Cover Page for Protocol

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NCT number	NCT04004325
Sponsor trial ID:	4101-MET-201
Official title of study:	A phase 1/2, randomized, double-blind, placebo controlled study evaluating the safety, tolerability and efficacy of FT-4101 in overweight/obese subjects with NASH
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Clinical Development FT-4101

Clinical Study Protocol 4101-MET-201

A PHASE 1/2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY, TOLERABILITY AND EFFICACY OF FT-4101 IN OVERWEIGHT/OBESE SUBJECTS WITH NASH

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[redacted]

Redacted protocol
Includes redaction of personal identifiable information only.

Version 2.0_23-Jul-2019

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided.

1.2 Document History

Version	Revision Date	Revision Description
1.0	**05-APR-2019**	**Original Document**
2.0	**23-JUL-2019**	**1. Incorporation of Administrative Letter/ Amendment dated 01 May 2019** a) Change of Inclusion Criterion # 3a**.** All subjects, including the subjects that meet the diagnosis of NASH with a previous liver biopsy, will undergo a FibroScan at screening. This is necessary as FibroScan is considered an endpoint and a pre-treatment (screening) result is necessary to evaluate the change from baseline to C4/D22. *Section 2.0 Study Summary, section 7.1 Inclusion Criteria* (Comment: This criterion is further amended under # 3 in this amendment [protocol version 2.0]) b) Change of number for rescheduling options at check-in from 2 to 1. *Section 9.1.12 Check-in Procedure* c) Clarification of Exclusion Criterion #26. The timepoint "1 year" was accidentally omitted in the protocol and was re-added again. *Section 2.0 Study Summary, section 7.2 Exclusion Criteria* d) Adjustments of language in order to comply with Clinical Data Interchange Standards Consortium (CDISC) controlled terminology for electronic datasets. *Section 10.3.3 Action Taken and Outcome* f) Adjustments of "X-marks" in the Schedule of Events to be consistent with protocol language. *Section 16.1, Appendix A* g) Clarification of footnote l under the Schedule of Events *Section 16.1, Appendix A*

		h) Clarification of terms Gastrointestinal was added in order to ensure that gastrointestinal system for the baseline physical examination is the same as the abdominal assessed at the abbreviated PE. *Section 9.1.4 Physical Examination* **2. Incorporation of Administrative Letter dated 29 May 2019** a) Capturing of SAEs was changed. From now on, SAEs will be entered electronically via EDC with an autogenerated email. The email will be sent to [redacted] Pharmacovigilance (PV) after completion and saving of an AE, with choosing the options "serious=yes". The paper SAE report form is only to be utilized if the site is unable to access EDC for any reason. *Section 10.2 Recording of Adverse Events and Serious Adverse Events, section 10.4.2 Serious Adverse Events and Suspected Unexpected Serious Adverse Serious Reactions (SUSARs)* **Changes for this Amendment:** **3. Change of Inclusion Criterion # 3a** LSM by FibroScan is deleted as an inclusion criterion. A FibroScan CAP value of ≥ 300 dB/m is still required as part of the eligibility criteria. LSM as entry criterion is eliminated, as it is specific for a progressive NASH. The FibroScan can be performed at screening or within 30 days prior to screening. *Section 2.0 Study Summary, section 7.1 Inclusion Criteria, 9.1.2 Screening, 9.1.17.4 FibroScan, section 16.1, Appendix A* **4. Change of Inclusion Criterion # 6c** Fasting plasma glucose (FPG) at screening was changed from < 180 mg/dL to < 240 mg/dL, in order to align with protocol section 9.1.14 Wash-Out Period *Section 2.0 Study Summary, section 7.1 Inclusion Criteria* **1. Change of Exclusion Criterion # 19** Adjustments to contraindications for MRI

		examination to adhere to specific guidance provided by local imaging centers on contraindications. *Section 2.0 Study Summary, section 7.2 Exclusion Criteria* **2. Change of Specified Timepoint for Prohibited Medications** Any medication that is a strong inducer or strong inhibitor of CYP3A4, is prohibited from 15 days prior to dosing unless half-life is greater than 72 hours, then it is prohibited for 5 half-lives prior to dosing. The timepoint of 30 days prior to dosing has been adjusted to the above statement to accommodate for the various drugs and half-lives. *Section 7.3.1 Prohibited Medications* **3. Allowing to Collect Additional Samples Covering all Types of Tissues for Potential Future Analysis** Additional samples (e.g., including blood samples, urine samples and all types of tissue samples) may be collected and stored for potential future analysis. *Section 9.1.8 Procedures for Clinical Laboratory Samples* **4. Incorporation of Updated IB, version 5.0** Updated language from IB and reference to updated version have been incorporated throughout the protocol. *Section 4.1 Background, section 4.3 Summary of Pre-Clinical/Clinical Studies* **5. Adding Sebum Collection Using Sebutape® for Fatty Acid Concentration at D-14.** This sample will be stored for potential future analyses. *Section 6.1 Study Design, section 16.1, Appendix A* **6. Clarification around Central Reader and Incidental Findings on MRI Scans** MRI readings for safety will not be performed by a central reader, but by the specific MRI imaging center. MRI incidental findings discovered at

		screening will not be entered as adverse events, but recorded as medical history, as these pre-existing conditions are found as a result of the screening procedure. *Section 9.1.17.6 MRI-PDFF* **7. Recording of Deuterated Water Intake** Missed doses of deuterated water will be entered into the CRF to check compliance. *Section 8.5.1 Deuterated Water* **8. Compliance of IP Intake** In order to achieve appropriate coverage of IP, subjects are not allowed to miss more than a specific number of doses during their dosing cycles. If subjects are non-compliant, they may be excluded from the study. *Section 8.5 Dose Regimen* **9. Exclusion of Cannabidiol Oil as Concomitant Drug** Cannabidiol is a CYP inhibitor and will be added to the list of CYP3A4 inhibitors and inducers. It is covered under "other food components" in the Exclusion Criteria. *Section 16.3, Appendix C* **10. Adjustment of Blood Volume** Blood sampling for PK assessments will need 2.0 mL per sample instead of the projected 3.0 mL per sample. This leads to a reduction of the total blood volume for the study. *Section 9.1.16 Pharmacokinetic Assessments and Schedule* **11. Adding Hyperglycemia to Blood Glucose Measurement at Hyperglycemia** Subjects' blood glucose might be measured by fingerstick whenever there are signs or symptoms of hypoglycemia or hyperglycemia. Hyperglycemia was added to ensure that subjects blood glucose is monitored across all ranges for the safety of the subject. *Section 9.1.13 Blood Glucose Monitoring by Fingerstick*

		12. Addition of ECG as primary safety endpoint Change from baseline in 12-lead ECG added as parameter in the objectives and endpoint sections in order to be consistent with the statistical analysis section of the protocol. ECG is used during the study as safety criterion but was not stated as is in specific section. *Section 2.0 Study Summary, section 5.1 Primary Objectives and Endpoints* **13. Change of sponsor contact title** Title of sponsor contact was changed from Translational Medicine to Clinical Development. *Section Title Page and Sponsor Protocol Approval Page* **14. Clarifications to the Protocol** a) Exclusion Criterion #6, the exclusion of liver cirrhosis by FibroSure® > 0.75, will be assessed by the "Fibrosis Score" test reported on the laboratory report. *Section 2.0 Study Summary, section 7.2 Exclusion Criteria* b) Inclusion Criterion #2, the exclusion of subjects with acute proliferative retinopathy, will be based on the history of the subject and not on an additional examination. *Section 2.0 Study Summary, section 7.1 Inclusion Criteria* c) Clarification around the Exclusion Criterion #16 Subjects with dry eyes due to wearing contact lenses can be included in the study. *Section 2.0 Study Summary, section 7.2 Exclusion Criteria* d) Clarification around Check-in Criterion #5 and Check-in Procedure #4 Adjustments of language in order to provide consistency throughout the protocol in regards to time and concomitant medications *Section 7.3.2 Check-in Criteria, section 9.1.12 Check-in Procedure*

		e) Clarification of Urinalysis Leucocyte esterase or equivalent may be used. *Section 9.1.8 Procedure for clinical laboratory samples* f) Row added in Schedule of Events for the assessment of TSH in order to be consistent with the protocol. *Section 16.1, Appendix A* g) Adjustment of wording for consistency. The word Patient will be exchanged to Subject throughout the section for the study conduct. h) Deletion of reference [Turner, et al. 2003] in text, as reference was not stated in the references section. Section 4.2 Rationale for the Proposed Study i) Correction of typographical errors throughout the protocol.

1.3 Approval

Representatives of Sponsor will sign the agreement on the protocol.

Investigators agreement on the protocol will be provided in a separate protocol approval document.

Sponsor Protocol Approval Page

Protocol Number:	**4101-MET-201**
Protocol Title:	**A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability and Efficacy of FT-4101 in Overweight/Obese Subjects with NASH**
Protocol Version:	**2.0**
Date:	**23-JUL-2019**

The Sponsor agrees to conduct the trial as outlined in this protocol in reference to national/local regulations and in accordance with current Good Clinical Practice (GCP) guidelines described in the International Committee for Harmonization (ICH) Guidance document E6 (R2), the FDA regulations for clinical trials, 21 CFR 312, the Health Insurance Portability and Accountability Act (HIPAA), and the most current version of the Declaration of Helsinki. Any modification to the Protocol must be agreed upon by both the Investigator and Sponsor and documented in writing. By written agreement to this protocol, the Sponsor agrees to allow direct access to all documentation, including source data, to authorized individuals representing the Sponsor (including monitoring staff and auditors), to Institutional Review Boards/Independent Ethics Committees (IRB/IEC) and/or to regulatory authorities.

Approved for the Sponsor by:

Name: [redacted]
Function: [redacted] Clinical Development
Address: FORMA Therapeutics, Inc.
500 Arsenal Street, Suite 100
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[redacted] _____ [redacted] _____ [redacted]

Name (printed) **Signature** **Date**

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LIST OF IN-TEXT FIGURES

2.0 STUDY SUMMARY

Name of Investigational Product	FT-4101
Protocol Number	4101-MET-201
Protocol Title	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability and Efficacy of FT-4101 in Overweight/Obese Subjects with NASH
Primary Objectives and Endpoints	To assess safety and tolerability of FT-4101 after administration of multiple doses in overweight/obese subjects with NASH by: • Incidence of treatment-emergent adverse events (TEAEs) • Incidence of clinical lab abnormalities • Incidence and severity of clinical findings on physical examination • Change from baseline in vital signs (blood pressure [BP], heart rate [HR], respiratory rate, and temperature]) • Change from baseline in 12-lead electrocardiogram (ECG) parameters To assess the preliminary efficacy of FT-4101 on liver fat after administration of multiple doses in overweight/obese subjects with NASH by: • Reduction (absolute and relative) of % liver fat on magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) at 12 weeks
Secondary Objectives and Endpoints	To assess the preliminary efficacy of FT-4101 on liver fat after administration of multiple doses in overweight/obese subjects with NASH by: • Reduction (absolute and relative) of % liver fat on MRI-PDFF at 6 weeks • Proportion of subjects experiencing a relative reduction of 30% or greater of % liver fat at week 12 as assessed by MRI-PDFF To assess the pharmacodynamic (PD) effect of FT-4101 on circulating biomarkers of liver inflammation after administration of multiple doses in overweight/obese subjects with NASH by: • Reduction of liver biochemistry marker: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST),

	Gamma-glutamyl transferase (γGT), Alkaline phosphatase, and Total bilirubin To assess the pharmacokinetic (PK) profile of FT-4101 after administration of a single dose and multiple doses in overweight/obese subjects with NASH including, but not limited to: • Maximum concentration (C_{max}) • Time to maximum concentration (T_{max}) • Area under the concentration-time curve for a dosing interval (AUC_{tau}) • Trough plasma concentrations (C_{trough}) at steady state
Exploratory Objectives and Endpoints	To assess the PD effect of FT-4101 on the inhibition of fasting hepatic de novo lipogenesis (DNL) after administration of multiple doses in overweight/obese subjects with NASH by using a 2-week deuterated water labeling protocol. To assess the PD effect of FT-4101 on skin surface sebum level using a Sebumeter® after administration of multiple doses in overweight/obese subjects with NASH by measuring: • Total sebum production To assess the PD effect of FT-4101 on sebum lipids using Sebutape® after administration of multiple doses in overweight/obese subjects with NASH by measuring: • Sebum fatty acid concentrations • Sebum DNL To assess the PD effect of FT-4101 after administration of multiple doses in overweight/obese subjects with NASH by assessment of circulating biomarkers of liver injury and fibrosis, such as but not limited to: • Enhanced liver fibrosis (ELF) score: Hyaluronic acid (HA), Procollagen III amino terminal peptide (PIIINP), Tissue inhibitor of metalloproteinases 1 (TIMP-1) • Cytokeratin-18 (CK-18) fragments, e.g., CK-18 M30 and CK-18 M65 • FibroSure® • PRO-C3

	To assess the PD effect of FT-4101 after administration of multiple doses in overweight/obese subjects with NASH by assessment of circulating metabolic parameters, such as but not limited to:
	• Fasting Lipids
	  o Total cholesterol
	  o Low-density Lipoprotein cholesterol (LDL-c) direct
	  o High-density Lipoprotein cholesterol (HDL-c)
	  o Non-HDL cholesterol (non-HDL-c)
	  o Triglycerides (TG)
	  o Free fatty acids (FFA)
	• Glycemic parameters
	  o Fasting plasma glucose (FPG)
	  o Fasting insulin
	  o HOMA-IR
	  o HbA1c
	• Adiponectin (total and high molecular weight)
	• FGF-21
	• Malonyl carnitine
	
	To assess the PD effect of FT-4101 after administration of multiple doses in overweight/obese subjects with NASH by assessing steatosis (CAP) and liver stiffness (LSM) determined by FibroScan® at 12 weeks.
	
	To assess the effect of FT-4101 after administration of multiple doses in overweight/obese subjects with NASH on imaging parameters assessed by MRI-PDFF:
	• Liver Volume (L)
	• Liver Fat Volume Index (L)

Phase of Development	Phase 1/2
Number of Study Sites	Up to 3 sites

Study Population	Overweight/Obese subjects with NASH
Number of Subjects	At least 30 subjects, divided in 2 cohorts with at least 15 subjects per cohort. Drop-outs may be replaced in order to enroll sufficient subjects into the study, only after discussion with Sponsor and Investigator.
Summary of Study Design	This is a Phase 1/2, randomized, double-blind, placebo-controlled study evaluating the safety, tolerability and preliminary efficacy of an intermittent treatment with 3.0 mg and 4.5 mg FT-4101 over 12 weeks in overweight/obese subjects with NASH. The study may be conducted in up to 2 dosing cohorts, that will overlap. Cohorts will enroll 15 subjects each, randomized to FT-4101 or placebo in a ratio of 2:1 (10 on active, 5 on placebo). Cohort A will assess the administration of a dose of 3.0 mg FT-4101 given for 2 weeks, alternating with a 1 week of no investigational product (IP), continued for 12 weeks. This design leads to 4 dosing cycles (2-week daily IP followed by 1 week of no IP). After Cohort A (3.0 mg FT-4101) received 6 weeks of treatment (2 dosing cycles), a dose escalation meeting will be held and an advancement to Cohort B (4.5 mg FT-4101) will only be approved after the safety and tolerability data from Cohort A (3.0 mg FT-4101) are determined to be acceptable. Cohort B will be administered up to 4.5 mg FT-4101 with the same dosing design as in Cohort A. All subjects will undergo a screening visit, a run-in period, followed by multiple outpatient visits, 2 in-house treatment periods, and a follow-up visit. An optional wash-out period prior to dosing may be performed for subjects with T2DM on oral antidiabetic combination therapy. Safety, tolerability, PK and PD assessments will be performed throughout the study. Hepatic steatosis will be performed by MRI-PDFF. Hepatic and sebum DNL will be assessed using a 2-week deuterated water labelling protocol. Sebum and blood samples for additional PD and PK assessments will be collected throughout the study. For detail on all assessments, please see the Schedule of Events (SOE) in section 16.1.
Treatments	Treatment Schedule: Intermittent: Daily treatment for 2 weeks, alternating by 1 week without treatment; continuing until the end of week 12.

	Cohorts	Number of Subjects	Treatment Schedule	Drug Given
	Cohort A	N=10	Intermittent	FT-4101 3.0 mg
		N=5	Intermittent	Matching Placebo
	Cohort B	N=10	Intermittent	FT-4101 4.5 mg
		N=5	Intermittent	Matching Placebo
Route of Administration	Study drug will be administered orally with 240 mL of water. Subjects do not need to be in a fasting state.			
Duration of Participation	The duration of participation in this study, including Screening, Treatment Period and Follow-up will be approximately 20 weeks.			
Inclusion Criteria	Subjects who meet all applicable criteria at Screening will be included in the study: 1. Willing and able to give informed consent before any study-specific procedures being performed. 2. Male or female subjects ≥ 18 to ≤ 75 years. 3. Meets all of the following criteria: a) CAP ≥ 300 dB/m by FibroScan® collected at screening or within 30 days prior to screening. OR Liver biopsy within 24 months, consistent with NASH (defined as the presence of steatosis, inflammation, and ballooning) with stage 2-3 fibrosis according to the NASH Clinical Research Network (CRN) classification (or equivalent). Note criterion 3a must be met before evaluating 3b. b) Screening MRI-PDFF with ≥ 10% steatosis. 4. Body mass index (BMI) > 25.0 to < 45.0 kg/m^2. 5. Stable body weight, defined as no weight gain or weight loss > 5% over the previous 3 months. 6. Subjects with T2DM may also be included, if: a) Subject with T2DM is on stable doses of metformin monotherapy (subjects on combination therapy of metformin and sulfonylurea (SU) need to undergo washout period of 7 days of SU prior to dosing) with no changes in medication within the previous 6 months. b) HbA1c < 9% (one retest is permitted with the result of the last test being conclusive).			

	c) Fasting plasma glucose (FPG) < 240 mg/dL (< 13.3 mmol/L) (one retest is permitted with the result of the last test being conclusive). 7. Waist circumference ≤ 57 inches. 8. Female subjects must be non-pregnant and non-lactating. Females may be surgically sterile, postmenopausal or of child-bearing potential. Females of childbearing potential must be using a highly effective method of birth control as outlined in section 9.1.9 Contraception. Males must be surgically sterile, abstinent or if engaged in sexual relations of child-bearing potential, the subject and his partner must be using highly effective contraceptive methods. For details see section 9.1.9 Contraception. 9. Willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures and study restrictions.
Exclusion Criteria	Subjects who meet any of the following criteria at Screening will be excluded from the study: 1. Type 1 diabetes and type 2 diabetic subjects on insulin therapy. 2. Diabetic complications, such as history of acute proliferative retinopathy. 3. Recurrent severe hypoglycemia (more than 1 event ≤ 6 months) or hypoglycemic unawareness or recent severe ketoacidosis (hospitalization ≤ 6 months), as judged by the Investigator. 4. Subjects with a history of, or active, chronic liver disease due to alcohol, auto-immune, primary biliary cholangitis, HIV, HBV or active HCV-infection, Wilson's, α-1-antitrypsin deficiency, hemochromatosis, etc., and not due to NASH disease. 5. Any history of clinically significant or decompensated chronic liver disease including esophageal varices, ascites, encephalopathy or any hospitalization for treatment of chronic liver disease; or MELD score ≥ 10. 6. History of significant cirrhosis of the liver or FibroSure® > 0.75 at Screening (as shown on the laboratory report under Fibrosis Score). 7. Alcohol consumption greater than 14 drinks per week for men or greater than 7 drinks per week for women and/or positive alcohol breath test. (One drink is defined as 12 fluid ounces of regular beer (5% alcohol), 5 fluid ounces of wine (12%

	alcohol), or 1.5 fluid ounces of 80 proof (40% alcohol) distilled spirits.) 8. Introduction of an anti-obesity drug in the past 6 months prior to screening. 9. History of gastrointestinal malabsorptive bariatric surgery, any other gastrointestinal surgery that may induce malabsorption, history of bowel resection > 20 cm, any malabsorption disorder, severe gastroparesis, any GI procedure for weight loss (including LAP-BAND®), as well as clinically significant gastrointestinal disorders (e.g. peptic ulcers, severe gastrointestinal reflux disease [GERD]) within less than 5 years. 10. Ingestion of drugs known to produce hepatic steatosis including corticosteroids, high-dose estrogens, methotrexate, tetracycline or amiodarone in the previous 6 months. 11. Ingestion of drugs (as listed in the Table Prohibited Medication) from time points specified until completion of the study. 12. History of, or current cardiac dysrhythmias and/or a history of cardiovascular disease events, including congestive heart failure (class C and D of the American Heart Association [AHA]), unstable coronary artery disease, myocardial infarction. 13. Significant systemic or major illnesses other than liver disease, including cerebrovascular disease, pulmonary disease, renal failure, organ transplantation, serious psychiatric disease, malignancy that, in the opinion of the investigator, would preclude treatment with FT-4101 and/or adequate follow up. 14. History of chronic skin conditions such as psoriasis, eczema or any recurring rash/dermatitis requiring oral or topical corticosteroids or other topical applications within 12 months. 15. Hair loss or unexplained alopecia within 12 months. 16. History of chronic eye conditions, Sjögren syndrome or any history of dry eyes or allergic conjunctivitis requiring artificial tears or medicated eye drops or previous refractive surgery within 12 months (Subjects with dry eyes due to wearing contact lenses are eligible). 17. History of major depression, anxiety, suicidal behavior or attempts, or other unstable psychiatric disorders (within 2 years of screening), requiring medical treatment. (Subjects on stable antidepressants are allowed).

	18. Uncontrolled hypertension, defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure ≥ 100 mmHg at screening (reading may be repeated on a different day). (Subjects with uncontrolled hypertension may be rescreened after 3 months, following initiation or adjustment of antihypertensive therapy). 19. Any device or other contraindication with the MRI examination, as per local imaging centers. 20. Ingestion of deuterated water within the previous 6 months. 21. Positive test for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV Ab), or human immunodeficiency virus type 1 (HIV-1) or type 2 (HIV-2) antibody. 22. Abnormal laboratory results: a) Alanine aminotransferase (ALT) > 5 x upper limit of the normal range (ULN) b) Total bilirubin > 1 x ULN, except with diagnosis of Gilbert's syndrome c) International normalized ratio (INR) > 1.2 unless on anticoagulant therapy d) Fasting Triglycerides > 300 mg/dL. e) Platelet count < 100,000 /mm3 f) Abnormal kidney function test with glomerular filtration rate [GFR] < 60 mL/min/1.73m^2 as estimated using the MDRD equation. 23. Participation in any other clinical interventional study receiving active treatment within the previous 30 days or 5 half-lives, whichever is longer. 24. Have a known hypersensitivity to any of the ingredients or excipients of the study products. 25. Subject is unable to abstain from smoking during confinement periods. 26. History of illicit drug abuse as judged by the Investigator within approximately 1 year and positive test at Screening. 27. Clinically under the effect of marijuana at screening, as per Investigator evaluation. 28. Unwillingness to abstain from grapefruit (grapefruit containing food and beverages), star fruit (carambola), pomegranate, Seville orange and other food components that may interact with CYP3A4 from check-in throughout the entire course of the study. 29. Donation or loss of > 500 mL of blood or blood product within 56 days of dosing.

	30. Any other condition which, in the opinion of the investigator would impede competence or compliance or possibly hinder completion of the study.
Sample Size	A sample size of 15 subjects per cohort is empirically determined to assess the safety of the dose and characterize the PK. The total number of subjects will be approximately 30; 20 treated with FT-4101 and 10 with placebo. With 10 evaluable subjects in the treated group and 10 evaluable subjects in the control group, there is 84% power to detect a difference of 20% between the high dose treated group (cohort B) and the pooled placebo subjects from cohorts A and B in MRI-PDFF, assuming a standard deviation of 14% using a one-sided Wilcoxon-Mann-Whitney test with an alpha of 0.05.
Statistical Methods	Data analyses will follow a statistical analysis plan (SAP). The overall safety profile of FT-4101 will be assessed as the percentage of participants experiencing TEAE, serious TEAEs, TEAEs leading to premature study drug discontinuation, and treatment-emergent clinically significant laboratory abnormalities. Safety analysis will involve examination of the descriptive statistics and individual subject listings for any effects of study treatment on clinical tolerability and safety. Efficacy, PK and PD assessments for all dose groups will be analysed using descriptive methods; figures (bar charts or line plots) may also be generated to visualize the data. The primary preliminary efficacy analysis of the reduction (absolute and relative) of % liver fat on magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) at 12 weeks will be analyzed using a Wilcoxon rank-sum test. The test will be one-sided and use a significance level of 0.05. Subjects in each dose group will be tested against the pooled placebo subjects from each cohort. If more than one dose of FT-4101 is evaluated, control of the alpha level will be accomplished using Holm's Sequential Bonferroni procedure [Holm 1979] to test each FT-4101 dose against the pooled placebo subjects. The secondary preliminary efficacy analysis of the reduction (absolute and relative) of % liver fat on magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) at 6 weeks will be analyzed similarly. The secondary preliminary efficacy analysis of the proportion of subjects with ≥ 30% relative reduction in liver fat at week 12 assessed by MRI-PDFF will be analyzed using a Fisher's exact test.

	Secondary pharmacodynamic endpoints and exploratory endpoints of fasting hepatic DNL will be analyzed using MMRM with the change from baseline as the dependent variable, baseline as a covariate and the factors, treatment group, visit, and the interaction of treatment group and visit. The least squares (LS) mean and its corresponding 95% confidence interval and p-value will be presented. The LS mean difference between treatment groups will be presented along with the 95% confidence interval and the p-value.

3.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
BW	Body weight
CAP	Controlled attenuation parameter
CDM	Clinical data management
C_{max}	Maximum concentration
CRF	Case report form
CRO	Clinical Research Organization
CV	Coefficient of variation
DMP	Data management plan
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic CRF
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
FSFV	First subject first visit
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HbA_{1C}	Glycosylated hemoglobin
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICH	International Conference on Harmonization
ICU	Intensive care unit
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
Kg	Kilogram
lb	Pound
LS mean	Least square mean
Mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
NDA	New Drug Application

Nmol	Nanomol
Non-HDL-c	Non-HDL cholesterol
PD	Pharmacodynamics
PE	Physical examination
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SOE	Schedule of events
SRC	Safety Review Committee
SU	Sulfonylurea
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal insulin half-life
TEAE	Treatment emergent adverse event
TG	Triglycerides
TSH	Thyroid-stimulating hormone
U	Unit
ULN	Upper limit of normal
US	United States
USP	Unites States Pharmacopeia
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Nonalcoholic steatohepatitis (NASH) is a chronic liver disease characterized pathologically by steatosis, or lipid accumulation in the liver, with evidence of cellular damage, inflammation, and fibrosis [Musso et al. 2016]. Currently, there are no effective treatments approved for NASH, which can progress to cirrhosis, hepatitis and ultimately hepatocellular carcinoma [Musso et al. 2016]. There are at least 16 million patients in the United States (US) and Canada with NASH, which is the second leading cause of liver transplants in the US [Sayiner et al. 2016]. NASH presents a significant healthcare burden with a high, unmet medical need. Ideally, treatment approaches to NASH would target multiple pathogenic axes of the disease, such as steatosis, inflammation and fibrosis.

Accumulating evidence points towards increased hepatic de novo lipogenesis (DNL) as a key mediator in NASH pathophysiology. Uncontrolled DNL is a key contributor for liver steatosis through excessive triglyceride (TG) synthesis and deposition [Postic et al. 2008]. Chronic activation of hepatic DNL and increase in the traffic of free fatty acids within hepatocytes can lead to generation of toxic lipid metabolites. These lipotoxic metabolites act as reactive oxygen species (ROS), triggering endoplasmic reticulum (ER) stress, apoptosis and necrosis in the liver resident cells, hepatocytes, Kupffer cells and hepatic stellate cells (HSC) [Peverill al. 2014].

An emerging target for a multi-modal mechanism to treat NASH is fatty acid synthase (FASN), a key enzyme in the DNL pathway. FASN catalyzes the final step of DNL, converting acetyl-CoA and malonyl-CoA to the fatty acid palmitate, which can then undergo further modifications to other fatty acids and TGs [Kusakabe et al. 2000]. FASN gene expression level is aberrantly elevated in NASH patients as compared to healthy volunteers [Dorn et al. 2010; Mitsuyoshi et al. 2009]. Therefore, elevated FASN activity may be a major contributor to NASH through lipotoxicity-mediated tissue injury and cell death. Liver-specific ablation of the gene encoding FASN in mice (FASNLKO mice) results in malonyl-CoA increases and palmitate decreases in liver [Dentin et al. 2006]. FASNLKO mice on a standard diet show normal liver TG content, suggesting DNL may be dispensable in healthy liver and FASN inhibition may evade negative impact on non-diseased liver function [Chakravarthy et al. 2005].

In addition to FASN's role in steatosis and lipotoxicity, it may contribute to inflammation and the processes of fibrosis [Dorn et al. 2010]. Palmitate, the end product of the fatty acid synthesis pathway, upregulates toll-like receptor 4 (TLR4), pro-inflammatory cytokines and tumor necrosis factor-α (TNF-α) production in primary hepatocytes and Kupffer cells [Sawada et al. 2014]. DNL also generates the fatty acids necessary for T-Helper 17 (Th17) cell differentiation and function [Berod et al. 2014]. Recent studies strengthen the hypotheses regarding the role of Th17 cells and interleukin-17 (IL-17) in NASH progression since increased levels of Th17 cells in human liver are associated

with the progression from non-alcoholic fatty liver disease (NAFLD) to NASH [Nati et al. 2016; Rau et al. 2016; Tan et al. 2013; Tang et al. 2011]. IL-17 also promotes liver fibrosis in a mouse model of liver disease (carbon tetrachloride [CCl_4]–induced liver injury model) through HSC activation and subsequent collagen production [Meng et al. 2012; Tan et al. 2013]. Stimulation of HSC activation occurs both by elevation of IL-17 and by palmitate in mice [Harley et al. 2014; Xu et al. 2013; Tan et al. 2013]. Therefore, modulation of FASN offers a promising approach to treating NASH.

FT-4101 is a potent, selective, orally bioavailable, small-molecule inhibitor of FASN, able to potently inhibit DNL and thus influence steatosis, being developed by FORMA Therapeutics Inc. and is intended as a treatment for patients with NASH. The clinical hypothesis is that FASN **inhibition** will reduce the rate of DNL, thereby reducing lipid accumulation in the liver responsible for the cellular damage, inflammation, and fibrosis that characterizes the pathology of NASH.

4.2 Rationale for the Proposed Study

Inhibition of fractional DNL can be measured through use of stable isotopically labeled tracers in studies of metabolic kinetics [Hellerstein et al.1991; Lemieux et al. 1999] Metabolic infusion studies with sodium acetate ($1\text{-}^{13}C_1$) have been utilized to describe a temporal pattern of DNL in the postprandial state of healthy subjects and NAFLD patients. [Timlin and Parks 2005; Donnelly et al. 2005] More recently, deuterated (heavy) water (^2H_2O) labeling studies have demonstrated that in the non-stimulated setting, hepatic DNL is elevated in NASH patients compared to healthy controls [Lawitz et al. 2018].

GS-0976, an inhibitor of ACC1/2, (enzymes upstream of FASN in the DNL pathway), has demonstrated a significant (60-70%) inhibition of DNL in healthy obese adult volunteers after a single dose or when administered chronically. [Westlin et al. 2016; Kirby et al. 2017]. However, a reduced level of DNL inhibition (~30%) was observed when an equivalent dose of GS-0976 was administered chronically to NASH subjects [Lawitz et al. 2018]. The almost > 2-fold difference in DNL inhibition (67-70% inhibition in HV vs ~30% inhibition in NASH) would indicate that a higher and/or a more sustained rate of DNL inhibition may be required in the treatment of NASH.

This study will provide an opportunity to evaluate a dose range of FT-4101 that inhibited DNL in an obese, otherwise healthy adult population in a defined NASH patient population (defined as metabolically and cardiovascular stable) with further developed translational biomarker strategy for monitoring FASN inhibition, and extended safety assessment in this population. Clinical development of FT-4101 in a larger population of patients with NASH can then occur once FT-4101 has demonstrated acceptable safety and clinical activity in this defined NASH population.

4.3 Summary of Pre-Clinical /Clinical Studies

The preclinical in vivo studies have shown adverse effects in the skin and eye, that were reversible upon dose de-escalation and interruption. The exposure of FT-4101, necessary to demonstrate FASN inhibition in experimental models is below the NOAEL exposure in rats, the more sensitive species evaluated. Additional preclinical information is found in the Investigator's Brochure (IB) version 5.0.

To date, three clinical studies have enrolled subjects and are completed/clinically completed. As 01-May-2019, a total of 123 healthy volunteers have received FT-4101 in these studies, including 59 subjects with single doses, 10 subjects with two doses, 19 subjects with multiple doses for up to 14 days, and 35 subjects with multiple doses for up to 28 days. A brief summary of each study is provided below; additional information is found in the IB version 5.0.

FT-4101 has been evaluated in humans in a First-in-Human clinical study (Protocol No. 4101-HVS-101) entitled "A randomized, placebo-controlled, double-blind, single ascending and multiple ascending dose study to assess the safety, pharmacokinetics and pharmacodynamics of FT-4101 in healthy adult volunteers". This initial Phase 1 clinical study was a single center, double-blind dose escalation study of FT-4101 in healthy adult volunteers. FT-4101 was first administered as a single dose in single ascending dose (SAD) cohorts, and then administered daily for 14-28 days in multiple ascending dose (MAD) cohorts. The preliminary safety profile from this study demonstrated that 9 mg daily for 14 days continuously was tolerable while a dose of 27 mg daily for 14 days was not tolerated (due to AE's, including dry eye and skin and alopecia). The safety profile of 3 mg of FT-4101 administered daily for up to 4 weeks continuously was tolerable and per protocol criteria were met for consideration of additional dose escalation in healthy volunteers. The pharmacokinetic (PK) and pharmacodynamic (PD) profile from a daily dose of 3 mg FT-4101 indicated an exposure that was sufficient for sustained FASN inhibition in healthy obese volunteers based on accumulation of plasma malonyl carnitine and a 50% reduction in sebum palmitate.

Higher daily doses of 4.5 mg and 6.0 mg of FT-4101 for up to 4 weeks continuously were then evaluated in clinical study FT-4101-CP-001 entitled "A phase 1, double-blind, randomized, placebo-controlled, multiple-dose study to assess the safety, pharmacokinetics, and pharmacodynamics of FT-4101 in obese but otherwise healthy adult subjects". The preliminary safety profile of both the 4.5 mg and 6.0 mg dose of FT-4101 administered daily for up to 4 weeks continuously was considered tolerable per protocol. However, 44% (4 of 9) subjects receiving 6 mg FT-4101 daily for 4 weeks reported grade 1 adverse events of dry skin and alopecia by the end of the 4-week dosing interval (all recovered in follow-up), suggesting continuous dosing of 6 mg FT-4101 beyond 4-weeks would not be tolerable. One subject (11%) in the 4.5 mg treatment group reported a grade 1 adverse event of dry skin after 2-weeks of dosing, treated topically, and did not worsen with continued dosing. No AE's of alopecia were reported in the 4.5 mg treatment group.

The Clinical Study 4101-HVS-102, entitled "A randomized, placebo-controlled, double-blind, pharmacodynamic study of a single oral dose of FT-4101 in healthy adult subjects" was a Phase 1, single center, 3-cohort study designed to characterize the pharmacodynamic effect of FT-4101 on FASN by conducting metabolic infusion studies using sodium acetate (1-$^{13}C_1$) for the measurement of fractional de novo lipogenesis (DNL) inhibition in the liver. A single dose of 3 mg, 6 mg or 9 mg of FT-4101 administered to 10 subjects resulted sustained inhibition of fractional hepatic DNL of 24%, 43% and 80% respectively. Based on a 1.6 to 2-fold accumulation, a chronic daily dose of 3.0 mg to 4.5 mg of FT-4101 would be predicted to achieve a sustained hepatic DNL inhibition rate from > 24% to up 80% over the dosing interval. This predicted range of hepatic DNL inhibition is consistent with the initial PD effects of inhibiting hepatic DNL (based on malonyl carnitine accumulation) and inhibiting sebum DNL (reduction in sebum palmitate/triglycerides) observed to date in the clinical studies.

4.4 Rationale for Treatment and Dose

Based on the safety, PK and PD studies of FT-4101 in healthy adult volunteers, a study to confirm the safety and evaluate the PK/PD effects of FT-4101 administered chronically over 12 weeks in NASH patients is proposed. The initial starting dose of 3.0 mg of FT-4101 administered as intermittent therapy is planned based on the safety profile of this dose administered daily for 28 days in healthy obese adult volunteers. To reduce the risk for ≥ Grade 2 adverse effects due to chronic non-hepatic DNL inhibition, an empiric treatment interruption schedule will be evaluated. Subjects (n=15), will be randomized 2:1 to receive FT-4101 or placebo for 4 treatment cycles. The duration of each treatment cycle is 3 weeks: subjects will receive FT-4101or placebo for 2 weeks followed by 1 week of no treatment (2-weeks on/1-week off).

Based on the experience reported by GS-0976, it is possible that NASH patients may require a higher level of FASN inhibition to achieve meaningful clinical activity as measured by a reduction in liver enzymes, hepatic steatosis by MRI-PDFF and hepatic DNL inhibition by deuterated water incorporation. Therefore, if after 6 weeks a 3 mg dose of FT-4101 or placebo given for 2-weeks on/1-week off, is found to be tolerable, a 4.5 mg dose of FT-4101 or placebo given for 2-weeks on/1-week off may be evaluated in a second cohort of NASH patients.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objectives and Endpoints

To assess safety and tolerability of FT-4101 after administration of multiple doses in overweight/obese subjects with NASH by:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of clinical lab abnormalities
- Incidence and severity of clinical findings on physical examination
- Change from baseline in vital signs (blood pressure [BP], heart rate [HR], respiratory rate, and temperature])
- Change from baseline in 12-lead electrocardiogram (ECG) parameters

To assess the preliminary efficacy of FT-4101 on liver fat after administration of multiple doses in overweight/obese subjects with NASH by:

- Reduction (absolute and relative) of % liver fat on MRI-PDFF at 12 weeks

5.2 Secondary Objectives and Endpoints

To assess the preliminary efficacy of FT-4101 on liver fat after administration of multiple doses in overweight/obese subjects with NASH by:

- Reduction (absolute and relative) of % liver fat on MRI-PDFF at 6 weeks
- Proportion of subjects experiencing a relative reduction of 30% or greater of liver fat at week 12 as assessed by MRI-PDFF

To assess the PD effect of FT-4101 on circulating biomarkers of liver inflammation after administration of multiple doses in overweight/obese subjects with NASH by:

- Reduction of liver biochemistry marker: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma-glutamyl transferase (γGT), Alkaline phosphatase, and Total bilirubin

To assess the PK profile of FT-4101 after administration of a single dose and multiple doses in overweight/obese subjects with NASH including, but not limited to:

- Maximum concentration (C_{max})
- Time to maximum concentration (T_{max})
- Area under the concentration-time curve for a dosing interval (AUC_{tau})
- Trough plasma concentrations (C_{trough}) at steady state

5.3 Exploratory Objectives and Endpoints

To assess the PD effect of FT-4101 on the inhibition of fasting hepatic DNL after administration of multiple doses in overweight/obese subjects with NASH by using a 2-week deuterated water labeling protocol.

To assess the PD effect of FT-4101 on skin surface sebum level using Sebumeter® after administration of multiple doses in overweight/obese subjects with NASH by measuring:

- Total sebum production

To assess the PD effect of FT-4101 on sebum lipids using Sebutape® after administration of multiple doses in overweight/obese subjects with NASH by measuring:

- Sebum fatty acid concentrations
- Sebum DNL

To assess the PD effect of FT-4101 after administration of multiple doses in overweight/obese subjects with NASH by assessment of circulating biomarkers of liver injury and fibrosis, such as but not limited to:

- Enhanced liver fibrosis (ELF) score:
  Hyaluronic acid (HA), Procollagen III amino terminal peptide (PIIINP), Tissue inhibitor of metalloproteinases 1 (TIMP-1)
- Cytokeratin-18 (CK-18) fragments, e.g., CK-18 M30 and CK-18 M65
- FibroSure®
- PRO-C3

To assess the PD effect of FT-4101 after administration of multiple doses in overweight/obese subjects with NASH by assessment of circulating metabolic parameters, such as but not limited to:

- Fasting Lipids
  - Total cholesterol
  - Low-density Lipoprotein cholesterol (LDL-c) direct
  - High-density Lipoprotein cholesterol (HDL-c)
  - Non-HDL cholesterol (non-HDL-c)
  - Triglycerides (TG)
  - Free fatty acids (FFA)
- Glycemic parameters
  - Fasting plasma glucose (FPG)
  - Fasting insulin
  - HOMA-IR
  - HbA1c

- Adiponectin (total and high molecular weight)
- FGF-21
- Malonyl carnitine

To assess the PD effect of FT-4101 after administration of multiple doses in overweight/obese subjects with NASH by assessing steatosis (CAP) and liver stiffness (LSM) determined by FibroScan® at 12 weeks.

To assess the effect of FT-4101 after administration of multiple doses in overweight/obese subjects with NASH on imaging parameters assessed by MRI-PDFF

- Liver Volume (L)
- Liver Fat Volume Index (L)

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a Phase 1/2, randomized, double-blind, placebo-controlled study evaluating the safety, tolerability and preliminary efficacy of an intermittent treatment with 3.0 mg and 4.5 mg FT-4101 over 12 weeks in overweight/obese subjects with NASH.

The study will be conducted in up to 2 dosing cohorts, that will overlap. Cohorts will enroll 15 subjects each, randomized to FT-4101 or placebo in a ratio of 2:1 (10 on FT-4101, 5 on placebo)

Cohort A will assess the administration of a dose of 3.0 mg FT-4101 given for 2 weeks, alternating with 1 week of no investigational product (IP), continued for 12 weeks. This design leads to 4 dosing cycles (2-week daily IP followed by 1 week of no IP). Each cycle (C) will include 21 days (D) (e.g., C1/D1 to C1/D21)

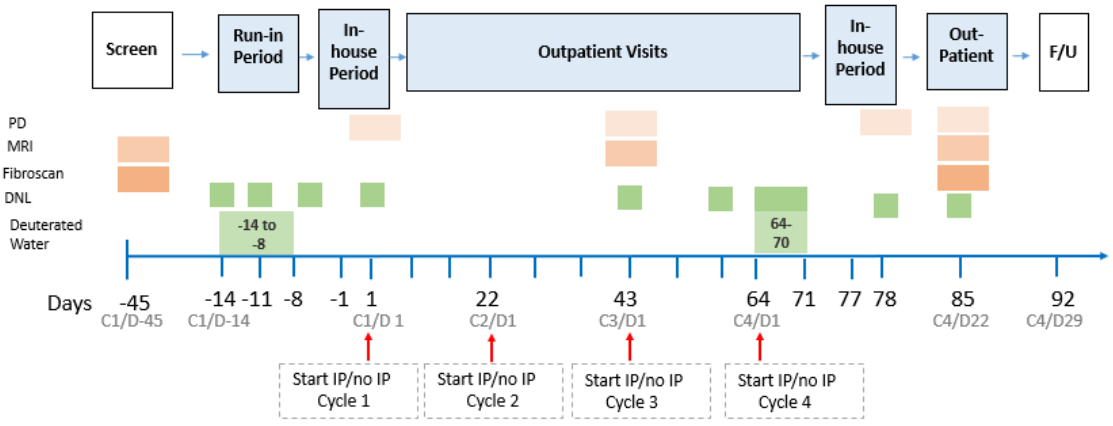
After 6 weeks, a dose escalation meeting will be held and an advancement to a higher dosing cohort will only be approved after the safety data from the ongoing cohort is determined to be acceptable.

If the IP is deemed to be safe after 6 weeks of treatment (2 dosing cycles), an additional Cohort B may be added. Cohort B will comprise of up to 4.5 mg FT-4101, administered as in Cohort A, which is given for 2 weeks, alternating with a 1 week of no IP for 12 weeks.

If dose escalation does not proceed; dose de-escalation may occur in subsequent cohorts to a dose of 1.5 mg FT-4101 to further refine the dose or additional cohort may be added to evaluate the 3.0 mg dose cohort. The IP will be administered as in cohort A, given for 2 weeks, alternating with a 1 week of no IP, continued for 12 weeks.

Safety, tolerability, PK and PD assessments will be performed throughout the study.

Figure 6-1 Study Design Schematic



This study schematic includes study days assuming no visit windows or study interruptions due to AEs are being utilized.

6.2 Study Description

Screening:

A Screening Visit will be performed between Day -45 (C1/D-45) and Day-14 (C1/D-14) of Cycle 1 to identify subjects for the study. All screening evaluations except MRI-PDFF will be performed first. Only eligible subjects will then undergo an MRI-PDFF for the assessment of liver fat within 30 days of C1/D-14 (results to be available prior to C1/D-14).

Wash-out period:

In this optional wash-out period, only subjects with T2DM treated with a combination of metformin and SU will be washed off their SU, for at least 7 days prior to the start (C1/D-14) of the first deuterated water administration period.

Run-in Period:

Outpatient Visit on C1/D-14 (Start of first deuterated water administration period):

Subjects will check into the clinic in the morning of C1/D-14 in fasting conditions. Sebum and blood for PD assessments will be collected prior to the administration of deuterated water. Subjects will be provided with the first administration of 50 mL deuterated water under in-house surveillance for subjects' safety. Subjects will be provided with a supply of deuterated water and will get instructions on how to continue the administration of the deuterated water at home. Subjects will be asked to record their deuterated water intake in a subject diary for compliance reason. Subjects will be contacted/called daily to ensure compliance during the water labeling period. Subjects will be counseled to maintain their normal diet and exercise regimen.

Outpatient Visits on C1/D-11 and C1/D-7:

Subjects will return to the clinic in fasting conditions on C1/D-11 and on C1/D-7 in order to undergo fasting blood sampling for hepatic DNL assessment. The first (morning) drink of deuterated water will be administered in the clinic (after fasting blood sampling is completed) on C1/D-11. Deuterated water accountability will be performed, and subjects will be provided with additional deuterated water supply as needed.

In-house Period 1 on C1/D-1 and C1/D1:

C1/D-1: Subjects will check into the clinic in the morning of C1/D-1 in fasting condition. Blood sampling for laboratory and safety parameters will be performed. Subjects will be randomized to FT-4101 or placebo. Standardized conditions and meals will be provided. Subjects will then fast overnight.

C1/D1: Vital signs and clinical assessments will be performed. Blood samples for baseline PD parameters (in fasting conditions) and for PK (pre-dose and post-dose) will be drawn. Sebum will be collected using Sebutape® and Sebumeter® assessments will be performed under standardized conditions. The investigational product (IP) or placebo will be administered by qualified study staff after PD assessments are completed. This

will be the start of the first 3-week intermittent dosing cycle. Subject will be instructed on how to administer the study drug over the next 2 weeks, will be supplied with the study drug and a diary to record IP administrations, and will be sent home to start the first 2-week continuous daily dosing period.

A telephone call will be performed after the first week of IP administration for compliance reason and to assess safety and need for treatment interruption (see section 6.6 for Dose Interruption/Dose Modification).

Outpatient Visit on C1/D15:

Subjects will return to the clinic on C1/D15 in in fasting condition in order to undergo safety, PK and PD assessments and to undergo an abbreviated focused physical exam. Drug accountability will be performed. Subjects will not be supplied with any study drug and will be sent home to start the first week of no dosing. Subject diaries will be checked.

Outpatient Visit on C2/D1:

Subjects will return to the clinic in the morning of C2/D1 in fasting condition in order to undergo safety, PK (pre-dose) and PD assessments and to undergo an abbreviated focused physical exam. Subjects will receive the first dose of the second IP cycle by qualified staff. Subject will be instructed on how to administer the study drug over the next 2 weeks, will be supplied with the study drug and will be sent home to start the second 2-week continuous daily dosing period. A telephone call may be performed during the week of IP administration for compliance reason and to assess safety/need for treatment interruption.

Outpatient Visit on C2/D15:

Subjects will return to the clinic on C2/D15 in fasting condition in order to undergo safety, PK and PD assessments and to undergo an abbreviated focused physical exam. Drug accountability will be performed. Subjects will not be supplied with any study drug and will be sent home to start the corresponding week of no dosing.

Outpatient Visit on C3/D1:

Subjects will return to the clinic in the morning of C3/D1 in fasting condition in order to undergo safety and PD assessments, as well as an abbreviated focused physical exam. An MRI will be performed up to 4 days prior to C3/D1. Subjects will receive the first dose of the next IP cycle by qualified staff. Subject will be instructed on how to administer the study drug over the next 2 weeks, will be supplied with the study drug and will be sent home to start the third 2-week continuous daily dosing period. Subjects will be reminded to maintain their regular diet and exercise regimes. A telephone call may be performed during the week of IP administration for compliance reason and to assess safety and need for treatment interruption.

Safety assessments will be evaluated, and a decision will be made if it is safe to start with Cohort B in parallel to cohort A.

Outpatient Visit on C3/D15:

Subjects will return to the clinic on C3/D15 in fasting condition in order to undergo safety, PK and PD assessments and to undergo an abbreviated focused physical exam. Drug accountability will be performed. Subjects will not be supplied with any study drug and will be sent home to start the corresponding week of no dosing.

Outpatient Visit on C4/D1 (start of second deuterated water administration period):

Subjects will check into the clinic in the morning of C4/D1 in fasting condition to undergo safety and PD assessments prior to the administration of deuterated water. Subjects will drink the first dose of deuterated water (50 mL) under in-house surveillance for subjects' safety. Subjects will be provided with a supply of deuterated water and will get instructions on how to continue the administration of the deuterated water at home. Subjects will be asked to record the administration in a subject diary for compliance reason. Subjects will be contacted/called daily to ensure compliance during the deuterated water labeling period. Subjects will be counseled to maintain their normal diet and exercise regimen.

Additionally, subjects will receive the first dose of the next IP cycle in-house by qualified staff. Subject will be supplied with the study drug and will be sent home to start the fourth 2-week continuous daily dosing period. A telephone call may be performed during the period of IP administration for compliance reasons and to assess safety and need for treatment interruption.

Outpatient Visits on C4/D4 and C4/D8:

Subjects will return to the clinic in fasting condition on C4/D4 and on C4/D8 in order to undergo fasting blood sampling for DNL and PK (pre-dose) assessments. The first (morning) drink of deuterated water will be administered in the clinic (after fasting blood sampling) on C4/D4. Deuterated water accountability will be performed, and subjects will be provided with additional supply of deuterated water as needed.

In-house Period 2 on C4/D14 and C4/D15:

Subjects will check into the clinic in the morning of C4/D14 in fasting condition for an overnight in-house stay. Standardized conditions and meals will be provided during the in-house stay. Laboratory, safety, PK (pre-dose and post-dose) and PD assessments, an abbreviated focused physical exam and drug accountability will be performed according to the SOE in section 16.1. Subjects will not be supplied with any study drug and will be sent home to start the corresponding week of no dosing.

Outpatient Visits on C4/D22:

Subjects will return to the clinic on C4/D22 in fasting condition to undergo safety and PD assessments and to undergo an abbreviated focused physical exam. Subjects will undergo an MRI-PDFF for the assessment of liver fat up to 4 days prior to C4/D22.

Follow-up Visit:

A follow-up visit will take place on C4/D29 in order to collect final safety assessments.

For details on all assessments please see the SOE in section 16.1.

For details on deuterated water administration and blood and sebum sampling for DNL assessments, please see section 9.1.17.5 De Novo Lipogenesis (DNL) Assessment.

6.3 Rationale for Study Design and Endpoints

This MAD study will assess the safety and tolerability, PK and preliminary PD of FT-4101 in overweight/obese subjects with NASH compared to placebo.

Two (2) cohorts will be assessed in ascending order, but may overlap, to determine the response to an intermittent dosing cycle (2 weeks of doing followed by 1 week off dosing).

Randomization is used to avoid bias introduced through an association between study drug allocation order and subject characteristics.

A double-blind design has been chosen to avoid bias and to maintain the blind between the administration of the study drug and placebo for subjects and clinical staff.

The placebo control group will control for changes in percent liver fat that may be caused by subjects' lifestyle and diet changes that may occur over the period of study participation.

Subjects with NASH will participate in the study, as these subjects are an important target population for FT-4101. Enrollment criteria will favor the target population. Percent liver fat will be determined by MRI-PDFF.

The proposed PK endpoints are well-established, commonly used parameters to characterize pharmacological profiles of drugs.

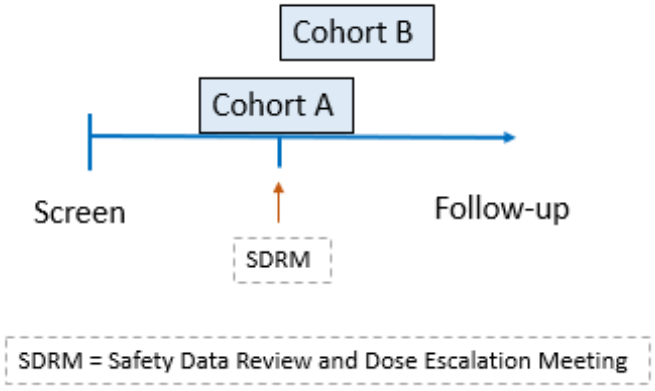
This is an exploratory study designed for proof of concept.

6.4 Dose Escalation

Data from at least 12 subjects of Cohort A who have completed 2 of the 4 cycles of treatment (2 week on /1 week off) is required for safety review before dose escalation to Cohort B, provided no more than one subject had an early discontinuation suspected of being related to FT-4101. The safety and tolerability data will be reviewed and if deemed appropriate by the Safety Review Committee (SRC) consisting of the coordinating PI, the Sponsor medical monitor and at least 1 additional participating center PI, a dose escalation decision to proceed to Cohort B will be made that is based on the reviewed data. If there are no safety concerns, the next cohort may start and may partially overlap with the previous one.

The blind of the study will be maintained throughout.

Figure 6-2 Dose Escalation Schematic



6.5 Study Discontinuation and Stopping Criteria

6.5.1 Dose Escalation Stopping Criteria

Dose escalation may be stopped if one of the following conditions applies:

- Death of a subject (AE grade 5 toxicity) in a cohort, at any time, that is considered related to the IP FT-4101 by the Investigator;
- Two (2) or more of the subjects in a cohort have experienced a serious adverse event (SAE) or medically significant adverse events (e.g., common terminology criteria for adverse events (CTCAE) ≥ grade 3 may be used as a grading scale at the discretion of Investigator), that is judged by the Investigator to be possibly or probably related to the IP FT-4101;
- Two (2) or more subjects in a cohort develop an AE (CTCAE grade ≥ 2 may be used as a grading scale at the discretion of the Investigator) that persists for more than 7 days and is considered related to the IP FT-4101 by the Investigator;
- Two (2) or more FT-4101-treated subjects in a cohort develop an AE (CTCAE grade ≥ 2) of any duration associated with the skin (including hair) or eye that is considered to be at least possibly related by the Investigator;
- Two (2) or more subjects in a cohort develop similar clinically significant laboratory, significant ECG or vital signs abnormalities, or severe AEs in the same organ class, indicating dose-limiting intolerance. Dose escalation may proceed if after review of the data by the coordinating Investigator/medical monitor and discussion with Sponsor, it is concluded that the events are not related to the IP FT-4101;
- It is determined that the limit of safety and/or tolerability of FT-4101 has been reached. Decision will be made between Sponsor and Medical Monitor/coordinating Investigator.

6.5.2 Study Advancement after Dose Escalation Stopping Criteria

After stopping criteria are met, the following may occur:

- Dose escalation may be stopped.
- Dose escalation may continue as originally planned. This is only permissible if the AE(s) that met stopping criteria is judged, after unblinded review, as not being related to FT-4101;
- A lower dose (lower than the dose that met stopping criteria) cohort may be added.

If the SRC decides on any action other than continuing dose escalation as planned, they will communicate to the Unblinded Statistician the subject numbers who they believe meet stopping criteria. The Unblinded Statistician will check the treatment assignment of that subject; if the subject received placebo then the stopping criteria are not triggered for that subject, otherwise the stopping criteria will be triggered. The Unblinded Statistician will communicate to the SRC their agreement that the stopping criteria are met after review of the treatment assignments, if applicable. If stopping criteria are not met due to events of concern occurring in placebo subjects, the Unblinded Statistician will communicate that the stopping criteria were not met, and communicate the subject numbers, who do not qualify based on receiving placebo. This unblinding will only occur in cases where the SRC has identified events potentially meeting stopping criteria, and will be limited only to subject numbers, experiencing the events in question. The whole cohort will not be unblinded to the SRC.

6.5.3 Criteria for Early Termination of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Administrative Reasons, (e.g., Sponsor, an institutional review board (IRB)/ independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site)

If the Sponsor, IRB/IEC, or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

6.5.4 Criteria for Early Termination of Individual Subjects

Subjects may withdraw their consent to participate in the study at any time.

If a subject withdraws consent, the date and reason for consent withdrawal should be documented. Subjects will be encouraged to remain in the clinic for safety assessments until the Investigator deems that it is safe for the subject to be discharged. Subject data will be included in the analysis up to the date of the consent withdrawal.

Criteria:

- AE or SAE that requires discontinuation at the discretion of the Investigator
- Protocol violation or concurrent illness: If protocol violation or concurrent illness occurs, which, in the clinical judgment of the Investigator or after discussion with the Sponsor, may invalidate the study by interfering pharmacokinetically or pharmacodynamically with the investigational products, the subject will be withdrawn by the Investigator (e.g., lack of compliance with study protocol, or lack of compliance with IP ingestion, as determined per Investigator)
- Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
- Voluntary withdrawal of consent (mandatory removal from study)
- Discretion of Investigator (document reason on CRF)
- Subject becomes pregnant or begins breastfeeding (mandatory)
- Study discontinuation by Sponsor

Wherever possible, the tests and evaluations, including those listed for the Follow-up Visit should be performed for all subjects who discontinue prior to the completion of the study.

In the event the Investigator determines to terminate a subject participation in the Clinical Study, the Investigator must notify the Sponsor of such decision and rationale immediately in writing. In all cases, the appropriate IRB/IEC and other applicable regulatory authorities shall be informed.

6.6 Treatment Interruption with Dose Modifications

If a subject has an adverse event that is judged by the Investigator as related to study drug (i.e., assessed as unrelated to the underlying disease, intercurrent illness, or concomitant medications), then a treatment interruption with dose modification can be made according to the guidelines in Table 6-1 below. Deviations from these guidelines (e.g., drug interruption for a Grade 1 AE of skin or eye) may occur if agreed upon by the Principal Investigator and Medical Monitor. There should be no attempt to make up doses omitted due to toxicity.

Table 6-1 FT-4101 Recommended Treatment Interruptions and Dose Modifications for Adverse Events

Severity of Adverse Events (AE)	Proposed Treatment Interruption and Dose Modification	
	Non-skin or eye	Skin or eye
Grade 1	Symptomatic treatment allowed: Continue FT-4101/placebo through treatment period. No dose modifications required.	Symptomatic treatment allowed: Continue FT-4101/placebo through treatment period. • If AE resolves < 7 days: continue FT-4101/placebo at same dose at next treatment cycle; • If resolves ≥ 7 days: dose reduction recommended at next treatment cycle; • If AE not resolved at start of next treatment cycle, delay start of next treatment cycle for up to 7 days until resolution and dose reduce (discontinue study treatment if AE delay in next treatment > 7days due to AE resolution).
Grade 2	Symptomatic treatment allowed: Continue FT-4101/placebo treatment through the treatment period. If dose interruption is clinically indicated; • If resolved to baseline within 72 hours of treatment interruption, resume dosing at same dose level • If resolved to baseline or Grade 1 > 72 hours of treatment interruption, dose reduce (or discontinue if prior dose reduction)	Symptomatic treatment allowed: Dose interruption for the rest of treatment period required. Resumption of a reduced dose of FT-4101/placebo at the start of the next treatment may be considered if the following are met: • Complete resolution of AE ≥ 7 days before start of next treatment cycle • No prior dose reduction • Discussed and approved by Medical Monitor
Grade 3 or higher	Permanently discontinue treatment[a]	Permanently discontinue treatment

[a]Exception: In the setting of grade 3 nausea, vomiting, or diarrhea, hold treatment and if the subject is responsive to treatment measures within 72 hours, restarting FT-4101/placebo (at same dose or a reduced dose) may be considered after discussion with Medical Monitor.

Subjects are allowed one dose reduction in this study. Recommended dose reductions based on the subject's FT-4101/placebo starting dose are outline in Table 6-2 below:

Table 6-2 Dose Reduction

Starting dose	Reduction level -1
3.0 mg FT-4101/placebo	1.5 mg FT-4101/placebo
4.5 mg FT-4101/placebo	3.0 mg FT-4101/placebo

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Subjects who meet all applicable criteria at Screening will be included in the study:

1. Willing and able to give informed consent before any study-specific procedures being performed.
2. Male or female subjects ≥ 18 to ≤ 75 years.
3. Meets all of the following criteria:
   a) CAP ≥ 300 dB/m by FibroScan® collected at screening or within 30 days prior to screening.
      OR
      Liver biopsy within 24 months, consistent with NASH (defined as the presence of steatosis, inflammation, and ballooning) with stage 2-3 fibrosis according to the NASH Clinical Research Network (CRN) classification (or equivalent).
      Note criterion 3a must be met before evaluating 3b.
   b) Screening MRI-PDFF with ≥ 10% steatosis.
4. Body mass index (BMI) > 25.0 to < 45.0 kg/m^2.
5. Stable body weight, defined as no weight gain or weight loss > 5% over the previous 3 months.
6. Subjects with T2DM may also be included, if:
   a) Subject with T2DM on stable doses of metformin monotherapy (subjects on combination therapy of metformin and sulfonylurea (SU) need to undergo washout period of 7 days of SU prior to dosing) with no changes in medication within the previous 6 months.
   b) HbA1c < 9% (one retest is permitted with the result of the last test being conclusive)
   c) Fasting plasma glucose (FPG) < 240 mg/dL (<13.3 mmol/L) (one retest is permitted with the result of the last test being conclusive)
7. Waist circumference ≤ 57 inches.
8. Female subjects must be non-pregnant and non-lactating.
   Females may be surgically sterile, postmenopausal or of child-bearing potential. Females of childbearing potential must be using a highly effective method of birth control. See section 9.1.9 Contraception
   Males must be surgically sterile, abstinent or if engaged in sexual relations of child-bearing potential, the subject and his partner must be using highly effective contraceptive methods. For details see section 9.1.9 Contraception.
9. Willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures and study restrictions.

7.2 Exclusion Criteria

Subjects who meet any of the following criteria at Screening will be excluded from the study:

1. Type 1 diabetes and type 2 diabetic subjects on insulin therapy.
2. Diabetic complications, such as history of acute proliferative retinopathy.
3. Recurrent severe hypoglycemia (more than 1 event ≤ 6 month) or hypoglycemic unawareness or recent severe ketoacidosis (hospitalization ≤ 6 month), as judged by the Investigator.
4. Subjects with a history of, or active, chronic liver disease due to alcohol, auto-immune, primary biliary cholangitis, HIV, HBV or active HCV-infection, Wilson's, α-1-antitrypsin deficiency, hemochromatosis, etc., and not due to NASH disease.
5. Any history of clinically significant or decompensated chronic liver disease including esophageal varices, ascites, encephalopathy or any hospitalization for treatment of chronic liver disease; or MELD score ≥ 10.
6. History of significant cirrhosis of the liver or FibroSure® > 0.75 at Screening (as shown on the laboratory report under Fibrosis Score).
7. Alcohol consumption greater than 14 drinks per week for men or greater than 7 drinks per week for women and/or positive alcohol breath test. (One drink is defined as 12 fluid ounces of regular beer (5% alcohol), 5 fluid ounces of wine (12% alcohol), or 1.5 fluid ounces of 80 proof (40% alcohol) distilled spirits.)
8. Introduction of an anti-obesity drug in the past 6 months prior to screening.
9. History of gastrointestinal malabsorptive bariatric surgery any other gastrointestinal surgery that may induce malabsorption, history of bowel resection > 20 cm, any malabsorption disorder, severe gastroparesis, any GI procedure for weight loss (including LAP-BAND®), as well as clinically significant gastrointestinal disorders (e.g. peptic ulcers, severe gastrointestinal reflux disease [GERD]) within less than 5 years.
10. Ingestion of drugs known to produce hepatic steatosis including corticosteroids, high-dose estrogens, methotrexate, tetracycline or amiodarone in the previous 6 months.
11. Ingestion of drugs (as listed in the Table Prohibited Medication) from time points specified until completion of the study.
12. History of, or current cardiac dysrhythmias and/or a history of cardiovascular disease event, including congestive heart failure (class C and D of the American Heart Association [AHA]), unstable coronary artery disease, myocardial infarction.

13. Significant systemic or major illnesses other than liver disease, including cerebrovascular disease, pulmonary disease, renal failure, organ transplantation, serious psychiatric disease, malignancy that, in the opinion of the investigator, would preclude treatment with FT-4101 and/or adequate follow up.
14. History of chronic skin and hair conditions such as psoriasis, eczema or any recurring rash/dermatitis requiring oral or topical corticosteroids or other topical applications within 12 months.
15. Hair loss or unexplained alopecia within 12 months.
16. History of chronic eye conditions, Sjögren syndrome or any history of dry eyes or allergic conjunctivitis requiring artificial tears or medicated eye drops or previous refractive surgery within 12 months (Subjects with dry eyes due to wearing contact lenses are eligible).
17. History of major depression, anxiety, suicidal behavior or attempts, or other unstable psychiatric disorders (within 2 years of screening), requiring medical treatment. (Subjects on stable antidepressants are allowed).
18. Uncontrolled hypertension, defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure ≥ 100 mmHg at screening (reading may be repeated on a different day). (Subjects with uncontrolled hypertension may be rescreened after 3 months, following initiation or adjustment of antihypertensive therapy).
19. Any device or other contraindication with the MRI examination, as per local imaging centers.
20. Ingestion of deuterated water within the previous 6 months.
21. Positive test for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV Ab), or human immunodeficiency virus type 1 (HIV-1) or type 2 (HIV-2) antibody.
22. Abnormal laboratory results:
    a) Alanine aminotransferase (ALT) > 5 x upper limit of the normal range (ULN)
    b) Total bilirubin > 1 x ULN, except with diagnosis of Gilbert's syndrome
    c) International normalized ratio (INR) > 1.2 unless on anticoagulant therapy
    d) Fasting Triglycerides > 300 mg/dL
    e) Platelet count < 100,000 /mm3
    f) Abnormal kidney function test with glomerular filtration rate [GFR] < 60 mL/min/1.73m^2 as estimated using the MDRD equation.
23. Participation in any other clinical interventional study receiving active treatment within the previous 30 days or 5 half-lives whichever is longer.
24. Have a known hypersensitivity to any of the ingredients or excipients of the study products.
25. Subject is unable to abstain from smoking during confinement periods.

26. History of illicit drug abuse as judged by the Investigator within approximately 1 year and positive test at Screening.
27. Clinically under the effect of marijuana at screening, as per Investigator evaluation.
28. Unwillingness to abstain from grapefruit (grapefruit containing food and beverages), star fruit (carambola), pomegranate, Seville orange and other food components that may interact with CYP3A4 from check-in throughout the entire course of the study.
29. Donation or loss of > 500 mL of blood or blood product within 56 days of dosing.
30. Any other condition which, in the opinion of the investigator would impede competence or compliance or possibly hinder completion of the study.

7.3 Study Restrictions/Precautions

7.3.1 Prohibited Medications

Use of the agents listed below (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 7-1 Prohibited Medications

Medication or Class	Indication/Reason	From time point specified until the end of the study
Antihypertensive medication	Hypertension	Excluded unless on stable dose for at least 3 months prior to screening
Statins	Hyperlipidemia	Excluded unless on stable dose for at least 3 months prior to screening
Oral or systemic long-acting corticosteroids	E.g., chronic or acute non-infectious inflammatory conditions, auto-immune diseases	Within 3 months prior to screening
Antacids, anticholinergics, antispasmodics (e.g., modafinil, phenytoin), 5HT3 antagonists, dopamine antagonists, or opiates, antiemetics	Reduction/modification of GI motility	Within 2 weeks prior to screening
Orlistat, lorcaserin, sibutramine, etc., including over-the-counter and herbal supplements, or any medication with a labelled indication for weight loss or gain	Weight control treatment	Within 3 months prior to screening.

Medication that is a strong inducer or strong inhibitor of CYP3A4 Please see Appendix C in section 16.3.	Interaction with CYP3A4	Within 15 days prior to dosing, unless half-life is greater than 72 hours, then it is prohibited for 5 half-lives prior to dosing.

7.3.2 Check-in Criteria

At check-in for any in-house period(s), a subject will not be allowed to check in if they meet any of the following criteria and the treatment period may be rescheduled one time. The Sponsor will be notified about the rescheduling in a timely manner.

1. Positive alcohol breath test.
2. Positive urine drug screen test.
3. Positive urine pregnancy test in female subjects. If sample is positive, blood sample will be sent to local lab for confirmation. A negative test result is mandatory prior to dosing.
4. Any medical condition that could interfere with the study, as judged by the Investigator.
5. Any use of disallowed concomitant medications within the last 24 hours.
6. Consumption of grapefruit (grapefruit containing food and beverages), star fruit (carambola), pomegranate, Seville orange and other food components that may interact with CYP3A4, within 24 hours prior to check-in.

7.3.3 Anticipated Risks

Normal precautions taken for a human study, including the provision of emergency equipment, will be taken during this study. Qualified and well-trained physicians and medical staff will instruct the subjects.

Possible anticipated, risks from the study procedure are outlined below:

7.3.3.1 IP related adverse events

Dosing with the IP may have adverse effects on the skin (including alopecia) and eye. These effects were reversible upon dose interruption in previous studies. An assessment of hair loss at baseline and during the treatment cycles is recommended to adequately assess any potential AE of alopecia occurring during study participation. For further information, please see Norwood's Classification of Hair Loss in section 16.4, Savin's Pictorial Grading of Female Pattern Hair Loss in section 16.5 and the Investigator's Brochure (IB).

7.3.3.2 Deuterated Water adverse events

The adverse effect reported with the intake of deuterated water is transient dizziness if the deuterated intake is more rapid than planned in this study. Dizziness typically resolves within 2-3 hours. Deuterated water has been given to humans for more than 70 years without problems. Animals have been raised for many generations on deuterated water, without any problems. No risks have been observed in studies examining the effect of deuterated water on male or female reproduction tissues, including sperm function.

7.3.3.3 Procedure related adverse events

Study procedures involve the placement of a catheter which may lead to allergic reaction, redness, swelling, bruising, pain, bleeding or infection at catheter insertion site. The study procedures also involved the use of adhesive to secure the placement medical equipment. The adhesive may cause an allergic reaction, redness, swelling or itching when in contact with the skin.

7.3.3.4 Risks related to repeated blood draws

Subjects will participate in several blood draws throughout the course of the study which have the potential to cause a venous line-vasovagal response, bruising, tenderness, and rarely infection.

8.0 STUDY MATERIALS

8.1 Investigational Products

8.1.1 FT-4101

FT-4101 is a potent, selective, orally bioavailable, small-molecule inhibitor of Fatty Acid Synthase (FASN). It is a non-hygroscopic, crystalline solid, obtained as polymorph Type B. FT-4101 capsules contain only drug substance filled into capsules with no other excipients. FT-4101 capsules will be provided in 3 different unit strengths for oral administration. For this study, the following doses may be used: 1.5 mg active capsules: Size 3 White/White opaque, 3 mg active capsules: Size 3 White/White opaque and 4.5 mg active capsules: Size 3 White/White opaque will be used.

8.1.2 Placebo

Placebo capsule is matching in size and color to all the active capsules. Placebo capsule contain Avicel PH102, an inert and stable compendial excipient, and will be provided by the Sponsor.

8.2 Other Medicinal Products

8.2.1 Deuterated Water

Deuterated Water (70%) will be manufactured under cGMP conditions. Commercially available deuterated water will be provided by [redacted] from a qualified vendor.

Deuterated water will be provided as individual ready-to-use, single dose bottles each containing 50 mL of deuterated water (70 %).

8.3 Packaging, and Labeling of Products

Each dose strength of FT-4101 and matching placebo are packaged in high-density polyethylene (HDPE) induction sealed bottles. For this study, 66 capsules are packaged per bottle.

The Sponsor will provide the Investigator with the labeled IP in accordance with specific country regulatory requirements.

The deuterated water will be packaged in individual ready-to-use single dosing bottle (e.g. the bottle can only be used once) each containing 50 mL of deuterated water and labeled with specific country regulatory requirements.

8.4 Storage and Drug Accountability of Products

All clinical material must be kept in an appropriate, limited-access, secure location.

The investigational products (IP) and its storage instructions will be provided by the Sponsor. The IP FT-4101 must be stored securely at 15°C to 30°C.

The IP placebo must be stored at 15°C to 30°C.

The shipment of the IPs is recommended at 15°C to 25°C, packaged in a qualified shipper.

Individual bottles of deuterated water will be stored at room temperature (15°C to 30°C) according to instructions by the specific laboratory.

The IP will be shipped from the Sponsor to [redacted] drug depot. [redacted] will distribute the IP and deuterated water to each site.

The study staff is required to document the receipt, dispensing, and return/destruction of Study Products and supplies provided by or on behalf of the Sponsor.

Each study site may destroy IP or return deuterated water to drug depot per pharmacy manual's instructions after the close out visit.

The Investigator or Investigator's authorized staff must ensure the availability of proper storage conditions. The temperature of all study drugs will be monitored over 24 hours a day, 7 days a week (24/7). In case of incorrect storage, the Sponsor and monitor must be contacted without delay.

No study drugs may be dispensed to any person not enrolled in the study.

For further details please see the Pharmacy Manual.

8.5 Dose Regimen

The first dose of IP and deuterated water will be administered by qualified study staff while subjects are under observation in the clinical research unit. Accountability for deuterated water and IP will be performed to monitor compliance.

IP will be administered at t=0, orally with approximately 240 mL of water in the morning. Subjects do not need to be in a fasting state. A compliance check for the in-house dosing (hand and mouth check) will confirm that subjects have swallowed the complete dose. Actual time of dosing will be documented in the source documents and eCRFs.

During outpatient periods, subjects will take the IP at home once a day (QD) as instructed by study staff during the in-house period. Dosing will be intermittent, with 2 weeks of IP treatment and 1 week without any IP. Aim is to dose at approximately the same clock time on every dosing day.

Missed IP doses: Ideally, subjects should not miss more than 25% dosing days (>3 days) within 1 cycle. If more IP doses are missed than above, the PI will need to decide, with input from the Sponsor Medical Monitor, on whether the subject should be withdrawn from the study and replaced.

Details will be provided in the Operations Manual.

To maintain the double-blind aspect of the study, the investigational products will be prepared by unblinded staff that is not participating in investigational product

administration or interacting with study subjects in any other way. The study staff participating in other aspects of the study will be blinded to treatment.

Table 8-1 Dosing Schedule for Treatment Cycles

Cohorts	Number of Subjects	Treatment Schedule	Treatment-IP	No-IP	Treatment-IP	No-IP	Treatment-IP	No-IP	Treatment-IP	No-IP
			Cycle 1		Cycle 2		Cycle 3		Cycle 4	
Cohort A	N=10	Intermittent	FT-4101 3.0 mg QD Day 1-14	No IP Day 15-21	FT-4101 3.0 mg QD Day 1-14	No IP Day 15-21	FT-4101 3.0 mg QD Day 1-14	No IP Day 15-21	FT-4101 3.0 mg QD Day 1-14	No IP Day 15-21
	N=5	Intermittent	Matching Placebo QD Day 1-14	No IP Day 15-21	Matching Placebo QD Day 1-14	No IP Day 15-21	Matching Placebo QD Day 1-14	No IP Day 5-21	Matching Placebo QD Day 1-14	No IP Day 15-21
Cohort B	N=10	Intermittent	FT-4101 4.5 mg QD Day 1-14	No IP Day 15-21	FT-4101 4.5 mg QD Day 1-14	No IP Day 15-21	FT-4101 4.5 mg QD Day 1-14	No IP Day 15-21	FT-4101 4.5 mg QD Day 1-14	No IP Day 15-21
	N=5	Intermittent	Matching Placebo QD Day 1-14	No IP Day 15-21	Matching Placebo QD Day 1-14	No IP Day 15-21	Matching Placebo QD Day -14	No IP Day 15-21	Matching Placebo QD Day 1-14	No IP Day 15-21

8.5.1 Deuterated Water

Subjects will be instructed to drink 3 bottles of 50 mL of deuterated water (70%) daily on C1/D-14 through C1/D-8 and C4/D1 through C4/D7. Subjects will also be instructed to take each bottle of 50 mL of deuterated water at least 3 hours apart.

The first oral dose of deuterated water will be administered in-house in the morning of C1/D-14 and C4/D1 after Sebutape® and DNL blood sample collections. Subjects do not need to be in a fasting state. A compliance check for the in-house dosing will be performed. Actual time of dosing will be documented in the source documents and eCRFs. Subjects will then be instructed to continue the administration of deuterated water at home. The oral intake should occur at approximately the same time of day ± 3 hours on every dosing day. During the outpatient phase, subjects will fill in a log recording their daily deuterated water intake. If a dose is missed, it should be considered a "loss" and noted in the daily log and will be recorded in the CRF. Subjects must not double up on their intake (not take two doses at once).

If a deuterated water dose is missed, the subject should inform the study team and the team should record this information. There is no defined number of missed doses that constitutes non-compliance. Missed doses will be reported to the Sponsor Medical Monitor. The decision to withdraw a subject from study participation based on missed doses of deuterated water may be based on decision of the PI and the Sponsor Medical Monitor. If a subject is withdrawn, the subject can be replaced.

For more details please see the Operations Manual.

Table 8-2 Dosing Schedule for Deuterated Water

Cohorts	Subjects	Treatment Schedule	Treatment (7 days)	Treatment (7 days)
Cohort A	N=15	Daily	Deuterated Water TID 50 mL (at least three hours apart) C1/D-14 to C1/D-8	Deuterated Water TID 50 mL (at least 3 hours apart) C4/D1 to C4/D7
Cohort B	N=15	Daily	Deuterated Water TID 50 mL (at least three hours apart) C1/D-14 to C1/D-8	Deuterated Water TID 50 mL (at least three hours apart) C4/D1 to C4/D7

8.6 Overdose

If a study medication error occurs, it should be documented as Protocol Deviation. A brief description should be provided in the deviation, including whether the subject was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the subject takes a dose of Study Drug that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as an AE.

Should an overdose occur, the Investigator or designee should contact the Sponsor or designee within 24 hours of the investigator or qualified designee first becoming aware of the overdose.

8.7 Randomization and Blinding

Subjects will be randomized to the treatment according to an interactive web response system (IWRS). Randomization numbers will be generated from [redacted]. The IWRS will assign the next available randomization number at the time the site randomizes the subject, maintaining the 2:1 ratio (2 subjects on FT-4101 to 1 subject on placebo). Only authorized unblinded personnel will be able to see which treatment arm is assigned to a randomization number. Any replacement subjects will be randomized by IWRS to the same treatment arm that was assigned to the subject being replaced. The randomization number of the replaced subject will be incremented by 100 (e.g., subject [redacted] replaced with [redacted] subject [redacted] replaced with [redacted]).

8.8 Breaking of Blinded Code

The only persons with access to the treatment assignments during clinical conduct will be the designated pharmacy personnel who are responsible for the dispensing of study drug, the unblinded CRO operations team for investigational product accountability and serious adverse event (SAE) reporting, the unblinded statisticians who generate the randomization lists, and the bioanalyst for PK/PD samples. In general, the Sponsor Medical Monitor will remain blinded to treatment assignment. However, during the cohort safety review, if the decision is made to halt dose escalation due to an observed adverse event that potentially meets stopping criteria, the Sponsor Medical Monitor may be unblinded to that subject's data to ensure that the subject in question is indeed receiving FT-4101 and not placebo. This information will be conveyed via the unblinded statistician and will be limited to the subject with the safety issue of concern.

The code for a subject may be broken in a medical emergency, if knowing the identity of the treatment allocation would influence the treatment decision of the subject or if demanded by the subject. Unblinding will be done through the Electronic Data Capture (EDC), however if this is not available, the unblinded pharmacist at the site will have the subject list with treatment assignments, and as such would be able to break the blind in case of emergency. Whenever a code is broken, the person breaking the code must record the time, date, and reason as well as his/her initials in the source documents. During un-

blinding procedure in case of medical emergency, it should be ensured that no study personnel is unblinded to other subjects. Study site personnel and Sponsor personnel directly associated with the conduct of the study will not be unblinded.

If the study site needs to unblind a subject, the sponsor will, if possible, be contacted prior to breaking the blind. In all cases, the Study Monitor must be notified within 24 hours after emergency unblinding.

All codes (whether broken or not) must be kept throughout the trial period. Accountability of all broken or unbroken codes (hard copy or electronic) will be performed at or after trial closure and codes will be maintained in the Trial Investigator's File (TIF) at the site.

9.0 STUDY PLAN

9.1 Study Procedures

9.1.1 Informed Consent and HIPAA Release

Written informed consent will be obtained from each subject prior to performing any study-specific evaluations. The HIPAA release is embedded in the informed consent document. The informed consent document is subject to review and approval by the Sponsor and will be approved by a qualified IRB. The IRB-approved document must contain, at minimum, the eight basic elements of informed consent set forth in applicable law. Only the most recently IRB-approved informed consent document must be used to consent prospective study subjects. The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, will fully inform the potential study subject of all pertinent aspects of the Clinical Study, including written information given approval/favorable opinion by the IRB/IEC.

Prior to the potential subject's participation in the Clinical Study, the written informed consent form must be signed, name filled in and personally dated by the subject and by the person who conducted the informed consent discussion, and by the Investigator. One copy of the signed and dated informed consent document will be given to the subject and the original retained by the Investigator/site.

9.1.2 Screening

Investigators must account for all subjects who sign informed consent forms. The Investigator will keep a Subject Screening and Enrollment Log at the investigational site. Subjects who have screen failed may be allowed to re-screen once at the discretion of the Investigator. A new screening number will be assigned.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for this study. If subjects are fasting (only water for ≥ 10 hours), all screening assessments may be done on the same day. If subjects are not fasting, they will be invited to return for a second screening visit to complete any missing screening procedures (e.g. laboratory assessments).

Subjects will be instructed on influencing factors and restrictions such as grapefruit containing food and beverages, star fruit (carambola), pomegranate, Seville orange and other food components that may interact with CYP3A4, smoking or medication and illness/infection.

If subjects don't have a diagnosis of NASH stage 2/3 assessed by liver biopsy performed within 24 months, FibroScan® (CAP) will be evaluated instead to identify subjects who are likely to have a liver fat content of ≥ 10% at MRI-PDFF. Depending on the outcome/results of these values, the subjects will proceed to MRI-PDFF or not. For further details on

parameters and outcome for the determination to proceed to MRI-PDFF see the Operations Manual.

Subjects MELD score will be calculated according to the following formula:

MELD(i) = 0.957 × ln(Cr) + 0.378 × ln(bilirubin) + 1.120 × ln(INR) + 0.643

Then, round to the tenth decimal place and multiply by 10. For further details see the Operations Manual.

9.1.3 Demographics and Medical History

Demographic information, medical history and prior medications will be obtained at Screening.

9.1.4 Physical Examination

The baseline physical examination (PE) will consist of the following body systems: (1) eyes; (2) ears, nose, throat, neck, thyroid; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system, mouth; (6) dermatologic system, including hair; (7) extremities; (8) musculoskeletal system; (9) central and peripheral nervous system, (10) lymph nodes and (11) testicular examination in male subjects.

An abbreviated PE will be performed by the Investigator (or a qualified physician at the investigational site) at time points indicated in the SOE in section 16.1 for each cohort.

For abbreviated PEs, the following will be examined and/or measured by the Investigator or medically-qualified designee: skin (crust, erosion, ulcer, rash, inflammation, etc); eyes (dryness, conjunctivitis, etc); hair (assessment of male pattern baldness using the Norwood scale [see Appendix D in section 16.4] or assessment of female pattern hair loss using the Savin scale [see Appendix E in section 16.5]); lymph nodes; and respiratory, cardiovascular, abdominal (gastrointestinal), and musculoskeletal systems.

In addition, male subjects will undergo a testicular examination on C1/D-1 and C4/D29.

A complete physical examination may be performed in case the subjects have symptoms or at the discretion of the Investigator.

9.1.5 Height, Weight, and BMI

Height (without shoes) will be measured once, during the Screening visit

Weight (without shoes) will be measured fasting in the morning, with light clothing and post void at time points indicated in the SOE in section 16.1.

BMI (kg/m^2) will be calculated from height and weight.

9.1.6 Vital Signs

Vital signs will include body temperature (aural), supine blood pressure (after 5 minutes resting), respiration rate and pulse rate (after 5 minutes resting). Vital sign measurements will be performed at days indicated in the SOE in section 16.1.

9.1.7 Concomitant Illness and Therapy

Concomitant therapy is any medication given in addition to the investigational product (including over-the-counter medications, herbal medications, and vitamin supplements) administered between screening and follow-up.

Concomitant illness is any significant medical condition or disease that is present at study start (signing of informed consent). This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at Screening examination.

Details of all concomitant illnesses and therapies must be recorded at study entry and must be recorded on the subject's CRF. Any changes in concomitant medication must be recorded at each visit. If the change influences the subject's eligibility to continue in the study, the Sponsor must be informed. The information collected for each concomitant medication includes, at a minimum, start date, stop date or continuing, and indication.

AEs related to administration of these therapies or procedures must also be documented on the appropriate *e*CRF.

For prohibited medications, please see Table 7-1 Prohibited Medication.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken as described in the SOE in section 16.1.

Additional samples (e.g., including blood samples, urine samples and all types of tissue samples) may be collected and stored for potential future analysis. For details please see the Laboratory Manual.

Table 9-1 Clinical Laboratory Assessments

Hematology	Serum Chemistry	Urinalysis
CBC with differential: Hematocrit Hemoglobin mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC) red cell distribution width (RDW)	**Hepatic function panel:** Alanine aminotransferase (ALT/SGPT) albumin, serum alkaline phosphatase, serum aspartate aminotransferase (AST/SGOT) bilirubin, direct bilirubin, total	**Routine urinalysis with microscopic examination on positives**(a): Color appearance, specific gravity pH protein glucose ketones occult blood

Hematology	Serum Chemistry	Urinalysis
percentage and absolute differential counts platelet count (RBC) red cell count white blood cell count (WBC)	protein, total, serum gamma-glutamyl transferase (γGT) **Renal function panel:** Albumin, serum BUN BUN: creatinine ratio calcium, serum carbon dioxide, total chloride, serum creatinine, serum glucose, serum phosphorus, serum potassium, serum sodium, serum **Lipid panel:** Cholesterol, total high-density lipoprotein (HDL) cholesterol low-density lipoprotein (LDL) cholesterol (direct) triglycerides non-HDL cholesterol (calculated) Free fatty acid (FFA) **Additional parameters:** Lactic acid dehydrogenase (LDH) Magnesium Uric Acid	leukocyte esterase (or equivalent) nitrite bilirubin urobilinogen

Other Assessments

Serum/Plasma/Whole Blood	Urine	Breath
HBsAg Anti-HCV Anti HIV TSH PTT INR **Glucose Metabolism Parameter:** FPG Fasting Insulin HbA1c	**Drug Screen Profile** Urine drug screen via commercial kit at the investigational site. **Female Subjects Only** human chorionic gonadotropin (hCG) follicle-stimulating hormone (FSH) test for postmenopausal women (defined as amenorrheic	Alcohol breath test at timepoints stated in the SOE at the investigational site

	female subjects <55 years of age and not surgically sterile) at Screening.
Malonyl carnitine Adiponectin, total and high molecular weight FGF21	
Biomarkers: Hyaluronic acid (HA) Procollagen III amino terminal peptide (PIIINP) Tissue inhibitor of metalloproteinases 1 (TIMP-1) Cytokeratin-18 (CK-18) fragments FibroSure (NASH) PRO-C3	

(a) Microscopic analysis should be performed only if urine evaluations are abnormal.

The central laboratory will perform all necessary safety laboratory tests listed above. The results of safety laboratory tests and test to determine subjects' eligibility will be sent to the Investigator or designee, who is responsible for reviewing these results. All laboratory safety data will be faxed or transferred electronically.

Laboratory reports must be signed and dated by the Investigator or designee indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

All clinically significant laboratory abnormalities must be recorded as an AE. A clinically significant laboratory abnormality may be verified by retesting and may be followed upon discretion of the Investigator.

9.1.9 Contraception

Female subjects of non-childbearing potential

Female subjects of non-childbearing potential must meet the following criteria:

a) are either surgically sterile (hysterectomy, bilateral tubal ligation, bilateral salpingectomy, and/or bilateral oophorectomy) at least 6 months before the Screening Visit. If females' sterility is confirmed, no pregnancy testing is required during the study. The site will make an effort to retrieve medical records to document the sterility, however, the absence of records will not exclude the subject. In case that medical records cannot be obtained, serum pregnancy testing will be conducted at Screening, and urine pregnancy testing will be conducted throughout the study.

b) are post-menopausal, defined as spontaneous amenorrhea for > 12 months at the Screening Visit. Postmenopausal status will be confirmed through testing of FSH levels

outside the normal range (as specified by responsible lab) at screening for amenorrheic female subjects < 55 years of age.

Female subjects who state they are postmenopausal at the screening visit but have an FSH value that does not correspond with a postmenopausal FSH level, may have a serum hCG pregnancy test performed on a separate day. If test is negative and the subject agrees to be on a highly effective contraceptive method, subject may be enrolled in the study at the discretion of the Investigator.

c) a negative serum pregnancy test before starting study treatment.

Female subjects of child-bearing potential

Female subjects of child-bearing potential must meet the following criteria:

a) a negative serum pregnancy test before starting study treatment

b) must agree to refrain from egg donation or harvest for 90 days after last dose of study drugs.

c) If engaged in heterosexual intercourse must agree to use highly effective methods of contraception during intercourse, throughout the study period and for 90 days after the last dose of study drugs.

Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

Acceptable methods of contraception under this protocol are listed below.

Female subjects who are considered of childbearing potential must agree to use a highly effective method of contraception, which may include:

- IUD
- Abstinence: abstinence can be used, when in line with the preferred and usual lifestyle of the subject.
- If a female subject confirms that her male partner(s) has been confirmed to be clinically sterile, this method is acceptable as the only means of contraception.
- Hormonal implants

Note: Hormonal contraceptives alone are not considered an effective method of birth control for female subjects participating in this study. Oral contraceptives can be used in combination with a male barrier method. Furthermore, female condoms in combination with male condoms is not an acceptable method.

Childbearing Potential

For all subjects of childbearing potential, all methods of contraception, including abstinence, must be in use from the time of consent through the final study visit, and for 90 days after the last dose of study drug. Subjects who are not sexually active during the Screening Period must agree to the contraceptive requirements if they become sexually active with a partner of the opposite sex during the study and for 90 days after the last dose of study drug. Unique situations that may not fall within these specifications may be discussed with the Medical Monitor on an individual basis. Female subjects will be considered of childbearing potential after the onset of their first menstrual period.

During the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed for sterilized women, when medical records are not available. In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test at outpatient visits and check-in to in-house periods.

Male subjects

Male subjects must meet the following criteria:

a) are required to use barrier contraception (condom plus spermicide) during intercourse from Screening through study completions and for 90 days after the last dose of study drugs.

b) must refrain from sperm donation from Screening through at least 90 days after the last dose of study drugs.

Male subjects who can father a child must agree to use one highly effective method of contraception, which includes:

- Abstinence: abstinence can be used, when in line with the preferred and usual lifestyle of the subject.
- If a male subject confirms that his female partner(s) is not of childbearing potential (i.e., postmenopausal or post-surgical sterilization, as defined under child bearing potential) or is using a highly effective method of contraception, this is acceptable as the only means of contraception.

Examples of highly effective methods of contraception for male subjects' female partner(s) include:

  - Hormonal contraceptives in combination with male barrier contraception
  - Hormonal implants
  - Intrauterine device (IUD)

Male subjects with documented infertility or surgical sterilization (performed at least six months before the first dose of study drug) are exempt from the contraception requirement.

9.1.10 Pregnancy

In the event a subject becomes pregnant during the study, she should be withdrawn, and the study drug should be immediately discontinued. However, the subject will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy.

In addition, any pregnancies in the partner of a male subject during the study or for 90 days after the last dose should also be recorded.

If the pregnancy occurs at any time during the study and the 90 days of last dose of active study medication, the pregnancy should be reported immediately to the Sponsor, using a pregnancy notification form.

Study subjects will give consent on enrollment that the Investigator will report any pregnancy during the study to the Sponsor and that they will be asked to provide information about her pregnancy, delivery, and the health of her infant until age one month. Payment for all aspects of obstetrical care, child, or related care will be the subject's responsibility.

All reported pregnancies will be followed up to final outcome, using the pregnancy and pregnancy follow-up forms. The outcome, including any premature termination, will be reported to the Sponsor. An evaluation after the birth of the child may also be conducted.

Pregnancy complications must be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this must be reported and followed up as a serious adverse event.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded after 5 minutes in a supine position.

The Investigator (or designee) will interpret the ECGs by use of an electronic measurement using the following categories: within normal limits, abnormal but not clinically significant, or abnormal with clinical significance. ECGs are performed according to the SOE in section 16.1. The following parameters will be recorded from the subject's ECG trace as calculated by the machine algorithm: heart rate, QT interval, PR interval, QRS interval, RR interval, and QTc (corrected) using the Fridericia correction (QTcF = QT ÷ cube root of the R-R interval [where R-R is the duration of the entire cardiac cycle]).

When ECGs are to be collected at the same time point as a blood collection, ECGs should be collected first to avoid any artificially increased heart rates due to the blood collection.

In some cases, it may be appropriate to repeat abnormal ECGs. If a machine-read QTc value is prolonged, repeat measurements may not be necessary if the Investigator's interpretation determines that the QTc value is in the acceptable range.

9.1.12 Check-in Procedure

All subjects will check in to the clinic in the morning for the In-house Periods. The following will be assessed:

1. Alcohol breath test.
2. Urine drug screen.
3. Urine pregnancy tests. (The negative result of the urine pregnancy test will allow to check-in, while the negative test result of the serum pregnancy test must be available prior to dosing on C1/D1).
4. Any use of disallowed prescription or non-prescription concomitant medications within the last 24 hours.
5. Any medical condition that could interfere with glucose metabolism, as judged by the Investigator.
6. Consumption of grapefruit (grapefruit containing food and beverages), star fruit (carambola), pomegranate, Seville orange and other food components that may interact with CYP3A4, within 24 hours prior to check-in.

Subjects who fulfill one or more of the stated criteria at check–in, will not be able to continue onto the treatment period. The treatment period will be rescheduled. Each treatment period may be rescheduled one time. After that, the subject will be excluded from the study. Replacement of subjects for all dosing periods may be permitted in order to enroll sufficient subjects into the study, only after discussion with Sponsor and Investigator.

9.1.13 Blood Glucose Monitoring by Fingerstick

Blood glucose might be measured by fingerstick whenever there are signs or symptoms of hypoglycemia or hyperglycemia. A confirmation measurement of the blood glucose value may be performed by YSI.

9.1.14 Wash-Out Period

The wash-out period is optional and only subjects with T2DM on combination therapy with metformin and sulfonylurea will have to undergo a wash-out period to discontinue the oral drug sulfonylurea (SU) until the end of the study. Medication with metformin monotherapy will be continued throughout the entire study on the same stable dose. Discontinuation of the SU must start at least 7 days prior to C1/D-14, the start of the deuterated water labeling period (starting wash-out at least on C1/D-21). All subjects will be instructed to monitor and document their fasting plasma glucose levels daily, using a glucometer. The subjects will be instructed on how to use the glucometer. A diary will be supplied by the study site. For further details on capturing data and documentation in the diary, please see the Operational Manual. They will be frequently (at least twice weekly)

contacted by qualified study site staff in the washout period to review their fasting plasma glucose values. If a subject has a confirmed morning fasting plasma glucose level (after 8 hours of fasting) that is ≥ 240 mg/dL (13.3 mmol/L) and cannot be lowered to < 180 mg/dL (10.0 mmol/L) in 7 days, verified by a standard laboratory analysis (ie, YSI glucose analyzer at the site), this subject will be excluded from further participation in the study.

All subjects with T2DM will be provided with a blood glucose meter with sufficient supplies and test strips to monitor blood glucose at home during wash-out, run-in and/or outpatient periods. For further details on data capturing and documentation, please see the Operational Manual.

9.1.15 Standardized Meals and Dietary Counseling

Subjects will be counseled to maintain their normal diet and exercise regimen. They will be instructed not to start any new diets, supplements, or exercise programs during the study.

During in-house period(s), subjects will receive standardized meals. The same standardized meals will be served on C1/D-1 and C4/D14 to standardize conditions prior to the C1/D1 and C4/D15 assessments. These meals will be provided up to 12 hours prior to start of scheduled fasting DNL samples on C1/D1 and C4/D15.

The standardized weight maintaining meals will be provided using estimated BMR× activity factor of 1.5 to determine daily caloric intake. Daily calories are individualized to within 200 calories of estimated BMR x 1.5.

9.1.16 Pharmacokinetic Assessments and Schedule

Blood for PK analysis of the IP will be collected at the time points indicated in the SOE in section 16.1 and the PK sampling schedule in section 16.2. One 2.0 mL sample per scheduled time point will be collected and split equally to provide plasma for primary PK measurements and plasma as a secondary back-up sample. Instructions for sample processing and shipment will be provided in the Laboratory Manual. Pre-dose sampling will be taken within 15 minutes before dosing. PK blood sampling should be performed at the nominal time(s) specified in this clinical protocol. All actual PK sample collection times will be recorded in the source documents and CRF. Explanation should be provided in the source documents and CRF for missed or mishandled samples.
Concentrations of FT-4101 in plasma will be measured using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay.

9.1.17 Pharmacodynamic Assessments and Schedule

9.1.17.1 Laboratory Parameter

Blood for analyses of PD assessments will be collected at the time points indicated in the SOE in section 16.1. Sampling for fasting metabolic parameter (Lipids, FPG, fasting

insulin, HOMA-IR, HbA1c, Adiponectin (total and high molecular weight), FGF-21, and Malonyl carnitine), liver biochemistry (AST, ALT, γGT, AP, total bilirubin), liver injury and fibrosis biomarkers (CK-18 fragment, ELF score [HA, PIIINP, TIMP-1] [Guha et al. 2008], PRO-C3, FibroSure® [Ratziu et al. 2006]), will be collected.

Instructions for sample processing and shipment will be provided in the laboratory manual.

9.1.17.2 Sebumeter®

Sebumeter® is a measuring device to assess skin surface sebum levels.

The measurement is performed via application of a specialized probe composed of a sebum sensitive film on its surface. Results are expressed in µg/cm² and correspond to the total amount of sebum collected on the film.

For detailed instructions on use please see the Operations Manual.

9.1.17.3 Collection of Sebum using Sebutape®

The collection of sebum for the analysis of sebum fatty acid concentrations and sebum DNL will be performed with the Sebutape® technique. The Sebutape® (CuDerm Corp., Dallas TX) is comprised of an open-celled, microporous, hydrophobic polymeric film that is coated with an adhesive layer that will permit the passage of lipids as the Sebutape® tightly adheres to the skin surface. The surface area of one Sebutape® is ~5 cm^2. Further details of the procedure are described within the accompanying Operations Manual.

9.1.17.4 FibroScan® (vibration controlled transient elastography)

One-dimensional vibration controlled transient elastography (VCTE) assessed by FibroScan (EchoSens™, Paris, France) will be used in this study.

At Screening or within 30 days prior to screening, subjects will be examined with the FibroScan to assess the controlled attenuation parameter (CAP) and liver elasticity/liver stiffness measurements (LSM). Subjects with FibroScan results obtained within 30 days prior to screening don't need to undergo this procedure at screening.

Only CAP will be used in order to qualify for the inclusion in the study. An additional FibroScan measurement will be performed at week 12.

For the LSM, the device generates a low-frequency shear wave from a probe applied to the subject's skin between the ribs. The speed of the wave spread is then measured between two points within the liver to allow the livers stiffness to be quantified. The wave will travel more rapidly through stiff tissue. An examination using the FibroScan consists of ten signal acquisitions at a single point; the whole process lasts around 15 minutes. The results (LSM and CAP) are instantly displayed on a screen.

For details please see the Operations Manual.

9.1.17.5 De Novo Lipogenesis (DNL) Assessment

Steady state contribution of fractional DNL to plasma triglyceride (TG) palmitate (representing hepatic DNL) and sebum fatty acids (e.g. palmitate and/or sapienic acid) will be determined using mass isotopomer distribution analysis (MIDA). For the assessment of fractional hepatic DNL during the study, subjects need to be in fasting conditions (no food or drink, except for water for 10 hours prior). Fasting is not required for the assessment of sebum DNL. A 2-week deuterated water labeling approach will be used to allow fully labeling of newly synthesized fatty acids (DNL) in liver triglycerides and sebum. Multiple blood and sebum samples will be collected throughout the assessment period for the measurement of deuterium enrichment in fatty acids and body water.

Sampling time points on different days should be at approximately the same clock time.

For details please see the Operations Manual.

Table 9-2 Deuterated Water Administration and Blood/Sebum Sampling for the DNL Assessments

	Cycle / Days	Deuterated Water Intake (3 x 50 mL/day)	Blood Collection for hepatic DNL[a]	Sebum Collection for sebum DNL
RUN-IN PERIOD	C1/D-14	X	X[b]	X[b]
	C1/D-13	X	--	--
	C1/D-12	X	--	--
	C1/D -11	X	X	--
	C1/D -10	X	--	--
	C1/D -9	X	--	--
	C1/D-8	X	--	--
	C1/D-7	--	X	--
	C1/D-6	--	--	--
	C1/D-5	--	--	--
	C1/D-4	--	--	--
	C1/D-3	--	--	--
	C1/D-2	--	--	--
	C1/D-1	--	--	--
	C1/D1	--	X[c]	X

	Days	Deuterated Water Intake (3 x 50 mL/day)	Blood Collection for hepatic DNL[a]	Sebum Collection for sebum DNL
TREATMENT PERIOD	**C3/D1**	--	X	--
	C3/D15	--	X	--
	C4/D1	X	X[b,c]	X[b]
	C4/D2	X	--	--
	C4/D3	X	--	--
	C4/D4	X	X[c]	--
	C4/D5	X	--	--
	C4/D6	X	--	--
	C4/D7	X	--	--
	C4/D8	--	X[c]	--
	C4/D9	--	--	--
	C4/D10	--	--	--
	C4/D11	--	--	--
	C4/D12	--	--	--
	C4/D13	--	--	--
	C4/D14	--	--	--
	C4/D15	--	X	X
	C4/D22	--	X	X

[a]Blood samples for DNL taken after an overnight fast
[b]Blood and sebum samples for DNL taken prior to administration of deuterated water
[c]Blood samples taken prior to IP dosing

9.1.17.6 MRI-PDFF

Magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) deems as a noninvasive, quantitative, and accurate measure of percent liver fat or hepatic steatosis grade in this study to identify the study population and assess the treatment response.

MRI-PDFF will be performed using a standardized imaging acquisition calibration protocol and the results will be determined by a central reader during the screening period (as baseline value), during week 6 (within a window of 4 days prior to C3/D1) and week 12 (within a window of 4 days prior to C4/D22).

For details please see the Operations Manual.

Incidental MRI results will be reviewed by the PI. Those found at screening should not be recorded as AEs, but as medical history on the CRF. Results found after first dose will be recorded as AEs. For details see section 10.1.1 Adverse Events.

9.1.18 Blood Volume

The estimated blood sampling volume for subjects is not expected to exceed 500 mL. Even in case of further unexpected blood sampling, extension of blood sampling period or necessary retesting, sampling volume will not exceed 50 mL. Actual blood volumes will be listed in the lab manual.

10.0 ADVERSE EVENTS

The investigator or designee and research site staff are responsible for the detection, documentation, classification, reporting, and follow-up of events meeting the definition of an AE or serious AE (SAE). Procedures for managing AEs and SAEs are detailed in the research site's SOPs.

Spontaneously reported or observed AEs will be recorded throughout the study beginning at the time the subject gives informed consent. AEs will be elicited using a non-leading question at designated time points. Regardless of seriousness, intensity, or presumed relationship to study drug, all AEs will be recorded in the source documentation from the time of first contact with the subject (e.g. Screening) until the end of the follow-up period of the study. All measures required for management of AEs will be recorded in the source documentation.

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE is any undesirable and unintended medical event occurring to a subject in a clinical study, whether or not related to the study products. This includes events from the first study related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol. The following should not be recorded as AEs, if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first study related activity after the subject has signed the informed consent
- Pre-existing conditions found as a result of screening procedures
- Pre-existing events that has not worsened in intensity or frequency from baseline.

10.1.2 Treatment emergent Adverse Event (TEAE)

- A TEAE is defined as any untoward medical occurrence in a subject administered a medicinal product that does not necessarily have a causal relationship with this treatment.
- A TEAE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product.
- This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under

investigation that is not recorded elsewhere on the eCRF under specific efficacy assessments.

Anticipated fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening are not considered AEs.

If progression of the underlying disease (i.e., the condition being treated with study drug) might be reasonably anticipated given the nature and severity of the underlying disease, then progression of the underlying disease per se will not constitute an AE. However, if the progression of the underlying disease meets the criterion for "serious" categorization of AEs (e.g., the underlying disease results in death or hospitalization, etc.), then the progression of underlying disease should be reported as an SAE.

10.1.3 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that occurs at any dose (or, occurs after informed consent is given and prior to dosing) that:

- Results in death. Any event resulting in death during the reporting period [from signing of ICF through 28 days after last dose of study drug(s)] must be treated as an SAE and reported as such.
- Is life-threatening (subject is at immediate risk of death from the event as it occurred) NOTE*: this is different than Life-threatening severity criteria.*
- Requires in-subject hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on 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 events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or the development of drug dependency or drug abuse.

The following are not considered SAEs and therefore do not need to be reported as such:

- Pre-planned or elective hospitalization including social and/or convenience situations (e.g., hospitalization due to weather or travel issues)
- Overdose of either study drug or concomitant medication unless the event meets SAE criteria (e.g., hospitalization). However, the event should still be captured as a non-serious AE on the appropriate eCRF page

10.1.4 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the study drug is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant

10.2 Recording of Adverse Events and Serious Adverse Events

- Any AE that occurs after signing of ICF through 28 days after last dose of study drug(s) should be recorded on the AE eCRF.
- In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words.
- Whenever possible, the investigator should combine signs and symptoms that constitute a single disease entity or syndrome into a final diagnosis, if appropriate. For example, fever, cough, and shortness of breath may be reported as pneumonia, if that is the final diagnosis.
- Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.
- SAEs that occur during the study or within 28 days after last dose of study drug(s), whether related to study drug, must be immediately reported to the Sponsor/SAE designee. Clinical trial sites will enter SAE information directly into the EDC clinical database within 24 hours of knowledge of the event. After the 28-day reporting window, only SAEs assessed as related to study drug need to be reported.

10.3 Evaluation of Adverse Events and Serious Adverse Events

The investigator or designee is responsible for making an assessment as to the seriousness, intensity, causality, action taken, and outcome of an AE.

10.3.1 Intensity of AEs

Intensity refers to the severity of the AE. The Investigator must categorize the severity of each AE according to the NCI CTCAE version 5.0. CTCAE guidelines can be referenced

at the following website:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

For any term that is not specifically listed in the CTCAE scale, intensity will be assigned a grade of one through five using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

10.3.2 Causal Relationship to Study Treatment

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge or rechallenge.

Not Related or Unlikely to be related

- An AE that is clearly due to extraneous causes (e.g., concurrent disease, concomitant medications, disease under study, etc.)
- It does not follow a reasonable temporal sequence from administration of study drug
- It does not follow a known pattern of response to study drug
- It does not reappear or worsen when study drug is restarted
- An alternative explanation is likely even if not clearly identifiable

Related, Possibly related, or Probably related

- An AE that is difficult to assign to alternative causes
- It follows a strong or reasonable temporal sequence from administration of study drug
- It could not be reasonably explained by the subject's clinical state, concurrent disease, or other concomitant therapy administered to the subject
- It follows a known response pattern to study drug
- It is confirmed with a positive rechallenge or supporting laboratory data

10.3.3 Action Taken and Outcome

The investigator will record the action taken and outcome for each AE according to the following criteria:

Action Taken with Study Drug

- None; Dose not changed
- Dose reduced
- Study drug temporarily interrupted
- Study drug permanently discontinued
- Other (specify); i.e., unknown or not applicable

Outcome

- Recovered
- Recovered with sequelae
- Ongoing; Not recovered
- Death; Fatal
- Lost to follow-up; Unknown

10.4 Reporting Procedures

10.4.1 Any Adverse Event

Regardless of seriousness, intensity, or presumed relationship to study drug, all AEs will be recorded in the source documentation. Whenever possible, diagnoses will be recorded, when signs and symptoms are due to a common etiology. In addition, the investigator must record his or her opinion as to the intensity of the AE and whether the AE is related to study drug. All measures required for management of the AE will be recorded in the source documentation.

10.4.2 Serious Adverse Events and Suspected Unexpected Serious Adverse Serious Reactions (SUSARs)

All SAEs, regardless of relationship to study drug, must be reported to the Sponsor/SAE designee within 24 hours of knowledge of the event, according to the procedures below. It is important that the investigator provide an assessment of relationship of the SAE to study treatment at the time of the initial report. Clinical trial sites will enter SAE information directly into the EDC clinical database within 24 hours of knowledge of the event.

The Sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the U.S. Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32; and to other applicable regulatory authorities, according to national law and/or local regulations.

All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC). In accordance with the European Commission Clinical Trials Directive (2001/20/EC), the Sponsor or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions as individual notifications or through periodic line listings.

The Sponsor or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements (i.e., within 7 days for treatment related unexpected fatal or life-threatening events; within 15 days for all other treatment related unexpected serious events).

10.4.3 Pregnancy or Drug Exposure during Pregnancy

- If a subject becomes pregnant during the study the investigator is to stop dosing with study drug(s) immediately.
- A pregnancy is not considered to be an AE or SAE; however, it must be reported to the Sponsor using the Pregnancy Report Form within the same timelines as an SAE. This applies to a female subject or the female partner of a male subject (note: additional consent may be required to obtain information from the female partner).
- The pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Reporting Form should be completed and reported to the Sponsor.
- AEs or SAEs that occur during pregnancy will be assessed and processed according to the AE or SAE processes using the appropriate AE or SAE forms.

11.0 DATA HANDLING AND MANAGEMENT

Clinical Data Management (CDM) is the responsibility of [redacted] Chula Vista, USA.

11.1 Data Management

The full details of procedures for data handling will be documented in the Data Management Plan (DMP).

AEs and medical history will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) WHO Drug Global dictionary. The MedDRA version used will be recorded in the Study Master File documentation.

Unique numbers will identify the subject and the biological material obtained from the subject. Appropriate measures such as encryption or deletion will be enforced to protect the identity of human subjects in all presentations and publications as required by local/regional/national requirements.

Data from screening failures will be entered into the database. The data for screen failures will be limited to ICF date, demographics, and eligibility assessment including reason(s) for screen fail.

Laboratory data from the central laboratory will be electronically transferred to [redacted] for database reconciliation purposes and loading into EDC for data review purposes. In cases where sensitive non-PK laboratory data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The laboratory will provide one copy of the laboratory reports to the site staff. The site staff will receive all laboratory data electronically or based on FAX reports directly from the laboratory. An Investigator must review, evaluate, sign and date the laboratory print-outs upon receipt. The signed print-out of the laboratory reports are source data.

All other results, including PK, PD data, and laboratory tests will be transferred electronically to the responsible Data Management Unit.

11.2 CRFs (Electronic)

11.2.1 Clinical Data Management Workflow

Electronic CRFs will be developed by the CDM, in collaboration with the clinical study team and statistician. CDM will document the process workflow in the DMP. After data entry, monitor(s) will source data verify (SDV) the eCRFs against the source documents. Queries may be issued to clarify the data entered. The PI will electronically sign the eCRFs after all data have been entered, source data verified, and all queries have been resolved. If corrections and/or resolution of queries are required after PI approvals, those eCRFs affected by changes will be re-signed by the PI. The database may be locked after the PI approvals are completed and the Sponsor has reviewed the data and authorized lock.

After database lock, CDM study design documentation and locked eCRFs (PDF) will be created and will be provided to the Sponsor.

11.2.2 Data Entry of eCRFs

Data required for analyses and subject safety assessments will be entered from source documentation into eCRFs. Instructions for data entry will be provided in the eCRF Completion Guidelines, developed by [redacted] CDM department. All site staff involved with entering data into the eCRFs will be trained prior to gaining access to the study database.

11.2.3 Corrections to eCRFs

Queries may be generated by the eCRF system during data entry, and queries may be generated by CDM staff, monitors, PIs, the Sponsor, and other data reviewers during the course of the study. Only specific site personnel will be authorized to make corrections to the eCRFs; CDM will train personnel prior to granting access in the eCRF system. Corrections will be made directly in the eCRF – by modifying existing data, adding new data, or deleting data, as appropriate. All data corrections will be logged in the electronic audit trail.

11.2.4 PI Approval of eCRF Data

The Investigator or Investigator's authorized staff must ensure that all information derived from source documentation is consistent with the source information and accurately reflected in the eCRFs. By electronically signing the eCRFs, the Investigator confirms that the information is complete and correct.

11.3 Retention of Documents

At the completion of the study, all records created by and under the supervision of the Investigator should be maintained in accordance with the requirements of the regulatory authority guideline and the GCP Guideline. These will be available for inspection at any time by the Sponsor or the FDA.

Clinical study documents are archived upon completion of the study and maintained for at least 15 years from the study closure or longer in accordance with local regulation and applicable regulatory authority guidelines, and the study sponsor will be notified prior to destruction of study records.

Current FDA guidelines require records to be retained for a period of 2 years following the date a marketing application is approved for the drug, for the indication for which it is being investigated. If no application is filed or if the application for the investigated indication is not approved, documents will be kept until 2 years after the investigation is discontinued and the FDA is notified. It is the sponsor's responsibility to inform [redacted] as to when essential documents are no longer needed to be retained

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

[redacted] will be responsible for the statistical services, including statistical analysis, statistical reports and the statistical analysis plan (SAP) to be developed prospectively prior to database final lock. With permission of the Sponsor, statistical services may be delegated under an agreement of transfer of responsibilities to a qualified vendor of [redacted]

The SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. It will also provide any changes or additions to the analyses that are not apparent in the protocol.

12.2 Analysis Sets

12.2.1 Safety Set

The Safety set will include all subjects who received IP (FT-4101 or Placebo) or deuterated water. The Safety set will be used for demographic, baseline characteristics and safety summaries.

12.2.2 Pharmacokinetic (PK) Set

The PK set will include all subjects who received FT-4101 or placebo with sufficient evaluable PK concentration data appropriate for the evaluation of interest (without major protocol deviations or violations that would have an impact on the absorption, distribution, metabolism, or excretion). The PK set will be used for analysis of PK endpoints.

12.2.3 Preliminary Efficacy Set

The Preliminary Efficacy set will include all subjects who received FT-4101 or placebo with at least one quantifiable baseline and one post baseline MRI-PDFF (without major protocol deviations or violations that would have an impact on the PD). The Preliminary Efficacy set will be used for analysis of MRI-PDFF endpoints.

12.2.1 Pharmacodynamic (PD) Set

The PD set will include all subjects who received FT-4101 or placebo without major protocol deviations or violations that would have an impact on PD. The PD set will be used for analysis of PD endpoints.

12.3 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects overall and by cohort and treatment. Summary statistics (e.g., number of subjects, mean, median, standard deviation, and range) will be generated for continuous variables (e.g., age and

weight) and the number and percentage of subjects within each category will be presented for categorical variables.

12.4 Analysis of the Pharmacokinetic Endpoints

Pharmacokinetic analysis will be performed for the PK set by treatment group if data is available.

12.4.1 Analysis of Secondary Pharmacokinetic Endpoints

12.4.1.1 Plasma Concentration of FT-4101

PK concentrations will be summarized descriptively by dose and by timepoint. Line plots of individual concentration profiles with treatment group mean (± standard deviation) may be generated.

12.4.1.2 Pharmacokinetic Parameters of FT-4101

The following parameters will be derived from individual serum profiles:

- Maximum concentration (C_{max})
- Time to maximum concentration (T_{max})
- Area under the concentration-time curve for a dosing interval (AUC_{tau})
- Trough plasma concentrations (C_{trough}) at steady state

PK parameters will be descriptively summarized.

12.5 Analysis of Preliminary Efficacy and Pharmacodynamic Endpoints

Preliminary Efficacy and pharmacodynamic analysis will be performed for the Preliminary Efficacy set using planned treatment assignment.

Figures (bar charts or line plots) may be generated to visualize the data.

12.5.1 Analysis of Primary Preliminary Efficacy Endpoints

Placebo subjects will be pooled for pharmacodynamic analyses.

The following is the primary preliminary efficacy endpoint:

- Reduction (absolute and relative) of % liver fat on magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) at 12 weeks

12.5.1.1 Liver Fat Assessed by MRI-PDFF at 12 weeks

The observed values and the change (absolute) from baseline and the percent change from baseline of liver fat estimated from MRI-PDFF will be analyzed descriptively by treatment group and visit.

Change at Week 12 (absolute and relative) in percentage of liver fat as assessed by MRI-PDFF will be analyzed by a Wilcoxon rank-sum test. The test will be one-sided and use a significance level of 0.05. Subjects in each dose group will be tested against the pooled placebo subjects from each cohort.

If more than one dose of FT-4101 is evaluated, control of the alpha level will be accomplished using Holm's Sequential Bonferroni procedure [Holm 1979] to test each FT-4101 dose against the pooled placebo subjects.

12.5.2 Analysis of Secondary Preliminary Efficacy and Pharmacodynamic Endpoints

The following are secondary preliminary efficacy endpoints:

- Reduction (absolute and relative) of % liver fat on magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) at 6 weeks

12.5.2.1 Liver Fat Assessed by MRI-PDFF

Reduction of % liver fat on MRI-PDFF at 6 weeks will be analyzed similarly as the primary preliminary efficacy endpoint.

In addition, a mixed effects model with repeated measures (MMRM) will be used to analyze the change from baseline, both absolute change and percent change (absolute and relative), to week 6 and week 12; the model will include baseline as a covariate and the factors, treatment group, visit, and the interaction of treatment group and visit. The least squares (LS) mean and its corresponding 95% confidence interval and p-value will be presented. The LS mean difference between treatment groups will be presented along with the 95% confidence interval and the p-value.

12.5.2.2 Proportion of Subjects with ≥ 30% Relative Reduction in Liver Fat at Week 12 Assessed by MRI-PDFF

The proportion of subjects experiencing a relative reduction of 30% or greater of liver fat at week 12 as assessed by MRI-PDFF will be summarized descriptively and analyzed using a Fisher's exact test. Subjects in each dose group will be tested against the pooled placebo subjects from each cohort.

12.5.2.3 Liver Biochemistry Markers

The following are secondary pharmacodynamic liver biochemistry marker endpoints:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma-glutamyl transferase (γGT)
- Alkaline phosphatase
- Total bilirubin

The observed values and the change from baseline of the liver biochemistry markers above be analyzed descriptively by treatment group and visit.

A MMRM will be used to analyze the change from baseline to C3/D1, C4/D15, and C4/D22; the model will include baseline as a covariate and the factors, treatment group, visit and the interaction between treatment group and visit. The least squares (LS) mean and its corresponding 95% confidence interval and p-value will be presented for each postbaseline visit. The LS mean difference between treatments will be presented along with the 95% confidence interval and the p-value for each postbaseline visit.

12.5.3 Analysis of Exploratory Pharmacodynamic Endpoints

In general, exploratory analysis will be descriptive, unless specified otherwise in the SAP.

The observed value and the change from baseline of the exploratory endpoint parameters will be analysed descriptively by treatment group and visit.

Fasting Hepatic DNL may be analysed using a statistical model.

12.5.3.1 Fasting Hepatic De Novo Lipogenesis

The following is the exploratory pharmacodynamic endpoint related to fasting hepatic de novo lipogenesis:

- Inhibition of fasting hepatic de novo lipogenesis (DNL) after administration of multiple doses in overweight/obese subjects with NASH by using a 2-week deuterated water labeling protocol

The derivation of the fasting hepatic DNL and the inhibition of hepatic DNL will be discussed in detail in the SAP.

The observed values and the change from baseline of fasting hepatic DNL and hepatic DNL inhibition (%) will be analyzed descriptively by treatment group and visit.

Inhibition of hepatic DNL over time will be analyzed graphically.

A MMRM, similar to the MMRM described previously, may be used to analyze the change from baseline of fasting hepatic DNL and hepatic DNL inhibition.

12.6 Analysis and Endpoints

12.6.1 Analysis of Primary Safety and Tolerability Endpoints

To assess safety and tolerability of FT-4101 after administration of multiple doses in overweight/obese subjects with NASH by:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of clinical lab abnormalities
- Incidence and severity of clinical findings on physical examination

- Change from baseline in vital signs (blood pressure [BP], heart rate [HR], respiratory rate, and temperature])
- Change from baseline in 12-lead electrocardiogram (ECG) parameters

Safety and tolerability of the study drugs will be assessed by collection and review of adverse events, tolerability, laboratory parameters, physical examination, vital signs, and ECG parameters throughout the duration of the study. Safety analysis will involve examination of the descriptive statistics and individual subject listings for any effects of study treatment on clinical tolerability and safety.

AEs will be summarized using the safety set.

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class.

Adverse event summaries will include the overall incidence (by system organ class and preferred term), events by maximum intensity, event by relationship to study treatment, events leading to discontinuation of study drug, and serious adverse events. Physical exam, vital signs, ECG, and laboratory parameters (hematology, chemistry, and urinalysis) will be summarized descriptively by treatment group.

12.7 Interim Analysis

No interim analysis is planned.

12.8 Determination of Sample Size

With 10 evaluable subjects in the treated group and 10 evaluable subjects in the control group, there is 84% power to detect a difference of 20% between the high dose treated group and the pooled placebo subjects in cohorts A and B in MRI-PDFF, assuming a standard deviation of 14% using a one-sided Wilcoxon-Mann-Whitney test with an alpha of 0.05.

The total sample size will be 30 subjects, 15 subjects per cohort randomized 2:1 to receive FT-4101 or placebo.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring

A representative of [redacted] will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of [redacted] Sponsor or Regulatory authority will conduct on-site visits to review, audit, copy study-related documents. These representatives will meet with the Investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

Monitoring will follow a Monitoring Plan.

13.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other circumstances arise that will require deviation from protocol-specified procedures, unless there is an emergency or immediate need, the Investigator should contact the medical monitor and Sponsor to review and discuss the implications of the deviation and determine the appropriate course of action. Any deviation must be documented, stating the reason and date, the action taken, and the impact for the subject and/or the study. The documentation must be kept in the Investigator's Study File and the Sponsor's Study Master File. The Investigator should report the deviation to their IRB/EC per their reporting requirements.

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted in accordance with the Protocol, the International Conference on Harmonization (ICH), current Guideline for Good Clinical Practice: Consolidated Guidance E6(R2) and applicable regulatory requirements including clinical research guidelines established by the Basic Principles defined in the U.S. 21 CFR Parts 50, 56, and 312 and the principles enunciated in the Declaration of Helsinki (revised version Fortaleza 2013).

14.1 Institutional Review Board and/or Independent Ethics Committee

Prior to commencement of the study, the protocol, any amendments, subject information/informed consent form, any other written information to be provided to the subject, subject recruitment procedures, information about payments and compensation available to subjects if not mentioned in the subject information, the Investigator's current CV and/or other documentation evidencing qualifications, and other documents as required by the local Independent Ethics Committee (IEC)/Institutional Review Board (IRB) should be submitted. Written approval/favorable opinion must be obtained from IEC/IRB prior to commencement of the clinical study start.

The Investigator shall provide to Sponsor or its designee a copy of the written and dated approval/favorable opinion by the applicable IRB/IEC.

During the study, the Investigator must promptly report the following to the IEC/IRB: Updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, substantial amendments to the protocol, non-substantial amendments, applicable deviations to the protocol, new information that may affect adversely the safety of the subjects or the conduct of the study (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the study status and other documents as required by the local IEC/IRB.

Substantial amendments must not be implemented before approval/favorable opinion, unless necessary to eliminate hazards to the subjects.

The Investigator must maintain an accurate and complete record of all submissions made to the IEC/IRB. The records should be filed in the Investigator's Study File and copies must be provided to the Sponsor.

14.2 Regulatory Authorities

Regulatory Authorities will receive the Clinical Study Application, Protocol, Amendments to the Protocol, reports on SAEs and the Integrated Clinical Study Report according to national regulations.

14.3 Responsibilities of the Investigator

The Investigator will conduct this clinical study in compliance with all applicable national, state, local or regional laws and regulatory requirements of the countries in

which the clinical study is performed. The Investigator will align his or her conduct in accordance with the "Responsibilities of the Investigator". The Investigator should ensure that all persons involved in the conduct of the study are informed about the protocol, protocol amendments, study procedures, and study-related duties.

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on Investigators by the FDA are summarized in the "Statement of Investigators" (Form FDA 1572), which must be completed and signed before the Investigator may participate in this study.

14.4 Informed Consent

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

14.5 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Subject records will be kept private except when ordered by law. The following individuals will have access to study subject records: Principal Investigator and designees, study Sponsor, monitors and auditors, the FDA, other government offices and the IRB.

Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

The Investigator must agree to permit the Sponsor's monitor or designee's monitor, representatives from any regulatory authority, the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's source data or documents, including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process. The confidentiality

of the verified data and the protection of the subjects must be respected during these inspections.

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed.

14.6 Publication, Disclosure, and Clinical Study Registration Policy

The Investigator will provide the Sponsor with truthful, accurate and complete test results and all data derived from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

[redacted] or its designee will be responsible for preparing the Clinical Study Report. When all data has been fully analyzed, [redacted] or Sponsor will communicate the results of the Clinical Study to the Investigator(s).

All information obtained as a result of this study or during the conduct of this study will be regarded as confidential. The conditions regulating dissemination of the information derived from this clinical trial are described in the Clinical Trial Agreement.

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16.0 APPENDICES

16.1 Appendix A - Schedule of Events

ASSESSMENT	SCREEN	RUN-IN PERIOD			IN-HOUSE PERIOD		OUTPATIENT VISITS								IN-HOUSE PERIOD		OUTPATIENT	FOLLOW-UP
StudyVisit[a] Cycle (C) / Day (D) (Visit Window)[a]	C1 D-45 to D-15	C1 D-14 (+1)	C1 D-11 (±1)	C1 D-7 (±1)	C1[b] D-1	C1[b] D1	C1 D15 (±1)	C2[c] D1 (±1)	C2 D15 (±1)	C3[c] D1 (±1)	C3 D15 (±1)	C4[c] D1 (±1)	C4 D4 (±1)	C4 D8 (±1)	C4[b] D14	C4[b] D15	C4[d] D22 (±1)	C4[e] D29 (±2)
DOSING[f]						X		X		X		X	X	X	X			
Informed consent	X																	
Assess eligibility criteria	X	X																
Demography	X																	
Medical history	X	X[g]																
Weight	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X
BMI	X					X				X							X	
Height	X																	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (PE)	X																	X
Abbreviated PE					X		X	X	X	X	X	X				X	X	
12-lead ECG	X				X			X		X		X						X
Hematology, serum chemistry & urinalysis	X				X		X	X	X	X	X	X				X	X	X
Coagulation	X				X					X								X
Fasting plasma glucose	X																	
Fasting lipid profile	X					X		X		X		X				X	X	
TSH	X																	
HbA1c	X					X				X							X	

ASSESSMENT	SCREEN	RUN-IN PERIOD			IN-HOUSE PERIOD		OUTPATIENT VISITS								IN-HOUSE PERIOD		OUTPATIENT	FOLLOW-UP
StudyVisit[a] Cycle (C) / Day (D) (Visit Window)[a]	C1 D-45 to D-15	C1 D-14 (+1)	C1 D-11 (±1)	C1 D-7 (±1)	C1[b] D-1	C1[b] D1	C1 D15 (±1)	C2[c] D1 (±1)	C2 D15 (±1)	C3[c] D1 (±1)	C3 D15 (±1)	C4[c] D1 (±1)	C4 D4 (±1)	C4 D8 (±1)	C4[b] D14	C4[b] D15	C4[d] D22 (±1)	C4[e] D29 (±2)
Hep B, Hep C, HIV	X																	
Pregnancy test (serum)	X																	
Pregnancy test (urine)		X	X	X	X		X	X	X	X	X	X	X	X	X		X	
FSH for postmenopausal	X																	
Urine drug screen	X				X					X							X	
Alcohol breath test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Deuterated Water Labeling Period (3 x 50 mL/day)[h]		C1/D-14 to C1/D-8										C4/D1 to C4/D7						
Blood collection for fasting hepatic DNL assessments[i,j]		X	X	X		X				X	X	X	X	X		X	X	
Blood collection for PK assessments[k]						X	X	X	X		X		X	X	X	X		
Sebum collection using Sebutape® for fatty acid concentration		X[n]				X						X				X	X	
Sebum collection using Sebutape® for DNL		X				X						X				X	X	
Sebumeter® for sebum production						X	X	X	X	X	X	X				X	X	X
Blood collection for circulating biomarkers[l]						X				X						X	X	
FibroScan® (LSM and CAP)	X[o]																X	

ASSESSMENT	SCREEN	RUN-IN PERIOD			IN-HOUSE PERIOD		OUTPATIENT VISITS								IN-HOUSE PERIOD		OUTPATIENT	FOLLOW-UP
StudyVisit[a] Cycle (C) / Day (D) (Visit Window)[a]	C1 D-45 to D-15	C1 D-14 (+1)	C1 D-11 (±1)	C1 D-7 (±1)	C1[b] D-1	C1[b] D1	C1 D15 (±1)	C2[c] D1 (±1)	C2 D15 (±1)	C3[c] D1 (±1)	C3 D15 (±1)	C4[c] D1 (±1)	C4 D4 (±1)	C4 D8 (±1)	C4[b] D14	C4[b] D15	C4[d] D22 (±1)	C4[e] D29 (±2)
MRI-PDFF	X									X[m]							X[m]	
FibroSure®	X									X							X	
Randomization					X													
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Deuterated water supply and accountability		X	X	X								X	X	X				
IP supply and IP accountability						X	X		X	X		X	X	X	X			
Subject Diary for -deuterated water intake - IP intake - if T2DM glycemic control	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standardized controlled conditions and meals					X	X									X	X		

[a]Cycle (C) 1 Day (D) 1 (C1/D1) is the start of the four 21-day treatment cycles. Study visits occurring before C1/D1 are based on a countdown to this date. Subsequent study visits are defined by the days from the start of the most recent treatment cycle.

[b]Study windows are not provided on these study dates. C1/D1 is the start of study treatment. C1/D-1 must occur on the day prior to C1/D1. C4/D14 and C4/D15 visits are required to occur starting on the last day of study treatment in cycle 4 (C4/D14), in order to obtain time and treatment day-dependent PK/PD samples.

[c]Day 1 of treatment cycles 2-4 expected to start 22 days (±1) from start of previous treatment cycle (except when dose delays required for AE's-see protocol).

[d]In subjects who discontinue study participation before completion of the study treatment period in Cycle 4, the end of treatment (EOT) visit (C4/D22) should occur approximately ≥6 days from last dose of FT-4202/placebo.

[e]In subjects who discontinue study participation before completion of the study treatment period in Cycle 4, a follow-up visit occurring approximately 28 days from the start of the last treatment cycle (Day1) is requested.

[f]Drug is administered QD on days 1-14 and held days 15-21 of each treatment cycle. Hold dose of IP in the morning of visits occurring during the active treatment period until all fasting visit procedures have been completed and as instructed per visit.

[g]Interim medical history

[h]Each bottle of deuterated water should be consumed at least 3 hours apart

[i]Subjects will be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. Blood for DNL needs to be taken prior to consumption of deuterated water on C1/D-14, C1/D-11, C4/D1, and C4/D4. Blood samples for DNL are taken pre-dose on days IP is administered also.

[j]Includes blood for deuterium enrichment in palmitate and body water. Samples should be collected same time of day.

[k]PK sampling will follow Appendix B (PK sampling schedule) in section 16.2.

[l]Sampling for fasting circulating biomarker include metabolic parameter (FPG, fasting insulin, HOMA-IR, HbA1c, Adiponectin (total and high molecular weight), FGF-21, and Malonyl carnitine), liver injury and fibrosis biomarkers (CK-18 fragment, ELF score [HA, PIIINP, TIMP-1], PRO-C3).

[m]To be performed within a window of 4 days prior to C3/D1 and C4/D22

[n]These Sebutape samples collected at D-14 will be stored for potential future fatty acid analysis.

[o]This FibroScan can be performed at screening or within 30 days prior to screening. Both LSM and CAP values are captured and recorded. Both LSM and CAP are PD endpoints but only CAP (≥300dB/m) is part of the eligibility criteria.

16.2 Appendix B – PK Sampling Schedule

Study Visit Cycle (C)/ Day (D)	PK Sample Collection Time Points	
C1/D1	Pre-dose	- 15 min
C1/D1	1 hour post-dose	± 15 min
C1/D1	2 hours post-dose	± 15 min
C1/D1	4 hours post-dose	± 15 min
C1/D1	6 hours post-dose	± 15 min
C1/D15	24 hours post-dose	± 4 hours
C2/D1	Pre-dose	± 15 min
C2/D15	24 hours post-dose	± 4 hours
C3/D15	24 hours post-dose	± 4 hours
C4/D4	Pre-dose	± 15 min
C4/D8	Pre-dose	± 15 min
C4/D14	Pre-dose	± 15 min
	1 hour post-dose	± 15 min
	2 hours post-dose	± 15 min
	4 hours post-dose	± 15 min
	6 hours post-dose	± 15 min
	8 hours post-dose	± 30 min
	12 hours post-dose	± 60 min
	16 hours post-dose	± 60 min
C4/D15	24 hours post-dose	± 4 hours
	30 hours post-dose	± 4 hours

16.3 Appendix C - CYP3A Strong Inhibitors and Inducers

Examples of strong clinical inhibitors for P450-mediated metabolism

	Strong inhibitors
CYP3A	boceprevir, cobicistat[a], conivaptan[a], danoprevir and ritonavir[b], elvitegravir and ritonavir[b], grapefruit juice[c,e], indinavir and ritonavir[b], itraconazole[a], ketoconazole, lopinavir and ritonavir[a,b], paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[b], posaconazole, ritonavir[a,b], saquinavir and ritonavir[a,b], telaprevir[c], tipranavir and ritonavir[c,d], troleandomycin, voriconazole
	clarithromycin[c], diltiazem[c], idelalisib, nefazodone, nelfinavir[c], cannabidiol (CBD) oil[f]

Note: Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively. Strong inhibitors of CYP3A causing ≥10-fold increase in AUC of sensitive index substrate(s) are shown above the dashed line.

[a] Strong inhibitor of CYP1A2 and CYP2C19, and moderate inhibitor of CYP2D6 and CYP3A.
[b] Strong inhibitor of CYP2C19 and moderate inhibitor of CYP2C9 and CYP3A.
[c] Inhibitor of P-gp (defined as those increasing AUC of digoxin to ≥1.25-fold).
[d] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
[e] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
[f] TY Kong et al. 2018. Archives of Pharmaceutical Research; 41:691-710

Examples of strong clinical inducers for P450-mediated metabolism

	Strong inducers
CYP3A	carbamazepine[c], enzalutamide[d], mitotane, phenytoin[b], rifampin[a], St. John's wort[e]

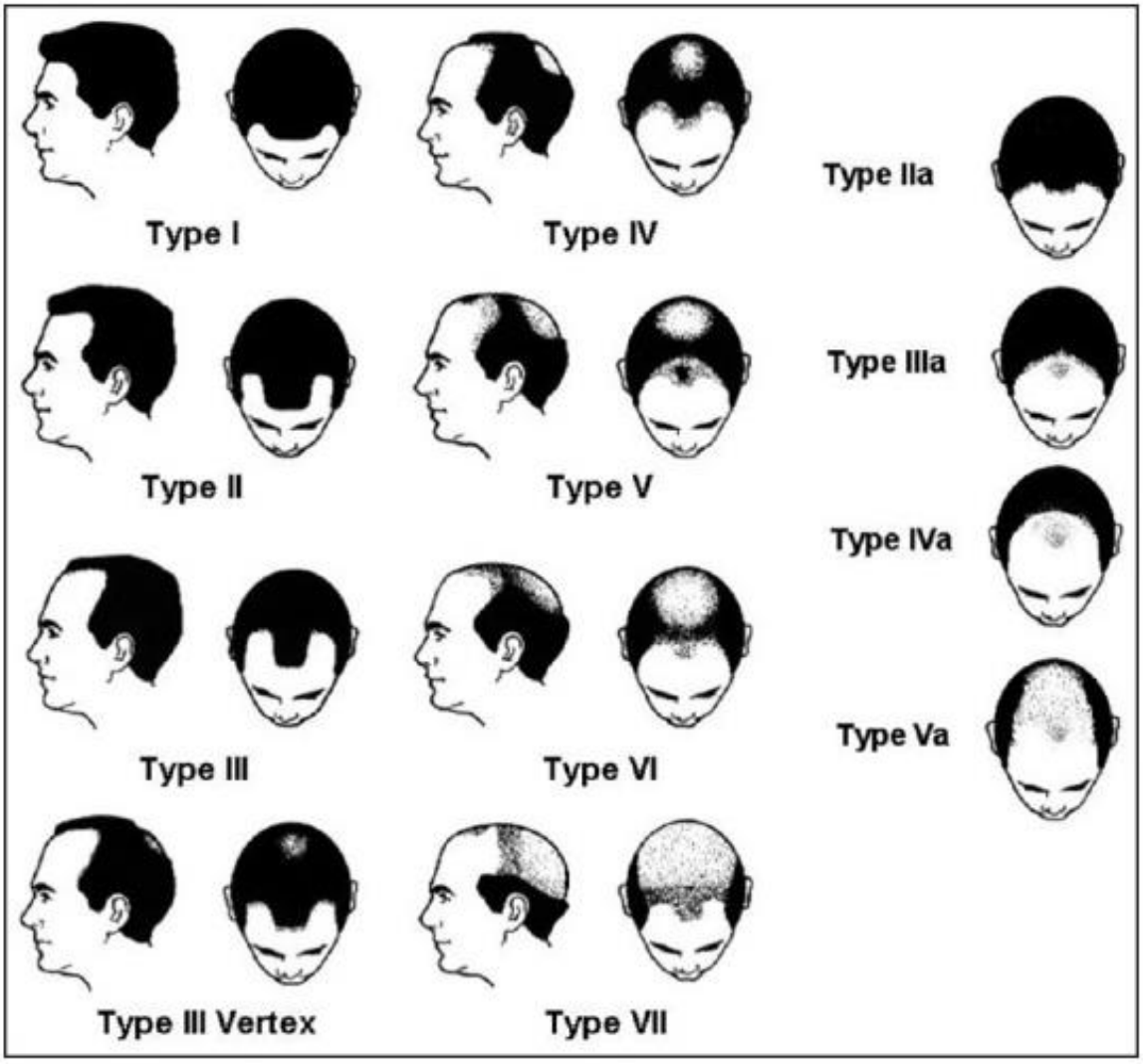
Note: Strong, moderate, and weak inducers are drugs that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%, ≥50% to <80%, and ≥20% to <50%, respectively.

[a] Strong inducer of CYP3A and moderate inducer of CYP1A2, CYP2C19.
[b] Strong inducer of CYP2C19, CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9.
[c] Strong inducer of CYP2B6, CYP3A, and moderate inducer of CYP2C9.
[d] Strong inducer of CYP3A and moderate inducer of CYP2C9, CYP2C19, CYP3A.
[e] The effect of St. John's wort varies widely and is preparation-dependent.

All tables are prepared to provide examples and are not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. 2010].

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

16.4 Appendix D - Norwood's Classification of Hair Loss

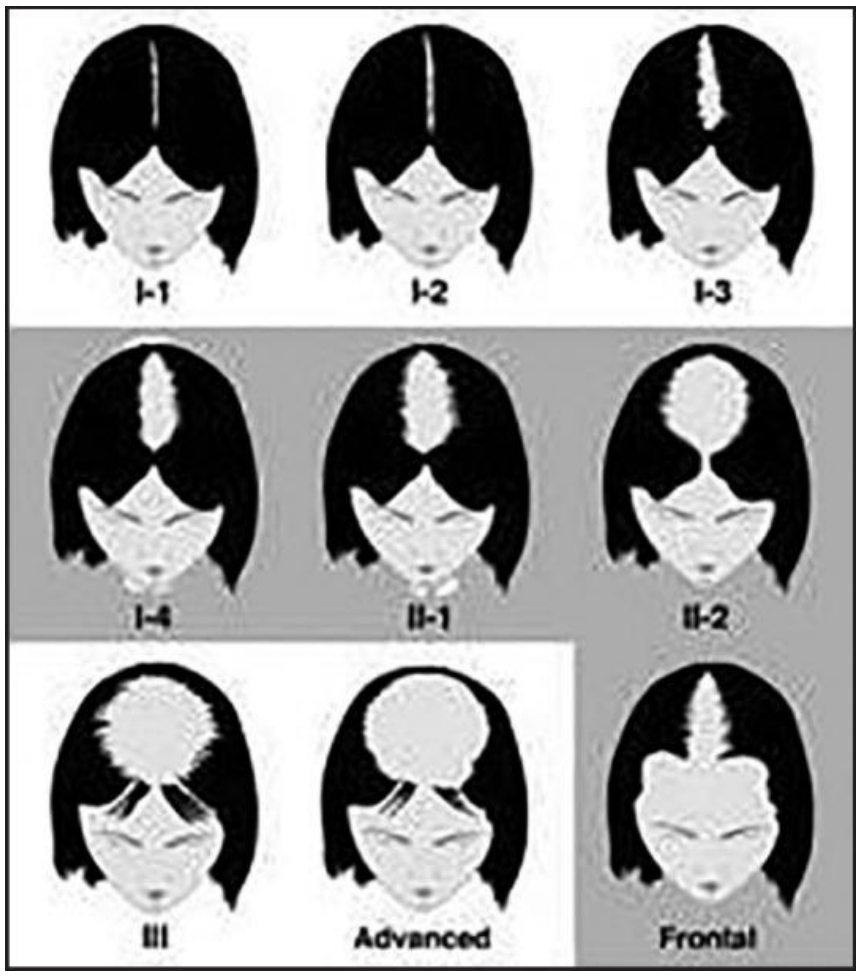


Type I:	There is minimal or no recession of the hairline.
Type II:	There are triangular, usually symmetrical, areas of recession at the frontotemporal hairline.
Variant IIA:	The hairline is anterior to the coronal plane 2 cm anterior to the external auditory meatus.
Type III:	This represents the minimal extent of hair loss, sufficient to be considered as baldness according to Norwood. There are deep symmetrical recessions at the temples that are bare or only sparsely covered by hair. In Type III vertex, the hair loss is primarily from the vertex with limited recession of the frontotemporal hairline that does not exceed the degree of recession seen in Type III.
Variant IIIA:	The hairline has receded back to a point between the limit of Type IIA and the level of the external auditory meatus.

Type IV:	The frontotemporal recession is more severe than in Type III and there is sparse hair or no hair on the vertex. The two areas of hair loss are separated by a band of moderately dense hair that extends across the top. This band connects with the fully haired fringe on the sides of the scalp.
Variant IVA:	The hairline has receded beyond the external auditory meatus but has not reached the vertex.
Type V:	The vertex hair loss region is still separated from the frontotemporal region, but it is less distinct. The band of hair across the crown is narrower and sparser and the vertex and frontotemporal regions of hair loss are bigger.
Variant VA:	The area of denudation includes the vertex. Hair loss more severe than Type VA cannot be distinguished from Types VI or VII.
Type VI:	The bridge of hair that crosses the crown is gone with only sparse hair remaining. The frontotemporal and vertex regions are joined together, and the extent of hair loss is greater.
Type VII:	The most severe form of hair loss and only a narrow band of hair in a horseshoe shape remains on the sides and back of the scalp. This hair is usually not dense and may be quite fine.

Source: [Norwood 1975]

16.5 Appendix E - Savin's Pictorial Grading of Female Pattern Hair Loss



Source: [Savin 1992]