related. Any changes in clinical status, routine labs, physical

examinations, etc. that is considered clinically significant by the study investigator are considered AEs. We are using National Cancer Institute's Common Terminology Criteria for Adverse Events version 5 (CTCAE v.5) grading system. The following grades, which refer the severity of the AE, are described here:

The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

An extensive description of the type of AE's described by this system can be found online (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

The most common side effects of idebenone have been reported to be diarrhea, nausea, and mild gastrointestinal symptoms. The CTCAE grading system will be used to grade these symptoms, as well as any others that arise during and shortly after the trial (< 30 days). The grade of these symptoms, rather than the presence of the symptoms themselves, will be used to determine if study drug administration should be stopped in individual patients or all patients within the study.

Monitoring and handling AEs:
The main symptoms described in previous trials are diarrhea, nausea and malaise. These were usually self-limited and observed at the beginning of the study.

1. Mild symptoms: diarrhea e.g. 2-3 loose stools a day, non-watery, may recommend supportive treatment e.g. fiber supplementation. For nausea taking the medication with meals is helpful. Nausea that interferes with daily activities or food intake will be addressed, as below.
2. Moderate to severe symptoms: diarrhea with stools >5 a day, watery stools, or nausea interfering with daily activities will mandate dose reduction, as described earlier.

Suspected Adverse Reaction (SAR)
A Suspected Adverse Reaction (SAR) is any adverse event for which there is a reasonable possibility that the investigational drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse

reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Monitoring for Drug-Induced Liver Injury (DILI)
This study follows the FDA's Guidance for Industry, Drug-Induced Liver Injury, Premarketing Clinical Evaluation guidelines (https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents/drug-induced-liver-injurypremarketing-clinical-evaluation). Of note, the patients recruited to this study will have other liver diseases excluded. Most of them will have mild increase in serum aminotransferases at baseline as they have NASH diagnosis. In prior trials severe DILI with idebenone was not noted. Preexisting liver disease has not been thought to make patients more susceptible to DILI but it may be that a diminished liver reserve or the ability to recover could make the consequences of injury worse.

To monitor for cholestatic liver injury, we have outlined the biochemical triggers for close monitoring and potential DILI evaluation based on AT baseline, as listed below:

Normal Baseline Status
ALT≥3x ULN or AST ≥3x ULN and TB ≥2x ULN
ALT≥5x ULN or AST ≥5x ULN
ALT≥8x ULN or AST ≥8x ULN
ALT≥3x ULN or AST ≥3x ULN and INR > 1.5
ALP/GGT ≥2 ULN

Elevated Baseline Status
ALT≥3x BL or AST ≥3x BL and TB ≥2x BL
ALT≥3x BL or AST ≥3x BL
ALT≥5x BL or AST ≥5x BL
ALT≥2x BL or AST ≥2x BL and INR > 1.5
ALP/GGT ≥2x BL and > ULN
ALP/GGT ≥2x BL and > ULN and ALP/GGT ≥2x BL and > ULN

The following Standardized MedDRA Queries (SMQs) will be used as the triggers to identify subjects meeting the liver toxicity adverse events:

- Trigger S1: Cholestasis and jaundice of hepatic origin (SMQ). Drug related hepatic disorders- severe events only (SMQ)
- Trigger S2a: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)
- Trigger S2b: Hepatitis, non-infectious (SMQ)
- Trigger 3: Liver related investigations, signs and symptoms (SMQ)
- Trigger 4: Liver related coagulation and bleeding disturbance (SMQ)

In accordance with Hy's law, cholestatic liver injury will be assumed if no other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury. In all patients, regular physical monitoring (symptoms,

physical signs e.g. rash), and monitoring of ALT, AST and GGT will be done as per the protocol synopsis (initially every 2 weeks).

If we observe 3-fold or greater elevations, we will confirm results within 48 hours, including bilirubin levels. We will obtain history of recent or acute illnesses, concurrent or new medications or exposures. Depending on these further investigations will be initiated e.g. acute hepatitis panel, ethyl glucuronide, Tylenol level, cardiac workup. Discontinuation of treatment will be considered if:
-ALT or AST >8xULN
-ALT or AST >5xULN for more than 2 weeks
-ALT or AST >3xULN and (TBL >2xULN or INR >1.5) • ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Serious Adverse Event Definition
An adverse event or suspected adverse reaction or adverse reaction is considered serious if, in the view of either the PI or sponsor, it results in any of the following outcomes:

- Grade 5: - Death
- Grade 4:
  - Life-threatening AE: it is considered "life-threatening" if its occurrence, in the opinion of the investigator or sponsor, places the participant at immediate risk of death from the reaction as it occurred. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- Grade 3:
  - Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - Inpatient hospitalization or prolongation of existing hospitalization
  - Congenital abnormality or birth defect
  - Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious adverse event.

Unexpected Adverse Event Definition
An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or package insert or is not listed at the specificity, severity or rate of occurrence that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the IND or protocol.

Identification of Adverse Events
As all participants in this study will have pre-existing medical conditions. Those pre-existing conditions will not be considered as adverse events. New events that occur or worsening through frequency or intensity of pre-existing conditions will be reported as adverse events.

Adverse events (including SAEs) may be discovered through any of these methods:
- Observing or interviewing the participant.
- Procedures and laboratories as performed as part of participating in the study.
- Receiving an unsolicited complaint from the participant.

The investigator will provide the following information about an AE:
- Date of onset and resolution
- Severity
- Action taken with study drug product
- Changes in study drug dosing
- Causal relationship to study drug
- Outcome

All reportable drug adverse events as defined above will be recorded on the appropriate AE/SAE paper CRF form starting after consent has been obtained until 30 days after the last dose of study drug.

Follow-up of Adverse Events
All adverse events (drug related or not) must be followed until resolution, until 30 days after the study completion, or until 30 days after the participant prematurely withdraws (or is withdrawn from the study), whichever occurs first. All SAEs will be followed until resolution, even if not resolved by the 30 day follow-up.

Guidelines for Determining Causality
The Investigator will use the following question when assessing causality of an adverse event to study drug.
-Is there a reasonable possibility that the drug caused the event? (Yes/No)
An affirmative answer designates the event as a suspected adverse reaction.

Adverse Events Reporting Procedures

Serious Adverse Events
The investigator will report to the Sponsor all serious adverse events within 24 hours of becoming aware of the event, regardless of relationship or expectedness. For serious adverse events, all requested information on the AE/SAE paper CRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE paper CRF will be updated and submitted. Investigators or Sponsor must also submit safety reports locally as required by their IRB.

Unexpected Non-Serious Adverse Events
An unexpected, non-serious adverse event that is of Grade 2 severity or higher and study related will be recorded and reported to the Sponsor under the serious adverse event reporting procedure above (i.e. within 24 hours).

Reporting to Health Authority

The Sponsor of the IND will report all AEs and SAEs to the FDA within the reporting time limits set forth by the FDA.

1) Standard Reporting (IND Annual Report)
This option applies if the AE is classified as one of the following:
- Serious, expected, suspected adverse reactions
- Serious and not a suspected adverse reaction
- Pregnancies

* Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual IND Report.

2) Expedited Reporting

The Sponsor must report in an IND safety report any suspected adverse reaction to study drug that is both serious and unexpected. The time frame for submitting an IND safety report to FDA and all participating investigators is no later than 15 calendar days after the sponsor determines that the suspected adverse reaction or other information qualifies for reporting.

Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and, therefore, must be reported more rapidly to FDA. The requirement for reporting any unexpected fatal or life-threatening suspected adverse reaction to FDA is no later than 7 calendar days after the sponsor's initial receipt of the information. Investigators must submit IND safety reports as required by their IRB. Documentation of the submission and receipt by the IRB must be retained for each IND safety report.

Contraception and Pregnancy

All men and women of child-bearing potential must agree to practice at least two preventive measures regarding pregnancy with the prevention measures of their choosing during the study and for 30 days after the last administration of idebenone. Acceptable birth control methods include: sexual abstinence; vasectomy and documentation of zero sperm count in the semen; and use of barrier contraception in combination with use of effective birth control by the female partner. Study participants will be required to disclose their method of pregnancy prevention at the initial screening/baseline visit.

During the course of the study, any participant who becomes pregnant will be instructed to contact the study team immediately, and she will be required to cease dosing with her treatment immediately. She will be seen in an unscheduled visit during which a physical examination and laboratories will be performed (CBC with differential, Na+, K+, Cl-, CO2, glucose, serum creatinine, BUN, Ca++, Phosphorus, total bilirubin, AST, ALT, GGT, Alkaline phosphatase, total bilirubin, albumin, total protein). Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy and the outcome must be reported. Information requested about the delivery shall include: Gestational age at delivery; Birth weight, length, and head circumference; Gender;

Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, if available; Any abnormalities. Any complication to pregnancy such as a congenital abnormality or birth defect shall be recorded as an SAE using the SAE reporting procedures described above and to the FDA.

SAFETY MONITORING

Formal Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) will not be formed given the single-site, and small sample size. Instead, the PI, and study personnel will perform study safety reviews on an ongoing basis.

HALTING CRITERIA

During the course of the study, if the PI discovers conditions that indicate that the study should be discontinued, an appropriate procedure for terminating the study will be instituted, including notification of the FDA and IRB.

Halting of Study Drug in Participant & Reasons for Early Termination

Study drug administration must be halted, and the participant withdrawn from the study if any of the following occurs:

1. Participant develops a serious adverse reaction (Grades 3-5).
2. Participant desires to discontinue participation in the study.
3. Participant is unwilling or unable to comply with the protocol.
4. Participant becomes pregnant.
5. The investigator feels that is in the participant's best interest to discontinue treatment with study drug.

Halting the Study

The study will be halted for a safety review if:

1. If 1 patient experiences a Grade 5 CTCAE,
2. 2 patients experience the same Grade 4 CTCAE,
3. 3 patients experience the same Grade 3 CTCAE,
4. 4 patients experience the same Grade 2 CTCAE, enrolment of new patients into the trial should be paused.
5. If at any point in the study the Sponsor and/or Investigators feel that there are safety concerns in this study that put the participants at increased risk as compared to the original information on risk in the consenting process, the Investigators and/or Sponsor in discussion with the FDA can choose to stop the study.

A consensus decision to halt the study will be made by the Sponsor and Investigator. Such a decision with its supporting documentation and possible future plans for the study will be submitted to, and discussed with, the FDA.

RECRUITMENT and ENROLLMENT

Potential participants will be identified by the study investigator, Dr. Natalie Torok and her colleagues in the Hepatology clinics, who are experts in NASH and regularly care for these patients. Once it has been determined that patient meets entry criteria, a

knowledgeable member of the research team will be introduced to the participant and will initiate the informed consent process. Enrollment will be by invitation only.

FACILITIES

Study visits

a) Stanford Medicine, Liver Clinic, [redacted] Redwood City, CA 94063

b) MRE/MR-PDFF: Stanford Hospital, Radiology, [redacted] Palo Alto CA 94304

ETHICAL CONSIDERATIONS

Prior to any study-related procedures, the investigator or designee will obtain from the participant a signed and dated written Informed Consent consistent with FDA/ICH regulations and the HIPAA Privacy Rule. A HIPAA Privacy Rule Authorization language will be included in the Informed Consent and must be IRB approved prior to study implementation. In addition, the document of Bill of Rights will be attached to the Informed Consent form so that the participants can read and understand the same.

WITHDRAWAL FROM STUDY

Participants may stop being in the study at any time and all study procedures discontinued. However, every attempt will be made to schedule an Early Termination Visit for any participant who is enrolled and subsequently is withdrawn, discontinues or drops out of the study for any reason and he/she does not complete the final 12 month study visit.

Early Termination Visit, at these visits the following will occur:

- Monitor for adverse events.
- Procedures done as part of standard of care:
  - Physical exam including heart rate, blood pressure, respiratory rate, and weight will be performed.
  - Blood tests: CBC with differential, Na+, K +, Cl-, CO2, glucose, serum creatinine, BUN, Ca++, Phosphorus, total bilirubin, AST, ALT, GGT, Alkaline phosphatase, albumin, total protein.

DURATION OF THE STUDY

If enrollment proceeds as planned, the enrollment phase will take 24 months (12 months of recruitment followed by 12 months of follow-up after last patient enrolled). An additional ~6 months will be needed for data analysis after the end of enrollment.

Table 2. Timetable

Research Activity	-3 to 0 months	0-24 months	24-36 months
Study Preparation (IRB Training, etc.)	X		
Study Enrollment		X	
Data Analysis			X
Manuscript Preparation			X

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