CLINICAL STUDY PROTOCOL

A PHASE 1, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF ARAMCHOL IN SUBJECTS WITH HEPATIC IMPAIRMENT

PROTOCOL NO. Aramchol-019

Sponsor:	Galmed Research and Development Ltd 16 Tiomkin Street Tel Aviv 6578317, Israel
Principal Investigator:	[redacted]
Sponsor Contact:	[redacted]
Version of Protocol:	1.0
Date of Protocol:	14 October 2019

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation Guideline E6(R2): Good Clinical Practice.

SIGNATURE PAGE

PROTOCOL TITLE: A Phase 1, Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Aramchol in Subjects With Hepatic Impairment

PROTOCOL NUMBER: Aramchol-019

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled "A Phase 1, Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Aramchol in Subjects With Hepatic Impairment" in accordance with the guidelines and all applicable government regulations, including US Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

Principal Investigator	Date

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PROTOCOL SYNOPSIS

PROTOCOL NO.: Aramchol-019

TITLE: A Phase 1, Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Aramchol in Subjects With Hepatic Impairment

STUDY PHASE: 1

STUDY SITES: 3 clinical sites in the United States

OBJECTIVES:
The primary objective of this study is to compare the pharmacokinetic (PK) profile of aramchol administered orally in subjects with hepatic impairment with that of healthy subjects.

The secondary objective of this study is to assess the safety and tolerability of aramchol administered orally in subjects with hepatic impairment.

STUDY DESIGN:
This is a Phase 1, multicenter, open-label, 2-part, single- and multiple-dose study designed to assess the effect of hepatic insufficiency on the PK of aramchol.

Each part of the study will consist of a screening period, a check-in day, a treatment period, and an end-of-study (EOS) visit.

In Part 1 (single-dose), up to 48 subjects are planned: 8 subjects each in the mild (Cohort A), moderate (Cohort B), and severe (Cohort C) hepatic impairment cohorts and 8 to 24 healthy control subjects with normal hepatic function (Cohort D). Enrollment of 8 subjects with mild hepatic impairment (Cohort A) will proceed only if there is evidence of reduced clearance of aramchol in Cohort B. At screening, subjects will be assigned to a study cohort according to the Child-Pugh classification system as follows:

Cohort	Hepatic Condition	Child-Pugh Grade	Number of Subjects
A[(a)]	Mild impairment	Class A (Score of 5 to 6)	8
B	Moderate impairment	Class B (Score of 7 to 9)	8
C	Severe impairment	Class C (Score of 10 to 15)	8
D	Healthy (control)	—	8 to 24

[(a)] Enrollment of subjects into Cohort A will only proceed if there is evidence of reduced clearance of aramchol in Cohort B.

Healthy control subjects (Cohort D) will be matched with hepatically impaired subjects (Cohorts A, B, and C) according to gender, age (±10 years), and body mass index (±20%).

Safety data and PK profiles of aramchol from at least 4 subjects with moderate hepatic impairment (Cohort B) will be obtained and reviewed while enrollment to this cohort continues. These 4 subjects in Cohort B must demonstrate satisfactory safety (no serious adverse events [AEs] or severe AEs related to aramchol) and PK results for up to 4 days after dosing before enrollment of subjects with severe hepatic impairment (Cohort C) is initiated. Two subjects with severe hepatic impairment must demonstrate satisfactory safety and tolerability (no serious AEs or severe AEs related to aramchol) for up to 4 days after dosing before the remaining subjects with severe hepatic impairment may be dosed.

Enrollment of subjects into Cohort A (mild hepatic impairment) will proceed only if there is evidence of reduced clearance of aramchol in the first 4 subjects in Cohort B (moderate hepatic impairment), defined as a reduction in apparent total oral clearance (CL/F) of greater than 30% compared with values in historical healthy control subjects.

In Part 2, a cohort of at least 8 subjects comprising of mild and moderate or moderate and severe hepatic impairment subjects will be administered aramchol as multiple doses to obtain the PK profile of aramchol at steady state. A decision on the severity of hepatic impairment of subjects to participate in Part 2 (multiple-dose) will be made by the sponsor based on the available safety and PK results from Part 1 (single-dose).

Healthy control subjects will be matched with the hepatically impaired subjects according to gender, age (±10 years), and body mass index (±20%).

Single Dose (Part 1):

On Day 1, subjects will receive a single oral dose of 600 mg aramchol administered with water in the morning, after an overnight fast of at least 10 hours, and approximately 30 minutes after consuming a standardized breakfast. Subjects will remain fasted except for water for 2 hours after dosing. During the study, subjects may consume water on an ad libitum basis. Hepatically impaired subjects will receive a diet standardized for hepatic impairment and healthy control subjects will receive a similar diet.

Serial blood samples for PK analysis of aramchol concentrations in plasma will be collected before dosing (0 hour) and up to 168 hours for healthy subjects and 240 hours for hepatically impaired subjects after administration of aramchol.

Subjects will be confined to the clinical site from Day –1 until discharge on Day 8 for healthy control subjects and on Day 11 for hepatically impaired subjects. The duration of the study, excluding screening, is approximately 23 days.

Multiple Dose (Part 2):

Multiple dosing will involve twice daily (approximately 12 hours apart) oral administration of aramchol for 11 days with a single AM dose on Day 12 to achieve steady state. The dosage will not exceed 300 mg twice daily but may be adjusted to give lower exposure depending on review of available data on any reduction in clearance associated with hepatic impairment seen with single doses in Part 1. Subjects will consume a standardized meal 30 minutes prior to the AM and PM doses of aramchol. Subjects will remain fasted except for water for 2 hours after dosing. During the study, subjects may consume water on an ad libitum basis. Hepatically impaired subjects will receive a diet standardized for hepatic impairment and healthy control subjects will receive a similar diet.

Blood samples for analysis of aramchol concentrations in plasma will be collected before the AM dose on Days 1, 4, 8, 9, 10, 11, and 12 and at intervals to 12 hours after the AM dose on Day 12. Samples of plasma will also be stored for analysis of metabolites pending results of a mass balance study.

Subjects will be confined to the clinical site from Day –1 until discharge on Day 13. The duration of the study, excluding screening, is approximately 28 days.

STUDY POPULATION:

Inclusion Criteria:
Each subject must meet all of the following criteria to be enrolled in this study:

1. The subject is male or female 18 to 79 years of age, inclusive.
2. The subject has a body mass index of 19 to 40 kg/m^2, inclusive, at screening.
3. Females of childbearing potential must practice a highly effective method of contraception throughout the study period and for 1 month after treatment discontinuation. Highly effective methods are defined as those that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods, in accordance with the recommendations of the Clinical Trial Facilitation Group Working Group on Contraception include: hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormonal-releasing system, bilateral tubal occlusion, vasectomized partner, and sexual abstinence. All female subjects must have a negative pregnancy test at screening and before the first dose of study drug.
4. Male subjects with female partners of childbearing potential must be vasectomized, be willing to use an acceptable method of birth control, or practice abstinence during the study.
5. The subject has a resting pulse rate of ≥40 and <100 beats per minute with no clinically significant deviation as judged by the investigator.
6. The subject has a QT interval corrected for heart rate using Fridericia's formula of <500 msec.
7. The subject agrees to comply with all protocol requirements.
8. The subject is able to provide written informed consent.

Additional Inclusion Criteria for Healthy Subjects Only (Cohort D):

9. The subject has normal hepatic function.
10. The subject has a resting blood pressure of 90 to 150 mm Hg (systolic) and 50 to 100 mm Hg (diastolic).
11. The subject is judged by the investigator to be in good general health, as determined by medical history, clinical laboratory assessments, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

Additional Inclusion Criteria for Subjects With Hepatic Impairment Only (Cohorts A, B, and C):

12. The subject has cirrhosis with evidence of impaired liver function. The etiology of the cirrhosis may be alcoholic, autoimmune, nonalcoholic steatohepatitis, or chronic viral hepatitis type B or C.
13. The subject has chronic (more than 6 months) and stable hepatic impairment (ie, no acute episodes of illness within 30 days before screening due to deterioration of hepatic

function) as assessed by a Child-Pugh classification score of mild (5 to 6 points), moderate (7 to 9 points), or severe (10 to 15 points).

14. The subject has a resting blood pressure of 90 to 155 mm Hg (systolic) and 50 to 100 mm Hg (diastolic).
15. The subject is judged by the investigator to be in good general health, as determined by medical history, clinical laboratory assessments, vital sign measurements, 12-lead ECG results, and physical examination findings, except for findings that, as judged by the investigator, are consistent with the subject's hepatic impairment or other stable concomitant medical conditions.

Exclusion Criteria:
Subjects meeting any of the following criteria will be excluded from the study:

1. The subject has a history or clinical manifestations of a significant neurological, renal, cardiovascular, gastrointestinal, pulmonary, hematologic, immunologic, or psychiatric disease that would preclude study participation, as judged by the investigator.
2. The subject has a positive test result for human immunodeficiency virus type 1 or 2 antibodies at screening.
3. The subject has a history of drug abuse within 3 months before screening.
4. The subject has a history of alcoholism within 3 months before screening, or excessive alcohol consumption (regular alcohol intake >15 units per week) (1 unit is equal to approximately ½ pint [200 mL] of beer, 1 small glass [100 mL] of wine, or 1 measure [25 mL] of spirits).
5. The subject smokes >10 cigarettes daily and is unwilling to reduce to ≤5 daily from the time of screening through the last PK sample.
6. The subject is unable or unwilling to abstain from alcohol, caffeine, xanthine-containing beverages or food (eg, coffee, tea, chocolate, and caffeinated sodas, colas), grapefruit, grapefruit juice, Seville oranges, or products containing any of these, from 48 hours prior to study drug dosing until discharge.
7. The subject is involved in strenuous activity or contact sports within 24 hours of the first dose of study drug or during the study.
8. The subject has donated blood or blood products >450 mL within 3 months before the first dose of study drug.
9. The subject has a presence or history of relevant drug and/or food allergies (ie, allergy to aramchol, cholic acid, or any excipients, or any significant food allergy.
10. The subject has received study drug in another investigational study within 30 days of dosing.
11. In the opinion of the investigator, the subject is not suitable for entry into the study.

Additional Exclusion Criteria for Healthy Subjects Only (Cohort D):

12. The subject has clinically significant findings at screening including history, physical examination, ECG, or laboratory values.
13. The subject has used an herbal remedy (including St John's wort) known to interfere with liver enzymes during the 28 days before dosing with the study drug.

14. The subject has a past history of surgery or a medical condition that might affect absorption of medicines (hernia repair is acceptable).
15. The subject has a positive test result for hepatitis B surface antigen or antibodies to hepatitis C virus.
16. The subject has used any prescription (excluding hormonal birth control and hormone replacement therapy) or over-the-counter medications (except paracetamol [up to 2 grams per day]), including herbal or nutritional supplements, within 14 days before the first dose of study drug and throughout the study.
17. The subject has a positive test result for drugs of abuse or alcohol at screening or before the first dose of study drug.

Additional Exclusion Criteria for Subjects With Hepatic Impairment Only (Cohorts A, B, and C):

18. The subject has a current >Grade 1 (mild) encephalopathy. Subjects with a history of Grade 3 or 4 encephalopathy that have responded to treatment with medicines such as lactulose, rifaximin, or neomycin may be included with the subject receiving the point score for Grade 3 or 4 encephalopathy.
19. The subject has clinically demonstrated massive tense ascites. Subjects with a history of moderate or severe ascites that have responded to diuretics may be included with the subject receiving the higher score.
20. The subject has esophageal varices that have caused hemorrhage within a period of 8 weeks prior to dosing or are considered of high risk for hemorrhage.
21. The subject has the following types of liver disease: primary biliary cirrhosis, sclerosing cholangitis, hepatocellular carcinoma, cardiac cirrhosis, hemochromatosis, Wilson's disease, other genetic causes of liver disease.
22. The subject has clinically significant impairment of renal function (eCLcr <45 mL/min) as calculated by the Cockcroft-Gault equation.
23. The subject has a hemoglobin <8.5 mg/dL or platelets <30,000/µL.
24. The subject has fluctuating or rapidly deteriorating hepatic function, as indicated by recent history or worsening of clinical (ie, abdominal pain, nausea, vomiting, anorexia, or fever) and/or laboratory signs of hepatic impairment, as judged by the investigator.
25. The subject has evidence of acute viral hepatitis within 30 days before dosing with study drug.
26. The subject has evidence of hepatorenal syndrome.
27. The subject has used any prescription (excluding hormonal birth control and hormone replacement therapy) or over-the-counter medications, including herbal or nutritional supplements, within 14 days before the first dose of study drug and throughout the study, except those essential for the management of hepatic impairment or the treatment of stable concomitant medical conditions, as judged by the investigator. The dose of an approved medication must remain stable from 7 days before study drug dosing and throughout the study.

28. The subject has a positive test result for drugs of abuse (except positive test results associated with prescription medications that have been reviewed and approved by the investigator) at screening or before the first dose of study drug.

STUDY TREATMENTS:

Single Dose (Part 1):

Aramchol will be administered as a single oral dose of 600 mg (2 × 300-mg tablets) in the morning on Day 1 with water approximately 30 minutes after a standardized breakfast.

Multiple Dose (Part 2):

Aramchol will be administered as an oral dose that will not exceed 300 mg twice daily (approximately 12 hours apart) for 11 days and a single AM dose on Day 12 with water approximately 30 minutes after a standardized meal.

STUDY PROCEDURES:

Pharmacokinetic Assessments and Endpoints:

Single Dose (Part 1):

Blood samples for analysis of concentrations of aramchol and its metabolites in plasma will be collected at the following time points: before dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 24, 48, 72, 96, 120, 144, 168, 192, and 240 hours (the last 2 time points are for hepatically impaired subjects only) after administration of aramchol.

The following plasma PK parameters will be calculated as endpoints for aramchol using actual sampling times rather than scheduled sampling times:

- Area under the plasma concentration versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t})
- AUC from time 0 extrapolated to infinity (AUC_{0-inf})
- Maximum observed plasma concentration (C_{max})
- Time to reach maximum observed plasma concentration (T_{max})
- Time to the first measurable plasma concentration (T_{lag})
- Apparent terminal elimination half-life ($t_{1/2}$)
- Apparent oral clearance (CL/F)
- Apparent volume of distribution (V_z/F)
- Elimination rate constant (k_e)

Multiple Dose (Part 2):

Blood samples for analysis of concentrations of aramchol and its metabolites in plasma will be collected before the AM dose on Days 1, 4, 8, 9. 10, 11, and 12 and at the following times after the AM dose on Day 12: 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours.

The following plasma PK parameters on Day 12 will be calculated as endpoints for aramchol using actual sampling times rather than scheduled sampling times (if conducted):

- AUC from time 0 to the dosing interval tau at steady state ($AUC_{0-tau, ss}$)

- Maximum observed plasma concentration at steady state ($C_{max, ss}$)
- Time to reach maximum observed plasma concentration at steady state ($T_{max, ss}$)
- Minimum observed plasma concentration at steady state ($C_{min, ss}$)
- Time of minimum observed plasma concentration at steady state ($T_{min, ss}$)
- Average plasma concentration at steady state ($C_{avg, ss}$)

Time to reach steady state will also be estimated graphically by assessing trough plasma concentrations (ie, pre-AM dosing on Days 1, 4, 8, 9, 10, 11, and 12) over 12 days of administration.

Safety Assessments and Endpoints:
Safety and tolerability will be assessed by the following endpoints: monitoring and recording of AEs, clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements, 12-lead ECG results, and physical examination findings.

STATISTICAL ANALYSIS PLANS:
Sample Size:
For Part 1, up to 48 subjects are planned: 8 subjects each in the mild (Cohort A), moderate (Cohort B), and severe (Cohort C) hepatic impairment groups, and 8 to 24 healthy control subjects with normal hepatic function (Cohort D). For Part 2, at least 8 subjects with mild and moderate or moderate and severe hepatic impairment and up to 8 healthy control subjects with normal hepatic function are planned. The sample size was chosen for this study based on clinical and practical considerations and not on a formal statistical power calculation. The US Food and Drug Administration Guidance for Industry, Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling, was used as a guide to select the sample size, which is considered sufficient to adequately assess the safety and PK profiles of aramchol.

In the event of early withdrawals or discontinuations, subjects may be replaced at the discretion of the investigator, and after consultation with the medical monitor and sponsor if the number of completers will be less than 6 subjects in any cohort.

Analysis Sets:
The PK population will include subjects who receive at least 1 dose of aramchol and have sufficient concentration data to support accurate estimation of at least 1 PK parameter. In Part 1, subjects who experience vomiting within 6 hours after dosing will be excluded from the PK analysis.

The safety population will include all subjects who receive at least 1 dose of aramchol.

Pharmacokinetic Analyses:
Plasma concentrations will be listed and summarized descriptively (number of subjects, arithmetic mean, standard deviation [SD], coefficient of variation [CV], minimum, median, and maximum). Plasma concentration versus actual time profiles for each subject will be presented graphically. The mean plasma concentration versus scheduled time profiles will be presented graphically.

Pharmacokinetic parameters derived from plasma concentration data using noncompartmental methods will be summarized by hepatic group using descriptive statistics (number of subjects, arithmetic mean, SD, CV, minimum, median, and maximum). Geometric mean and geometric CV will also be calculated for AUCs and C_{max}. The $AUC_{0-t,}$ AUC_{0-inf}, and C_{max} values may also be expressed in terms of unbound drug concentrations.

An analysis of variance (ANOVA) model will be performed on the natural logarithms of AUC_{0-t}, $AUC_{0-inf,}$ and C_{max} to calculate the ratio of geometric means and its 90% confidence interval between subjects with hepatic impairment and the corresponding healthy control subjects, as appropriate. The ANOVA model will include hepatic group (normal matching mild, mild, normal matching moderate, moderate, normal matching severe, and severe, where applicable) as a fixed effect.

For AUC_{0-t}, AUC_{0-inf}, and C_{max}, a linear regression model will be performed on the natural logarithms of AUC_{0-t}, AUC_{0-inf}, and C_{max} as dependent variables and each of the following natural-log-transformed hepatic function estimates as independent variables: Child-Pugh classification score (in subjects with hepatic impairment only), baseline serum bilirubin, serum albumin, and prothrombin time. The regression coefficients representing the relationship between the PK parameters and the hepatic function estimates will be estimated together with their 90% confidence intervals from the regression model.

Sensitivity analyses may be conducted to investigate the potential impact of imbalance existing across hepatic impairment groups in the distribution of the baseline covariates used in subject matching (eg, body weight) and, if data suggest, appreciable differences in PK exposure (AUC_{0-t}, AUC_{0-inf}, and C_{max}) across different values of the same baseline covariate.

Detailed descriptions of the analyses in this study will be presented in the statistical analysis plan.

Safety Analyses:
Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by hepatic condition and overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to early discontinuation will also be presented in data listings.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by hepatic condition at each time point using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Shift tables will be generated for clinical laboratory test results. Clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings will be presented in data listings.

DATE OF PROTOCOL: 14 October 2019

1. INTRODUCTION

1.1 BACKGROUND

Aramchol is a novel conjugate of cholic acid (bile acid) and arachidic acid (saturated fatty acid), linked by a stable amide group. It is in development for treatment of nonalcoholic steatohepatitis (NASH) and fibrosis. Aramchol affects stearoyl coenzyme A desaturase 1, a key liver enzyme involved in regulating lipid metabolism. In animal models of NASH, it reduces steatosis, ballooning, inflammation, and fibrosis by down-regulation of stearoyl coenzyme A desaturase 1 expression in hepatocytes and hepatic stellate cells.

Aramchol is highly lipophilic and pharmacokinetic (PK) studies in humans show that plasma concentrations increase less than proportionally to dose due to poor absorption. Its mean terminal phase half-life ($t_{1/2}$) is approximately 3 days but most of the drug is cleared with a $t_{1/2}$ of about 35 hours and steady state on repeat dosing is achieved within 7 to 10 days. Aramchol is secreted in bile and is excreted in feces. [redacted]

[redacted] Two Phase 2 clinical studies have been completed including a placebo-controlled study in which subjects with NASH were treated for 52-weeks. Significantly more subjects who received aramchol 600 mg daily showed NASH resolution without worsening of fibrosis and a larger proportion of subjects showed at least a 1-point improvement in fibrosis score without worsening of steatohepatitis.

[redacted]

1.2 RATIONALE FOR STUDY

This study will compare the effect of varying degrees of hepatic impairment on the PK, safety, and tolerability of a single oral dose of 600 mg (2 × 300-mg tablets) aramchol in

Part 1 and multiple oral doses not to exceed 300 mg twice daily for 11 days and a single 300 mg AM dose on Day 12 in Part 2 with healthy subjects.

Hepatic impairment associated with cirrhosis may develop in subjects with NASH. Therefore, it is important to assess the effect of hepatic impairment on the PK and hence dosage requirements and safety of aramchol.

1.3 RATIONALE FOR DOSE SELECTION

A single oral dose of 600 mg aramchol in Part 1 and multiple oral doses not to exceed 300 mg aramchol twice daily for 11 days and a single AM dose on Day 12 in Part 2 will be evaluated in this study based on the recommendations provided in the US Food and Drug Administration (FDA) Guidance for Industry, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (DHHS 2003). Though single doses up to 900 mg have been studied in healthy subjects and tolerated well, the single dose of 600 mg represents the highest dose likely to be used and was the daily dose administered in the Phase 2b study. The multiple dose of 300 mg twice daily has been well tolerated by healthy subjects for 10 days and is the dose to be taken daily by subjects participating in a Phase 3 clinical trial.

The duration of multiple dosing is based on the apparent plasma elimination half-life of about 35 hours and time taken to reach steady state of about 7 days in healthy subjects. A duration of 10 days was chosen to ensure steady state has been achieved by all the healthy subjects and an additional 2 days is considered appropriate for subjects with hepatic impairment owing to the possibility of reduced clearance in this population.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to compare the PK profile of aramchol administered orally in subjects with hepatic impairment with that of healthy subjects.

2.2 SECONDARY OBJECTIVE

The secondary objective of this study is to assess the safety and tolerability of aramchol administered orally in subjects with hepatic impairment.

3. STUDY DESIGN

This is a Phase 1, multicenter, open-label, 2-part, single- and multiple-dose study designed to assess the effect of hepatic insufficiency on the PK of aramchol.

Each part of the study will consist of a screening period, a check-in day, a treatment period, and an end-of-study (EOS) visit.

In Part 1 (single-dose), up to 48 subjects are planned: 8 subjects each in the mild (Cohort A), moderate (Cohort B), and severe (Cohort C) hepatic impairment cohorts and 8 to 24 healthy control subjects with normal hepatic function (Cohort D). Enrollment of 8 subjects with mild hepatic impairment (Cohort A) will proceed only if there is evidence of reduced clearance of aramchol in Cohort B. At screening, subjects will be assigned to a study cohort according to the Child-Pugh classification system as follows:

Cohort	Hepatic Condition	Child-Pugh Grade	Number of Subjects
A[(a)]	Mild impairment	Class A (Score of 5 to 6)	8
B	Moderate impairment	Class B (Score of 7 to 9)	8
C	Severe impairment	Class C (Score of 10 to 15)	8
D	Healthy (control)	—	8 to 24

[(a)] Enrollment of subjects into Cohort A will only proceed if there is evidence of reduced clearance of aramchol in Cohort B.

Healthy control subjects (Cohort D) will be matched with hepatically impaired subjects (Cohorts A, B, and C) according to gender, age (±10 years), and body mass index (BMI) (±20%).

Safety data and PK profiles of aramchol from at least 4 subjects with moderate hepatic impairment (Cohort B) will be obtained and reviewed while enrollment to this cohort continues. These 4 subjects in Cohort B must demonstrate satisfactory safety (no serious AEs [SAEs] or severe AEs related to aramchol) and PK results for up to 4 days after dosing before enrollment of subjects with severe hepatic impairment (Cohort C) is initiated. Two subjects with severe hepatic impairment must demonstrate satisfactory safety and tolerability (no SAEs or severe AEs related to aramchol) for up to 4 days after dosing before the remaining subjects with severe hepatic impairment may be dosed.

Enrollment of subjects to Cohort A (mild hepatic impairment) will proceed only if there is evidence of reduced clearance of aramchol in the first 4 subjects in Cohort B (moderate hepatic impairment), defined as a reduction in apparent total oral clearance (CL/F) of greater than 30% compared with values in historical healthy control subjects.

In Part 2, a cohort of at least 8 subjects comprising of mild and moderate or moderate and severe hepatic impairment subjects will be administered aramchol as multiple doses to obtain the PK profile of aramchol at steady state. A decision on the severity of hepatic impairment of subjects to participate in Part 2 (multiple-dose) will be made by the sponsor based on the available safety and PK results from Part 1 (single-dose).

Healthy control subjects will be matched with the hepatically impaired subjects according to gender, age (±10 years), and BMI (±20%).

Single Dose (Part 1):

On Day 1, subjects will receive a single oral dose of 600 mg aramchol administered with 240 mL of water in the morning, after an overnight fast of at least 10 hours, and approximately 30 minutes after consuming a standardized breakfast. Subjects will remain fasted except for water for 2 hours after dosing. During the study, subjects may consume water on an ad libitum basis. Hepatically impaired subjects will receive a diet standardized for hepatic impairment and healthy control subjects will receive a similar diet.

Serial blood samples for PK analysis of aramchol concentrations in plasma will be collected before dosing (0 hour) and up to 168 hours for healthy subjects and 240 hours for hepatically impaired subjects after administration of aramchol.

Subjects will be confined to the clinical site from Day –1 until discharge on Day 8 for healthy control subjects and on Day 11 for hepatically impaired subjects. The duration of the study, excluding screening, is approximately 23 days.

Multiple Dose (Part 2):

Multiple dosing will involve twice daily (approximately 12 hours apart) oral administration of aramchol for 11 days with a single AM dose on Day 12 to achieve steady state. The dosage will not exceed 300 mg twice daily but may be adjusted to give lower exposure depending on review of available data on any reduction in clearance associated with hepatic impairment seen with single doses in Part 1. Subjects will consume a standardized meal 30 minutes prior to the AM and PM doses of aramchol. Subjects will remain fasted except for water for 2 hours after dosing. During the study, subjects may consume water on an ad libitum basis. Hepatically impaired subjects will receive a diet standardized for hepatic impairment and healthy control subjects will receive a similar diet.

Blood samples for analysis of aramchol concentrations in plasma will be collected before the AM dose on Days 1, 4, 8, 9, 10, 11, and 12 and at intervals to 12 hours after the AM dose on

Day 12. Samples of plasma will also be stored for analysis of metabolites pending results of a mass balance study.

Subjects will be confined to the clinical site from Day –1 until discharge on Day 13. The duration of the study, excluding screening, is approximately 28 days.

3.1 SCHEDULE OF EVENTS - SINGLE DOSE ARAMCHOL (PART 1)

Phase	Screening	Check-in	Treatment Period										EOS
Procedure[a] / Day	**–28 to –2**	**–1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**	**22 (±2)**
Admission to clinic		X											
Discharge from clinic										X[b]		X[c]	
Outpatient visit[d]													X
Informed consent	X												
Demographics	X												
Serology[e]	X												
Serum FSH[f]	X												
Inclusion/exclusion criteria	X	X											
Medical history	X	X											
Height, weight, and BMI[g]	X	X											X
Physical examination[h]	X	X											X
Vital sign measurements[i]	X	X	X	X	X	X				X[j]		X[k]	X
12-lead ECG[l]	X	X	X	X		X				X[j]		X[k]	X
Clinical laboratory testing[m]	X	X				X				X[j]		X[k]	X
Urine drug/alcohol screen[n]	X	X											
Urine pregnancy test[o]	X	X											X
Aramchol administration[p]			X										
PK blood sample collection[q]			X	X	X	X	X	X	X	X	X[k]	X[k]	
Adverse events[r]	←						X						→
Prior/concomitant medications	←						X						→

Abbreviations: AE, adverse event; BMI, body mass index; ECG, electrocardiogram; EOS, end of study; FSH, follicle-stimulating hormone; PK, pharmacokinetic.

Notes:

[a] When procedures overlap or occur at the same time point, all blood draws should follow vital sign measurements or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible.

[b] Discharge following all study procedures on Day 8 for healthy control subjects.

[c] Discharge following all study procedures on Day 11 for hepatically impaired subjects.

[d] An EOS visit will occur 11 days after the Day 11 (240-hour) PK blood sample.

[e] A complete list of serology assessments is provided in Section 6.2.2.

[f] Females only. Further details are provided in Section 6.2.2.

[g] Height and weight will be measured and BMI will be calculated at screening only. Only weight will be measured at check-in and EOS.

[h] A full physical examination will be performed at screening. A brief physical examination will be performed at check-in and EOS. Further details are provided in Section 6.2.5.

[i] Further details on vital sign measurements are provided in Section 6.2.3.

[j] Collected for healthy control subjects only.

(k) Collected for hepatically impaired subjects only.
(l) Further details on ECG recordings are provided in Section 6.2.4.
(m) Further details on clinical laboratory assessments, including a complete list of assessments, are provided in Section 6.2.2.
(n) Further details on drug/alcohol screening are provided in Section 6.2.2.
(o) Women of childbearing potential only.
(p) The time of aramchol dosing will be called "0" hour and occurs on the day denoted with grey shading. Further dosing details are provided in Section 5.1.
(q) Further details on the collection of blood samples for PK analysis are provided in Section 6.1.
(r) Further details on collection and reporting of AEs are provided in Section 6.2.1.

3.2 SCHEDULE OF EVENTS - MULTIPLE DOSE ARAMCHOL (PART 2)

Phase	Screening	Check-in	Treatment Period													EOS[b]
Procedure[a] Day	–28 to –2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	27 (±2)
Admission to clinic		X														
Discharge from clinic															X	
Outpatient visit																X
Informed consent	X															
Demographics	X															
Serology[c]	X															
Serum FSH[d]	X															
Inclusion/exclusion criteria	X	X														
Medical history	X	X														
Height, weight, and BMI[e]	X	X														X
Physical examination[f]	X	X														X
Vital sign measurements[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[h]	X	X				X				X				X		X
Clinical laboratory testing[i]	X	X				X				X				X		X
Urine drug/alcohol screen[j]	X	X														
Urine pregnancy test[k]	X	X														X
Aramchol administration[l]			X	X	X	X	X	X	X	X	X	X	X	X		
PK blood sample collection[m]			X			X				X	X	X	X	X		
AEs[n]	◄ X ►															
Prior/concomitant medications	◄ X ►															

Abbreviations: AE, adverse event; BMI, body mass index; ECG, electrocardiogram; EOS, end of study; FSH, follicle-stimulating hormone; PK, pharmacokinetic.
Notes:

[a] When procedures overlap or occur at the same time point, all blood draws should follow vital sign measurements or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible.
[b] An EOS visit will occur 14 (±2) days after discharge from clinic.
[c] A complete list of serology assessments is provided in Section 6.2.2.
[d] Females only. Further details are provided in Section 6.2.2.
[e] Height and weight will be measured and BMI will be calculated at screening only. Only weight will be measured at check-in and EOS.
[f] A full physical examination will be performed at screening. A brief physical examination will be performed at check-in and EOS. Further details are provided in Section 6.2.5.
[g] Further details on vital sign measurements are provided in Section 6.2.3.
[h] Further details on ECG recordings are provided in Section 6.2.4.
[i] Further details on clinical laboratory assessments, including a complete list of assessments, are provided in Section 6.2.2.
[j] Further details on drug/alcohol screening are provided in Section 6.2.2.

[k] Women of childbearing potential only.
[l] Aramchol dosing occurs twice daily (approximately 12 hours apart) on days denoted with grey shading. Further dosing details are provided in Section 5.1.
[m] Further details on the collection of blood samples for PK analysis are provided in Section 6.1.
[n] Further details on collection and reporting of AEs are provided in Section 6.2.1.

4. STUDY POPULATION

Up to 48 male and female subjects will be enrolled across 3 centers in the United States.

4.1 INCLUSION CRITERIA

Each subject must meet all of the following criteria to be enrolled in this study:

1. The subject is male or female 18 to 79 years of age, inclusive.
2. The subject has a BMI of 19 to 40 kg/m^2, inclusive, at screening.
3. Females of childbearing potential must practice a highly effective method of contraception throughout the study period and for 1 month after treatment discontinuation. Highly effective methods are defined as those that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods, in accordance with the recommendations of the Clinical Trial Facilitation Group Working Group on Contraception include: hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormonal-releasing system, bilateral tubal occlusion, vasectomized partner, and sexual abstinence. All female subjects must have a negative pregnancy test at screening and before the first dose of study drug.
4. Male subjects with female partners of childbearing potential must be vasectomized, be willing to use an acceptable method of birth control, or practice abstinence during the study.
5. The subject has a resting pulse rate of ≥40 and <100 beats per minute with no clinically significant deviation as judged by the investigator.
6. The subject has a QT interval corrected for heart rate using Fridericia's formula (QTcF) of <500 msec.
7. The subject agrees to comply with all protocol requirements.
8. The subject is able to provide written informed consent.

Additional Inclusion Criteria for Healthy Subjects Only (Cohort D):

9. The subject has normal hepatic function.

10. The subject has a resting blood pressure of 90 to 150 mm Hg (systolic) and 50 to 100 mm Hg (diastolic).

11. The subject is judged by the investigator to be in good general health, as determined by medical history, clinical laboratory assessments, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

Additional Inclusion Criteria for Subjects With Hepatic Impairment Only (Cohorts A, B, and C):

12. The subject has cirrhosis with evidence of impaired liver function. The etiology of the cirrhosis may be alcoholic, autoimmune, nonalcoholic steatohepatitis, or chronic viral hepatitis type B or C.

13. The subject has chronic (more than 6 months) and stable hepatic impairment (ie, no acute episodes of illness within 30 days before screening due to deterioration of hepatic function) as assessed by a Child-Pugh classification score of mild (5 to 6 points), moderate (7 to 9 points), or severe (10 to 15 points).

14. The subject has a resting blood pressure of 90 to 155 mm Hg (systolic) and 50 to 100 mm Hg (diastolic).

15. The subject is judged by the investigator to be in good general health, as determined by medical history, clinical laboratory assessments, vital sign measurements, 12-lead ECG results, and physical examination findings, except for findings that, as judged by the investigator, are consistent with the subject's hepatic impairment or other stable concomitant medical conditions.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study:

1. The subject has a history or clinical manifestations of a significant neurological, renal, cardiovascular, gastrointestinal, pulmonary, hematologic, immunologic, or psychiatric disease that would preclude study participation, as judged by the investigator.

2. The subject has a positive test result for human immunodeficiency virus type 1 or 2 antibodies at screening.

3. The subject has a history of drug abuse within 3 months before screening.

4. The subject has a history of alcoholism within 3 months before screening, or excessive alcohol consumption (regular alcohol intake >15 units per week) (1 unit is equal to approximately ½ pint [200 mL] of beer, 1 small glass [100 mL] of wine, or 1 measure [25 mL] of spirits).

5. The subject smokes >10 cigarettes daily and is unwilling to reduce to ≤5 daily from the time of screening through the last PK sample.

6. The subject is unable or unwilling to abstain from alcohol, caffeine, xanthine-containing beverages or food (eg, coffee, tea, chocolate, and caffeinated sodas, colas), grapefruit, grapefruit juice, Seville oranges, or products containing any of these, from 48 hours prior to study drug dosing until discharge.

7. The subject is involved in strenuous activity or contact sports within 24 hours of the first dose of study drug or during the study.

8. The subject has donated blood or blood products >450 mL within 3 months before the first dose of study drug.

9. The subject has a presence or history of relevant drug and/or food allergies (ie, allergy to aramchol, cholic acid, or any excipients, or any significant food allergy).

10. The subject has received study drug in another investigational study within 30 days of dosing.

11. In the opinion of the investigator, the subject is not suitable for entry into the study.

Additional Exclusion Criteria for Healthy Subjects Only (Cohort D):

12. The subject has clinically significant findings at screening including history, physical examination, ECG, or laboratory values.

13. The subject has used an herbal remedy (including St John's wort) known to interfere with liver enzymes during the 28 days before dosing with the study drug.

14. The subject has a past history of surgery or a medical condition that might affect absorption of medicines (hernia repair is acceptable).

15. The subject has a positive test result for hepatitis B surface antigen or antibodies to hepatitis C virus.

16. The subject has used any prescription (excluding hormonal birth control and hormone replacement therapy) or over-the-counter medications (except paracetamol [up to 2 grams per day]), including herbal or nutritional supplements, within 14 days before the first dose of study drug and throughout the study.

17. The subject has a positive test result for drugs of abuse or alcohol at screening or before the first dose of study drug.

Additional Exclusion Criteria for Subjects With Hepatic Impairment Only (Cohorts A, B, and C):

18. The subject has a current >Grade 1 (mild) encephalopathy. Subjects with a history of Grade 3 or 4 encephalopathy that have responded to treatment with medicines such as lactulose, rifaximin, or neomycin may be included with the subject receiving the point score for Grade 3 or 4 encephalopathy.

19. The subject has clinically demonstrable massive tense ascites. Subjects with a history of moderate or severe ascites that have responded to diuretics may be included with the subject receiving the higher score.

20. The subject has esophageal varices that have caused hemorrhage within a period of 8 weeks prior to dosing or are considered of high risk for hemorrhage.

21. The subject has the following types of liver disease: primary biliary cirrhosis, sclerosing cholangitis, hepatocellular carcinoma, cardiac cirrhosis, hemochromatosis, Wilson's disease, other genetic causes of liver disease.

22. The subject has clinically significant impairment of renal function (eCLcr <45 mL/min) as calculated by the Cockcroft-Gault equation.

23. The subject has a hemoglobin <8.5 mg/dL or platelets <30,000/µL.

24. The subject has fluctuating or rapidly deteriorating hepatic function, as indicated by recent history or worsening of clinical (ie, abdominal pain, nausea, vomiting, anorexia, or fever) and/or laboratory signs of hepatic impairment, as judged by the investigator.

25. The subject has evidence of acute viral hepatitis within 30 days before dosing with study drug.

26. The subject has evidence of hepatorenal syndrome.

27. The subject has used any prescription (excluding hormonal birth control and hormone replacement therapy) or over-the-counter medications, including herbal or nutritional supplements, within 14 days before the first dose of study drug and throughout the study, except those essential for the management of hepatic impairment or the treatment of stable concomitant medical conditions, as judged by the investigator. The dose of an approved medication must remain stable from 7 days before study drug dosing and throughout the study.

28. The subject has a positive test result for drugs of abuse (except positive test results associated with prescription medications that have been reviewed and approved by the investigator) at screening or before the first dose of study drug.

4.3 OTHER SCREENING CONSIDERATIONS

1. For inclusion and Child-Pugh categorization, clinical laboratory test results that are deemed inconsistent with the usual stage of hepatic impairment may be repeated.

2. For eligibility purposes, abnormal vital sign, clinical laboratory test, or ECG results may be repeated if an abnormal result is observed at the initial reading.

3. In the event that the participation of a subject in the study is delayed and some screening procedures are performed outside of the prescribed screening window, outdated screening procedures may be repeated.

4. Subjects who do not qualify based on a reversible medical condition or mild intercurrent illness may be reevaluated after further testing/examination or rescreened after the condition is resolved.

5. Subjects are categorized by hepatic impairment at screening. If the Child-Pugh classification scores change on Day −1 due to a change in clinical status or clinical laboratory test results that are not clinically significant, the subject will keep their original score.

4.4 WITHDRAWAL OF SUBJECTS FROM THE STUDY

4.4.1 Reasons for Withdrawal

Subjects can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment.

The investigator may withdraw a subject from the study if the subject:

1. Is noncompliant with the protocol;
2. Experiences an SAE or intolerable AE(s) that in the investigator's opinion requires withdrawal from the study;
3. Has laboratory safety assessments that reveal clinically significant hematological or biochemical changes from baseline values;
4. Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria;
5. Requires a medication prohibited by the protocol; or
6. Requests an early discontinuation for any reason.

The investigator can also withdraw a subject upon the request of the sponsor, or if the sponsor terminates the study. Upon occurrence of an intolerable SAE or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved, stable, or judged by the investigator to be not clinically significant.

4.4.2 Handling of Withdrawals

Subjects are free to withdraw from the study at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page in the electronic case report form (eCRF). Whenever possible, any subject who withdraws from the study prematurely will undergo all EOS assessments. Any subject who fails to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

4.4.3 Replacements

At the discretion of the investigator, and after consultation with the medical monitor and sponsor, any subject who withdraws before completing the study may be replaced to retain the target of 6 evaluable subjects based on clinical considerations. Any replacement subject will be assigned to receive the same treatment as the subject he or she is replacing.

5. STUDY TREATMENTS

5.1 TREATMENTS ADMINISTERED

All doses of study drug will be administered by mouth with 240 mL of room temperature water. During the study, subjects may consume water on an ad libitum basis.

Hepatically impaired subjects will receive a diet standardized for hepatic impairment and healthy control subjects will receive a similar diet. Subjects should receive these meals at the same time during each part of the study.

Single Dose (Part 1):

On Day 1, all subjects will receive a single oral dose of 600 mg (2 × 300-mg tablets) aramchol in the morning, after an overnight fast of at least 10 hours and approximately 30 minutes after a standardized breakfast.

Multiple Dose (Part 2):

Starting on Day 1, all subjects will receive an oral dose of aramchol that will not exceed 300 mg twice daily (approximately 12 hours apart) for 11 days and a single AM dose on Day 12 approximately 30 minutes after a standardized meal. The dose may be adjusted to give lower exposure depending on the review of available data on any reduction in clearance associated with hepatic impairment seen with single doses in Part 1.

5.2 INVESTIGATIONAL PRODUCTS

Aramchol will be supplied as 300-mg tablets.

[redacted]

[redacted]

5.2.1 Study Drug Packaging and Storage

The sponsor will provide the investigator and clinical site with adequate quantities of aramchol. The clinical site pharmacy will prepare the study treatments for each subject according to the schedule of events for Parts 1 and 2 (Section 3.1 and Section 3.2, respectively).

All study drugs must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary site personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions.

5.2.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. Accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, and to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or, with approval of the sponsor, destroyed according to applicable regulations.

5.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

This is a nonrandomized study. At screening, hepatically impaired subjects will be assigned to a study group based on their level of hepatic function according to the Child-Pugh classification system, as shown in Table 5–1. To allocate subjects to the appropriate cohort of hepatic impairment severity, a history of higher severity that has responded to medication will be taken into account. Thus, subjects with a history of Grade 3 or 4 encephalopathy that have responded to treatment with medicines such as lactulose or neomycin may be included with the subject receiving the point score for Grade 3 or 4 encephalopathy. Similarly, subjects with a history of moderate or severe ascites that have responded to diuretics may be included with the subject receiving the higher score.

Table 5–1 Child-Pugh Classification System

Points[a]	Bilirubin (mg/dL)	Albumin (g/dL)	Prothrombin Time (seconds prolonged)	Encephalopathy (grade)[b]	Ascites (grade)
1	<2.0	>3.5	<4	None (Grade 0)	Absent
2	2.0 to 3.0	2.8 to 3.5	4 to 6	1 or 2	Slight
3	>3.0	<2.8	>6	3 or 4 or subjects receiving medication(s) to prevent encephalopathy	Moderate or severe subjects on medication(s) to control ascites

Abbreviation: INR, international normalized ratio.

[a] For each category (bilirubin, albumin, prothrombin time or INR, encephalopathy grade, and ascites), points are assigned based on the subject's condition and the criterion met. The Child-Pugh class is assigned based on the sum of these points as follows: Child-Pugh Class A or mild hepatic impairment if the sum is 5 or 6 points; Child-Pugh Class B or moderate hepatic impairment if the sum is 7 to 9 points; and Child-Pugh Class C or severe hepatic impairment if the sum is 10 to 15 points.

[b] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 count-per-second waves.
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2-3 count-per-second delta activity.

Hepatically impaired subjects (Cohorts A, B, and C) will be enrolled as they become eligible and receive their allocated subject numbers in the order in which they are enrolled into their respective cohorts.

5.4 BLINDING

This is an open-label study.

5.5 TREATMENT COMPLIANCE

All doses of the study drug will be administered in the clinical site under direct observation of site personnel and recorded in the eCRF. Clinic personnel will confirm that the subject has received the entire dose of study drug.

The date and time of study drug dosing will be recorded on the appropriate page in the eCRF. If a subject is not administered study drug, the reason for the missed dose will be recorded.

5.5.1 Prior and Concomitant Medications

Restrictions for prior and concomitant medications and therapies are provided in Section 4.1 and Section 4.2. Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary available at initiation of the study.

5.5.1.1 Prior Medications

Information regarding prior medications taken by the subject within the 30 days before signing the informed consent form (ICF) will be recorded in the subject's eCRF.

5.5.1.2 Concomitant Medications

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. If a concomitant medication is taken, a joint decision will be made by the investigator and the sponsor to continue or discontinue the subject based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the safety of the subject or the interpretation of the data. The investigator is responsible for ensuring that details regarding the medication are adequately recorded in the eCRF.

6. STUDY PROCEDURES

Before performing any study procedures, all potential subjects will sign an ICF as outlined in Section 9.2.2.3. Subjects will undergo study procedures at the time points specified in the schedule of events for Parts 1 and 2 (Section 3.1 and Section 3.2, respectively).

The total amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

6.1 PHARMACOKINETIC ASSESSMENTS AND ENDPOINTS

Single Dose (Part 1):

Blood samples for analysis of concentrations of aramchol and its metabolites in plasma will be collected at the following time points: before dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 24, 48, 72, 96, 120, 144, 168, 192, and 240 hours (the last 2 time points are for hepatically impaired subjects only) after administration of aramchol. Acceptable time deviations are ±5 minutes for 0 to 4 hours, ±10 minutes for >4 to 8 hours, ±15 minutes for >8 to 24 hours, ±30 minutes for >24 to 72 hours, and ±60 minutes for >72 hours to 240 hours.

The following plasma PK parameters will be calculated as endpoints for aramchol using actual sampling times rather than scheduled sampling times:

- AUC from time 0 to the last quantifiable concentration (AUC_{0-t})

- AUC from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$)
- Maximum observed plasma concentration (C_{max})
- Time to reach maximum observed plasma concentration (T_{max})
- Time to the first measurable plasma concentration (T_{lag})
- Apparent terminal elimination half-life ($t_{1/2}$)
- Apparent oral clearance (CL/F)
- Apparent volume of distribution (V_z/F)
- Elimination rate constant (k_e)

Multiple Dose (Part 2):

Blood samples for analysis of concentrations of aramchol and its metabolites in plasma will be collected before the AM dose on Days 1, 4, 8, 9, 10, 11, and 12 and at the following times after the AM dose on Day 12: 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours. Acceptable time deviations are ±5 minutes for 0 to 4 hours, ±10 minutes for >4 to 8 hours, and ±15 minutes for >8 to 12 hours.

The following plasma PK parameters on Day 12 will be calculated as endpoints for aramchol using actual sampling times rather than scheduled sampling times (if conducted):

- AUC from time 0 to the dosing interval tau at steady state ($AUC_{0\text{-}tau, ss}$)
- Maximum observed plasma concentration at steady state ($C_{max, ss}$)
- Time to reach maximum observed plasma concentration at steady state ($T_{max, ss}$)
- Minimum observed plasma concentration at steady state ($C_{min, ss}$)
- Time of minimum observed plasma concentration at steady state ($T_{min, ss}$)
- Average plasma concentration at steady state ($C_{avg, ss}$)

Time to reach steady state will also be estimated graphically by assessing trough plasma concentrations (ie, pre-AM dosing on Days 1, 4, 8, 9, 10, 11, and 12) over 12 days of administration.

6.1.1 Pharmacokinetic Sample Collection

Details for the collection, processing, storage, and shipping of PK samples will be provided to the clinical site separately.

6.1.2 Pharmacokinetic Sample Analysis

Pharmacokinetic samples will be analyzed using a validated liquid chromatography coupled with tandem mass spectrometry assay for aramchol in human plasma. Assay results and validation details will be provided in a separate bioanalytical report. Stored samples of plasma will also be analyzed for aramchol metabolites pending results of a mass balance study.

6.2 SAFETY ASSESSMENTS AND ENDPOINTS

Safety and tolerability will be assessed by the following endpoints: monitoring and recording of AEs, clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements, 12-lead ECG results, and physical examination findings.

For all safety assessments, the investigator will determine whether results are clinically significant, which is defined as any variation in a result that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance will be documented and an AE reported on the AE page in the subject's eCRF. The investigator will monitor the subject until the result has reached the reference range or the result at screening, or until the investigator determines that follow-up is no longer medically necessary.

6.2.1 Adverse Events

Adverse events will be assessed from the time the subject signs the ICF until EOS and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and SAEs are reported to the sponsor, regardless of their relationship to study drug or clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

6.2.1.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Subjects will be instructed to contact the investigator at any time after signing the ICF if any symptoms develop.

A treatment-emergent AE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

An adverse reaction is any AE caused by a study drug. Adverse reactions belong to a subset of all suspected adverse reactions and indicate that there are reasons to conclude that the study drug caused the event.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator's brochure or if it occurs with specificity or severity that has not been previously observed with the study drug being tested.

An AE or suspected adverse reaction is considered an SAE/suspected unexpected serious adverse reaction if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent

one of the outcomes listed in this definition. 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that might have caused death if it had been more severe.

6.2.1.2 Eliciting and Documenting Adverse Events

Subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page in the eCRF (eg, laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

6.2.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded in the source documentation and on the AE page in the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dosage, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. The Medical Dictionary of Regulatory Activities will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE but will be recorded as medical history. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that is considered serious by the investigator or that meets SAE criteria (Section 6.2.1.1) must be reported to the sponsor (or the sponsor's designee) following the

guidelines provided on the study SAE form as soon as site personnel/investigator have become aware of the event and no later than 24 hours regardless of the relationship to the study drug. The investigator will assess whether there is a reasonable possibility that the study drug caused the SAE.

Serious AE report form completion and reporting must not be delayed even when information is incomplete at the time of the initial report. Any additional (follow-up) information that becomes available after the initial reporting should be forwarded in a follow-up SAE report form by the site personnel within 24 hours of the information becoming available.

All SAEs should be followed until resolution or stabilization of all parameters (including laboratory) return to baseline or until the investigator assesses them as stable or until the subject is lost to follow-up.

The sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in US Title 21 Code of Federal Regulations (CFR) Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly.

For this study, the following contact information will be used for SAE reporting:

6.2.1.4 Assessment of Severity

The severity (or intensity) of an AE refers to the extent to which it affects the subject's daily activities and will be classified as mild, moderate, or severe using the following criteria:

- Mild: These events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate: These events result in a low level of inconvenience or require minor therapeutic measures. Moderate events may cause some interference with normal functioning.
- Severe: These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow the duration of the event at each level of intensity to be assessed. An AE characterized as intermittent does not require documentation of the onset and duration of each episode.

6.2.1.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be classified as follows:

- Not related: There is not a reasonable possibility of relationship to study drug. The AE does not follow a reasonable temporal sequence from study drug administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

- Related: There is a reasonable possibility of relationship to study drug. The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, or concomitant medications), represents a known reaction to the study drug or other drugs in its class, is consistent with the known pharmacological properties of the study drug, and/or resolves with discontinuation of the study drug (and/or recurs with rechallenge, if applicable).

6.2.1.6 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

6.2.2 Clinical Laboratory Testing

Clinical laboratory tests will be performed by the clinical sites' local laboratories. Blood and urine samples will be collected and prepared using standard procedures.

Repeat clinical laboratory tests may be performed at the discretion of the investigator, if necessary, to evaluate inclusion and exclusion criteria or clinical laboratory abnormalities. The clinical laboratory that will perform the tests will provide the reference ranges for all clinical laboratory parameters. Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter.

Single Dose (Part 1):

Clinical laboratory testing will occur at screening; check-in; on Day 4; prior to discharge on Day 8 (healthy subjects) or Day 11 (hepatically impaired subjects); and at EOS.

Multiple Dose (Part 2):

Clinical laboratory testing will occur at screening; check-in; Days 4, 8, and 12; and at EOS.

The following clinical laboratory assessments will be performed for Parts 1 and 2:

Hematology	Absolute neutrophil count and differential, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, leukocyte count and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils [absolute and differential]), mean corpuscular volume, platelet count, red blood cell count, and red blood cell distribution width
Coagulation	International normalized ratio, partial thromboplastin time, and prothrombin time
Serum chemistry	Alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin (total), blood urea nitrogen, calcium, carbon dioxide, chloride, cholesterol (total, high-density lipoprotein, and calculated low-density lipoprotein), creatinine, gamma-glutamyltransferase, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein, triglycerides, and uric acid
Urinalysis	Bilirubin, color, glucose, ketones, leukocyte esterase, reflex microscopy (performed if dipstick is positive for protein or the blood value is 1+ or greater; and includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, occult blood, pH, protein, specific gravity, turbidity, and urobilinogen
Serology	Hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus antibody types 1 and 2 (screening only)
Other analyses	All subjects: Urine drug screen (alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, methamphetamines, methylenedioxymethamphetamine, and opiates [including heroin, codeine, and oxycodone]) Female subjects: Follicle-stimulating hormone (postmenopausal women; screening only), urine pregnancy test (human chorionic gonadotropin) (screening, check-in, and EOS [or early termination])

6.2.3 Vital Sign Measurements

All vital signs will be measured after the subject has been in the seated position for at least 5 minutes. Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

Single Dose (Part 1):

Vital signs will be measured at screening and check-in; prior to aramchol dosing; 4, 12, and 24 hours after dosing; Days 3 and 4; prior to discharge on Day 8 (healthy subjects) or Day 11 (hepatically impaired subjects); and at EOS.

Multiple Dose (Part 2):

Vital signs will be measured at screening and check-in, prior to the AM aramchol dosing on Day 1; 4 hours after the AM dose on Days 1 through 12; prior to discharge on Day 13; and at EOS.

6.2.4 Electrocardiograms

All ECGs will be measured after the subject has been in the supine position for at least 5 minutes. A single repeat measurement is permitted at screening for eligibility determination.

Electrocardiogram assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST-segment, T-wave, and U-wave abnormalities. In addition, measurements of the following intervals will be measured and reported: RR interval, PR interval, QRS width, QT interval, and QTcF.

Single Dose (Part 1):

Single 12-lead ECG recordings will be made at screening and check-in; at 6, 12, and 24 hours after dosing; on Day 4; prior to discharge on Day 8 (healthy subjects) or Day 11 (hepatically impaired subjects); and at EOS.

Multiple Dose (Part 2):

Single 12-lead ECG recordings will be made at screening and check-in; on Days 4, 8, and 12; and at EOS.

6.2.5 Physical Examinations

Subjects will undergo a physical examination at the time points specified in the schedule of events for Parts 1 and 2 (Section 3.1 and Section 3.2, respectively). A full physical examination will include, at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities. A brief physical examination will include, at minimum, assessment of skin, lungs, cardiovascular system, and abdomen (liver and spleen). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

Height and weight will be measured, and BMI will be calculated at screening only. Only weight will be measured at check-in and EOS (or early termination).

7. STATISTICAL ANALYSIS PLANS

7.1 SAMPLE SIZE CALCULATIONS

For Part 1, up to 48 subjects are planned: 8 subjects each in the mild (Cohort A), moderate (Cohort B), and severe (Cohort C) hepatic impairment cohorts and 8 to 24 healthy control subjects with normal hepatic function (Cohort D). For Part 2, at least 8 subjects with mild and moderate or moderate and severe hepatic impairment and up to 8 healthy control subjects with normal hepatic function are planned. The sample size was chosen for this study based on clinical and practical considerations and not on a formal statistical power calculation. The US Food and Drug Administration Guidance for Industry, Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (DHHS 2003) was used as a guide to select the sample size, which is considered sufficient to adequately assess the safety and PK profiles of aramchol.

In the event of early withdrawals or discontinuations, subjects may be replaced at the discretion of the investigator, and after consultation with the medical monitor and sponsor if the number of completers will be less than 6 subjects in any cohort.

7.2 ANALYSIS SETS

The analysis populations are as follows:

- The PK population will include subjects who receive at least 1 dose of aramchol and have sufficient concentration data to support accurate estimation of at least 1 PK parameter. In

Part 1, subjects who experience vomiting within 6 hours after study drug dosing will be excluded from the PK analysis.

- The safety population will include all subjects who receive at least 1 dose of aramchol.

7.3 STATISTICAL ANALYSIS

Details of all statistical analyses will be described in a statistical analysis plan. All data collected will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], minimum, median, and maximum).

Baseline demographic and background variables will be summarized by hepatic condition for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

7.3.1 Pharmacokinetic Analyses

Plasma concentrations will be listed and summarized descriptively (number of subjects, arithmetic mean, SD, coefficient of variation [CV], minimum, median, and maximum). Plasma concentration versus actual time profiles for each subject will be presented graphically. The mean plasma concentration versus scheduled time profiles will be presented graphically.

Pharmacokinetic parameters derived from plasma concentration data using noncompartmental methods with Phoenix® WinNonlin® (Certara USA Inc, Princeton, New Jersey) Version 8.0 or higher will be summarized by hepatic group using descriptive statistics (number of subjects, arithmetic mean, SD, CV, minimum, median, and maximum). Geometric mean and geometric CV will also be calculated for AUCs and C_{max}. The $AUC_{0-t,}$ AUC_{0-inf}, and C_{max} values may also be expressed in terms of unbound drug concentrations.

An analysis of variance (ANOVA) model will be performed on the natural logarithms of AUC_{0-t}, $AUC_{0-inf,}$ and C_{max} to calculate the ratio of geometric means and its 90% confidence interval between subjects with hepatic impairment and the corresponding healthy control

subjects, as appropriate. The ANOVA model will include hepatic group (normal matching mild, mild, normal matching moderate, moderate, normal matching severe, and severe, where applicable) as a fixed effect.

For AUC_{0-t}, AUC_{0-inf}, and C_{max}, a linear regression model will be performed on the natural logarithms of AUC_{0-t}, AUC_{0-inf}, and C_{max} as dependent variables and each of the following natural-log-transformed hepatic function estimates as independent variables: Child-Pugh classification score (in subjects with hepatic impairment only), baseline serum bilirubin, serum albumin, and prothrombin time. The regression coefficients representing the relationship between the PK parameters and the hepatic function estimates will be estimated together with their 90% confidence intervals from the regression model.

Sensitivity analyses may be conducted to investigate the potential impact of imbalance existing across hepatic impairment groups in the distribution of the baseline covariates used in subject matching (eg, body weight) and, if data suggest, appreciable differences in PK exposure (AUC_{0-t}, AUC_{0-inf}, and C_{max}) across different values of the same baseline covariate.

Detailed descriptions of the analyses in this study will be presented in the statistical analysis plan.

7.3.2 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by hepatic condition and overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to early discontinuation will also be presented in data listings.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by hepatic condition at each time point using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Shift tables will be generated for clinical laboratory test results. Clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings will be presented in data listings.

7.4 HANDLING OF MISSING DATA

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Mean BLQ concentrations will be presented as BLQ, and the SD

and CV will be reported as not applicable. Missing concentrations will be excluded from the calculations.

For the PK analysis, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

7.5 INTERIM ANALYSES

No formal interim analyses will be performed in this study.

8. REFERENCE LIST

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (US). Guidance for industry: Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling. May 2003 [cited 10 Jul 2019]. Available from: https://www.fda.gov/media/71311/download

Aramchol. Investigator's brochure, 3rd ed. Tel Aviv (Israel); 2019. 125 p.

9. APPENDICES

9.1 APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ANOVA	analysis of variance
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-inf}}$	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
$AUC_{0\text{-t}}$	area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
$AUC_{0\text{-tau, ss}}$	area under the plasma concentration versus time curve from time 0 to the dosing interval tau at steady state
BLQ	below the limit of quantification
BMI	body mass index
$C_{avg, ss}$	average plasma concentration at steady state
CFR	Code of Federal Regulations
CL/F	apparent total oral clearance
C_{max}	maximum observed plasma concentration
$C_{max, ss}$	maximum observed plasma concentration at steady state
$C_{min, ss}$	minimum observed plasma concentration at steady state
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
FDA	Food and Drug Administration
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
k_e	elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
NASH	nonalcoholic steatohepatitis
PK	pharmacokinetic(s)
QTcF	QT corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SD	standard deviation
$t_{1/2}$	apparent terminal phase half-life
T_{lag}	time to the first measurable plasma concentration
T_{max}	time to reach maximum observed plasma concentration
$T_{max, ss}$	time to reach maximum observed plasma concentration at steady state
$T_{min, ss}$	time of minimum observed plasma concentration at steady state
V_z/F	apparent volume of distribution

9.2 APPENDIX 2: STUDY GOVERNANCE

9.2.1 Data Quality Assurance

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current International Council for Harmonisation (ICH) guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice, the protocol, and standard operating procedures. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability.

Important protocol deviations, should they occur during the study, will be presented in Section 10.2 of the clinical study report.

9.2.2 Investigator Obligations

The following administrative items are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

9.2.2.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2.2.2 Institutional Review

Federal regulations and ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study that is to be provided to the subject or the subject's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

9.2.2.3 Subject Consent

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each subject before he or she enters the study or before performing any unusual or nonroutine procedure that involves risk to the subject. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or his/her legal guardian will be given a full explanation of the study and will be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give his or her consent to participate in the study by signing the ICF. A copy of the signed ICF will be provided to the subject/legal guardian.

9.2.2.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate.

9.2.2.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor the sponsor's designee is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor the sponsor's designee is financially responsible for further treatment of the disease under study.

9.2.2.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and US Title 21 of the CFR by providing essential documents, including but not limited to, the following:

- IRB approval.
- An original investigator-signed investigator agreement page of the protocol.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. Curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the subject or legal guardians.

- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with US Title 42 CFR Part 493.

9.2.2.7 Study Conduct

The investigator agrees to perform all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH E6(R2): Good Clinical Practice; the protocol; and all national, state, and local laws or regulations.

9.2.2.8 Case Report Forms and Source Documents

Site personnel will maintain source documentation, enter subject data into the eCRF as accurately as possible, and rapidly respond to any reported discrepancies.

Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and any subsequent investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

9.2.2.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.2.2.10 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

9.2.2.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authorities with any reports required.

9.2.2.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. The sponsor is responsible for informing the investigator/institution when these documents no longer need to be retained.

9.2.2.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without their prior authorization, but data and any publication thereof will not be unduly withheld.

9.2.3 Study Management

9.2.3.1 Monitoring

9.2.3.1.1 Monitoring of the Study

The monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and clinical site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records including eCRFs and source documentation, and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

9.2.3.1.2 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, the FDA, or other regulatory agencies access to all study records.

The investigator should promptly notify the sponsor and clinical sites of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

9.2.3.2 Management of Protocol Amendments and Deviations

9.2.3.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the subject, must be reviewed and approved by the sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator’s IRB for approval before subjects are enrolled into an amended protocol.

9.2.3.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that leads to a subject being discontinued from the study, or significantly affects the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH E6(R2) guidelines.

Protocol deviations will be documented by the monitor throughout the course of monitoring visits. Any additional protocol deviations that are found by the monitor during the course of monitoring visits will also be recorded by the monitor. The investigator will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations, if appropriate, in a timely manner.

9.2.3.3 Study Termination

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (including the EOS visit). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

9.2.3.4 Final Report

Regardless of whether the study is completed or prematurely terminated, the sponsor will ensure that clinical study reports are prepared and provided to the regulatory agency as required by the applicable regulatory requirement. The sponsor will also ensure that clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

Upon completion of the clinical study report, the investigators will be provided with the final approved clinical study report, as appropriate.