Cover Page for Statistical Analysis Plan

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Statistical Analysis Plan

Protocol 4101-MET-201

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

Phase 1/2

Protocol Version:
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Prepared by: [redacted]

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Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

Signature Page

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FORMA Therapeutics, Inc.

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Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemistry
$AUC_{0\text{-}inf}$	Area under the concentration-time curve in the sampled matrix from zero (predose) extrapolated to infinite time
$AUC_{0\text{-}last}$	Area under the concentration-time curve in the sampled matrix from zero (predose) to time of last quantifiable concentration
AUC_{tau}	Area under the concentration-time curve for a dosing interval
BLQ	Below the Limit of Quantitation
BP	Blood Pressure
CAP	Controlled Attenuation Parameter
CK-18	Cytokeratin-18
CL/F	Apparent systemic clearance after extravascular dosing
C_{max}	Maximum concentration
C_{max}/D	Dose-normalized Maximum Concentration
CO2	Carbon Dioxide
CTCAE	Common Toxicity Criteria for Adverse Events
C_{trough}	Trough plasma concentrations at steady state.
DNL	De Novo Lipogenesis
ELF	Enhanced Liver Fibrosis
FFA	Free Fatty Acids
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone
γGT	Gamma-glutamyl transferase
HA	Hyaluronic Acid
hCG	Human Chondroitin Beta
HDL-c	High-Density Lipoprotein Cholesterol
Hep B	Hepatitis B
Hep C	Hepatitis C
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IP	Investigational Product
LDL-c	Low-Density Lipoprotein Cholesterol
LS	Least Squares
LSM	Liver Stiffness Measurement
MedDRA	Medical Dictionary For Regulatory Activities
MMRM	Mixed Effects Model with Repeated Measures
MRI-PDFF	Magnetic Resonance Imaging- Proton Density Fat Fraction
NASH	Nonalcoholic Steatohepatitis
non-HDL-c	Non-High-Density Lipoprotein Cholesterol

PD	Pharmacodynamic
PIIINP	Procollagen III Amino Terminal Peptide
PK	Pharmacokinetic
QTcF	QT Corrected Using the Fridericia Correction
REML	Restricted Maximum Likelihood method
SAP	Statistical Analysis Plan
SOE	Schedule of Events
t1/2	Apparent terminal half-life
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
TG	Triglycerides
TIMP-1	Tissue Inhibitor of Metalloproteinases 1
T_{max}	Time to maximum concentration
Vz/F	Apparent volume of distribution following extravascular dosing
WHO	World Health Organization

1. INTRODUCTION

This document describes the statistical methods and procedures to be implemented in the analysis of treatment effect of FT-4101 in overweight/obese subjects with nonalcoholic steatohepatitis (NASH) compared to placebo. This statistical analysis plan (SAP) is based on the study protocol 4101-MET-201 (Version 2.0, 23-JUL-2019). If the data suggest and warrant it, deviations from this plan will be considered. Any deviations from this SAP must be substantiated by sound statistical rationale and documented in the final clinical study report; an amendment will be generated to document the revisions to the SAP.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objectives and Endpoint

The primary objectives of this study are:

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 parameters (heart rate, QT interval, PR interval, QRS interval, RR interval, and QTc [corrected] using the Fridericia correction [QTcF = QT/cubic root of the R-R interval, where R-R interval is the duration of the entire cardiac cycle])

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- Proton Density Fat Fraction (MRI-PDFF) at 12 weeks

2.2. Secondary Objectives and Endpoints

The secondary objectives and endpoints of this study are:

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/obsess 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 (C1/D1) and multiple doses (C4/D14-15) 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.

2.3. Exploratory Objectives and Endpoints

To assess the PD effect of FT-4101 on 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.

- Change in fasting hepatic DNL (%)

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 and liver stiffness determined by FibroScan® at 12 weeks.

- Controlled Attenuation Parameter (CAP)
- Liver stiffness measurement (LSM)

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)

3. STUDY OVERVIEW

3.1. 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.

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

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 (3.0 mg FT-4101) 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 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 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 washout 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 assessments 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.

3.2. Dose Reductions and Discontinuations

Subjects are allowed one dose reduction in the study, based on TEAE severity grade (Grade 1 or 2), system organ class (non-skin or non-eye vs skin or eye) and duration of TEAE resolution (< 7 days or ≥ 7 days). Subjects who experience TEAE with severity Grade 3 or higher will result in permanent treatment discontinuation. Please see protocol section 6.6 for more details.

3.3. Study Procedures

For detail on all the assessments, please see the Schedule of Events (SOE) in the Appendix A.

3.4. Sample Size Consideration

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% in MRI-PDFF between any dose of FT-4101 treated group and the pooled placebo subjects in cohorts A and B, 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.

4. ANALYSIS SETS

The number of subjects and percentage of subjects in each analysis set will be summarized. A memo will be finalized prior to database lock to adjudicate each subject's membership in each analysis set based on the following pre-specified definitions.

4.1. Randomized Analysis Set

The Randomized analysis set will include all randomized subjects. The Randomized analysis set will be used for summary of subject disposition, demographic, and baseline characteristics.

4.2. Safety Analysis Set

The Safety analysis set will include all randomized subjects who received IP (FT-4101 or Placebo) or deuterated water. Subjects who took deuterated water and were not randomized will be excluded. The Safety analysis set will be used for safety summaries.

4.3. Pharmacokinetic Analysis Set

The PK analysis set will include all subjects who received FT-4101 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 analysis set will be used for analysis of PK endpoints.

4.4. Preliminary Efficacy Analysis Set

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

4.5. Pharmacodynamic Analysis Set

The PD analysis 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 analysis set will be used for analysis of PD endpoints.

5. INTERIM ANALYSIS

No interim analysis is planned.

6. STATISTICAL METHODS OF DATA ANALYSIS

6.1. General Considerations

Unless otherwise specified, all data will be provided in subject level listings in addition to summary tables or figures.

6.1.1. Statistical Notation and Presentation

Continuous data will be summarized in tables using the number of subjects (n), mean, median, standard deviation (SD), minimum and maximum. For PK concentration and parameter data, the geometric mean, and its standard error and coefficient of variation (CV%) of geometric mean will be provided as well. Categorical data will be summarized by count and percentage. The denominator will be the number of subjects or the number of records, whichever is more appropriate.

Minimum and maximum values will use the precision of the original value in the database. Means, least squares (LS) means, and medians will be rounded to one decimal place greater than the precision of the original value. Estimates of SE, SD and the 90% confidence intervals will be rounded to two decimal places greater than the precision of the original value. Percentages will

be rounded to the nearest tenth digit. P-values will be presented with four decimal places, and p-values less than 0.0001 will be presented as <.0001.

6.1.2. Hypothesis Testing and Multiplicity Adjustment

The primary preliminary efficacy endpoint will be tested using a one-sided test at an alpha level of 0.05. The null hypothesis and alternative hypothesis are presented below.

H_0: Diff ≥ 0

H_a: Diff < 0

Where Diff is the mean difference: FT-4101 minus Placebo.

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

The p-values of the multiple comparisons will be ordered from smallest to largest. The corrected p-value from each comparison, starting from the smallest original p-value, will be calculated based on the following formula:

$$p_{Bonferroni,i|C} = (C - i + 1) * p$$

where the number of comparisons is *C*, index *i*, ranges from 1 to *C*, and the original p-value that is to be corrected, p. Corrected p-values less than 0.05 will be considered statistically significant.

6.1.3. Study Baseline

Unless otherwise specified, baseline will be defined as the last non-missing pre-dose measurement.

6.1.4. Handling of Multiple Observations

Priority will be given to scheduled visits. Unscheduled assessments will be used if there are no scheduled visit assessments in the visit window per SOE; visit window in general is ±1 day, unless specified otherwise; follow-up visit is ±2 days.

6.1.5. Handling of Missing or Partial Dates

Date imputation will only be used for computational purposes; e.g., treatment-emergent status or identifying concomitant medications. Actual data values as they appear in the clinical database will be shown in the subject data listings.

6.1.5.1. Adverse Event Date Imputations

In cases of incomplete dates for adverse events (AEs), the missing component(s) will be assumed as the most conservative value(s) to conservatively capture AEs with missing start dates as treatment-emergent AEs (TEAEs) unless TEAE status was disqualified based on a pre-treatment stop date/time. The imputation rules are as follows:

- If "day" is the only missing field, impute the "day" as the first randomized dose date if the month and year of randomization are equal to the AE start month and year; otherwise, impute the "day" as the first day of the AE start month.
- If "day" and "month" are missing, impute the "day" and "month" as the day and month of the first randomized dose date if "year" is the same as the year of randomization; otherwise, impute January 1 of the non-missing year.
- Missing time will not be imputed. If "time" is missing and the start date is the same as the first dose date, then the time is assumed to be after the first dose time so that the event will be classified as treatment emergent.
- If the start date is completely missing:
    - and from the end date (either complete or partial date) it cannot be deduced to be prior to the first dose date, then the AE will be assigned as a TEAE.
    - and from the end date (either complete or partial date) it can be deduced to be prior to the first dose date, then the AE will not be assigned as a TEAE.

6.1.5.2. Medication Date Imputations

Imputation of partial medication end dates is done for the purpose of classifying concomitant status of medications. The imputation rules are as follows:

For medications with partial end dates:

- If "day" is the only missing field, impute the "day" as the last day of the month.
- If "day" and "month" are the missing fields, impute the "month" and "day" to Dec 31.
- If end date is completely missing, then medication will be classified as a concomitant medication.

6.1.6. Handling of Missing Efficacy Data

Missing efficacy data will not be imputed.

6.2. Subject Disposition

Subject disposition will be presented for all subjects in the randomized analysis set. The count and percentage of subjects who are randomized, who are treated, who completed or discontinued from the study will be summarized by treatment group and overall. Furthermore, subjects who discontinued from the study will be summarized by reason for early discontinuation such as:

- Adverse event (or serious adverse event)
- Protocol Violation
- Lost to follow-up
- Voluntary withdrawal of consent
- Discretion of Investigator
- Pregnant or breast feeding
- Study discontinuation by Sponsor

- Other

6.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics such as, but not limited to, age, sex, race, ethnicity, height, weight, body mass index, waist circumference, MRI-PDFF, HbA1c and FPG will be summarized descriptively for all subjects overall and by treatment in the randomized analysis set. If composition of the Safety analysis set is different from that of the randomized population, demographics and baseline characteristics will be also summarized in the safety analysis set.

6.4. Medical History

Medical history will be summarized descriptively, with count and percentage, by coded term (using MedDRA version 22.0) and treatment group for the Safety analysis set.

6.5. Subject Eligibility

Subject eligibility data will only be listed.

6.6. Study Drug Administration

Subjects will receive their assigned dose orally with 240 mL of water. The total drug exposure (mg), the duration of exposure (days), drug dose modification, and the drug compliance will be summarized by treatment.

The duration of exposure is defined as (date of last dose – date of first dose + 1 + 7). The drug compliance is defined as number of capsules taken/{(date of last dose – date of first dose + 1 + 7)*2/3}*100. For each treatment group, drug compliance will be summarized by compliance category (<80%, 80-120%, and >120%).

6.7. Prior and Concomitant Medication

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

The latest version of the World Health Organization (WHO) Drug Global dictionary (Global B3 Mar 2019) will be used to categorize verbatim descriptions of non-study medications into the Anatomic Therapeutic Chemistry (ATC) classification system. Each verbatim name will be classified by anatomical main group (ATC level 1), therapeutic subgroup (ATC level 2), pharmacological subgroup (ATC level 3), chemical subgroup (ATC level 4), and trade name.

The number and percentage of subjects receiving any concomitant medications will be summarized by treatment group and ATC classification (ATC level 2 and level 4) for the Safety analysis set.

6.8. Protocol Deviations

Protocol deviations will be summarized by the category of important or non-important by treatment group for the Safety analysis set. Important protocol deviations are thought to have possible impacts on the analysis.

6.9. Analysis of Pharmacokinetics Endpoints

6.9.1. Plasma Concentration of FT-4101

PK concentrations will be summarized descriptively by treatment group, visit and nominal time point in the PK analysis set, including the arithmetic CV%. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics.

Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales with a separate graph for each dose level. Figures of arithmetic mean concentration-time data (±SD, as appropriate) will be presented for each treatment on linear and semi-logarithmic scales. Plots will be presented for PK samples collected during the first and last cycle and for all trough samples collected cumulatively across all cycles.

A subject's data listing of PK concentration will be provided. Subject's PK concentrations which are not included in PK parameter derivation will be flagged. Time difference between nominal time point and actual sampling time point will be presented.

6.9.2. Pharmacokinetic Parameters of FT-4101

For PK parameter calculations, BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile and will otherwise be treated as missing. Missing PK concentration data will not be imputed.

PK parameters will be estimated separately from single dose profiles (C1D1) and multiple dose profiles (C4D14/15). The following are the PK parameters that will be estimated for FT-4101 in plasma by non-compartmental methods using actual elapsed time from dosing:

- Maximum concentration (C_{max} [ng/mL])
- Dose-normalized C_{max} (C_{max}/D [mL^{-1}])
- Time to maximum concentration (T_{max} [h])
- Area under the concentration-time curve for a dosing interval, calculated by linear up/log down trapezoidal summation (AUC_{tau} [h*ng/mL])
- Area under the concentration-time curve in the sampled matrix from zero (predose) to time of last quantifiable concentration, calculated by linear up/log down trapezoidal summation ($AUC_{0\text{-}last}$ [h*ng/mL])
- Area under the concentration-time curve in the sampled matrix from zero (predose) extrapolated to infinite time, calculated by linear up/log down trapezoidal summation ($AUC_{0\text{-}inf}$ [h*ng/mL])
- Dose-normalized $AUC_{0\text{-}last}$ [h/mL]
- Dose-normalized AUC_{tau} [h/mL]

- Trough plasma concentrations (C_{trough} [ng/mL]) at steady state (C1D15 and all 24h post-dose time points thereafter)
- Apparent terminal half-life ($t_{1/2}$ [h])
- Apparent systemic clearance after extravascular dosing (CL/F [L/h])
- Apparent volume of distribution following extravascular dosing (V_z/F [L])

Half-life dependent parameters ($AUC_{0\text{-}inf}$, CL/F, Vz/F) will only be presented if the data indicate that the sample collection period is adequate to determine $t_{½}$.

PK parameters will be summarized descriptively by visit and treatment group in the PK analysis set.

6.10. Analysis of Preliminary Efficacy and Pharmacodynamic Endpoints

Analysis of preliminary efficacy and PD endpoints will use the planned treatment assignment. Placebo subjects will be pooled for analysis. The percent change will be considered primary over absolute change.

6.10.1. Analysis of Primary Preliminary Efficacy Endpoint

The primary preliminary efficacy endpoint is:

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

6.10.1.1. Reduction of Liver Fat Assessed by MRI-PDFF at 12 Weeks

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

The change and percent change at Week 12 in liver fat (%) as assessed by MRI-PDFF will be analyzed by a Wilcoxon-Mann-Whitney 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.

Multiplicity adjustment to control the alpha level will be accomplished using Holm's Sequential Bonferroni procedure as previously described.

If change or percent change of MRI-PDFF is not obvious deviated from symmetric distribution, a two-sample independent t-test will be carried out to compare liver fat (%) between FT-4101 treatment and the pooled placebo as supportive analysis, based on one-sided significance level of 0.05. P value will be corrected using Holm's Sequential Bonferroni procedure as previously described.

6.10.2. Analysis of Secondary Preliminary Efficacy and Pharmacodynamic Endpoints

The secondary preliminary efficacy endpoints are:

- 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

The secondary PD endpoints are:

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

6.10.2.1. Reduction of Liver Fat Assessed by MRI-PDFF at 6 Weeks

The reduction of liver fat assessed by MRI-PDFF at 6 Weeks will be analyzed similar to the primary preliminary efficacy endpoint.

A supportive analysis using 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 change in liver fat (%) on MRI-PDFF (absolute and relative) as dependent variable, treatment group as independent variable, covariates including baseline liver fat (%), visit, interaction term of treatment and visit, and a random slope and intercept per subject. Model parameters will be estimated using the restricted maximum likelihood method (REML). An unstructured covariance matrix will be used to estimate the intercept-slope covariance. In case of convergence problem, other covariance structure will be used in the order of compound symmetry and variance component. The least squares (LS) means and their corresponding 90% confidence intervals and p-values at one sided test will be presented. The LS mean difference between treatment groups will be presented along with the 90% confidence interval and p-value.

The following SAS code will be used for the MMRM analysis:

```
Proc mixed method=reml;
    Class usubjid visit treat;
    Model change [or percentchange] = baseline visit treat
treat*visit /ddfm=kr solution alpha=0.05;
    repeated visit /subject=usubjid type=un;
Run;
```

Where treat=treatment group (pooled placebo, FT4101 3.0 mg, FT 4101 4.5 mg), baseline = baseline liver fat (%), change = absolute change in liver fat (%) from baseline, percentchange = relative percent change in liver fat (%) from baseline, visit=study visit (Week 6, Week 12), usubjid = subject ID.

6.10.2.2. 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 compared to the pooled placebo subjects

from each cohort. P-values will be corrected using Holm's Sequential Bonferroni procedure as previously described.

6.10.2.3. Reduction of Liver Biochemistry Markers

Liver biochemistry markers and the change from baseline will be summarized descriptively by visit and cohort and treatment group. A MMRM will be used to analyze the change from baseline to Week 6, Week 11, and Week 12; the model will include change from baseline as dependent variable, treatment group as independent variable, baseline and visit and interaction term of treatment and visit as covariates, and a random slope and intercept per subject. Model parameters will be estimated using REML. An unstructured covariance matrix will be used to estimate the intercept-slope covariance. In case of convergence problem, other covariance structure will be used in the order of compound symmetry and variance component. The LS mean and standard error and its corresponding 90% confidence intervals and p-values will be presented for each post-baseline visit. The LS mean difference between treatment and placebo will be presented along with its 90% confidence interval and the p-value for each post-baseline visit. Similar SAS code as described in Section 7.3.2.1 will be used.

Each liver biochemistry marker (mean ± SD) will be also plotted over time by treatment group using line plot.

6.10.3. Analysis of Exploratory Pharmacodynamic Endpoints

In general, analysis of exploratory PD endpoints will be descriptive.

The exploratory PD endpoints are:

- Change from baseline in fasting hepatic DNL
- **Sebumeter®:**
  - Change from baseline in total sebum production
- **Sebutape®:**
  - Change from baseline in sebum free fatty acid concentrations
  - Change from baseline in sebum DNL
- **Circulating Biomarkers of Liver Injury and Fibrosis:**
  - Change from baseline in ELF score: Hyaluronic acid (HA), Procollagen III amino terminal peptide (PIIINP), Tissue inhibitor of metalloproteinases 1 (TIMP-1)
  - Change from baseline in Cytokeratin-18 (CK-18) fragments, e.g., CK-18 M30 and CK-18 M65
  - Change from baseline in FibroSure®
  - Change from baseline in PRO-C3
- **Circulating Metabolic Parameters:**
  - Change from baseline in 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)
  - Change from baseline in glycemic parameters:
    - Fasting plasma glucose (FPG)
    - Fasting insulin
    - HOMA-IR
    - HbA1c
  - Change from baseline adiponectin (total and high molecular weight)
  - Change from baseline in FGF-21
  - Change from baseline in malonyl carnitine
- **FibroScan®:**
  - Change from baseline in CAP
  - Change from baseline in LSM
- **MRI-PDFF:**
  - Change from baseline in liver volume
  - Change from baseline in liver fat volume index

6.10.3.1. Change from Baseline in Fasting Hepatic De Novo Lipogenesis

Multiple blood samples will be collected at C1D-11, C1D-7, and C1D1 and post-dose at C4D4, C4D8, C4D15, and C4D22 to measure deuterium enrichment in plasma body water and plasma triglyceride-palmitate. Fractional DNL will be determined by the quantification of newly synthesized palmitate through the DNL pathway in blood sampled in the fasting state after two weeks labeling period.

Fractional hepatic DNL (%) and its absolute and percentage changes from baseline will be summarized by visit and treatment group. P value from one-sided Wilcoxon-Mann-Whitney test at significance level of 0.05 will be provided. In addition, the change from C4D15 to C4D22 will be presented to evaluate rebound of DNL.

A MMRM model will be used to analyze the absolute change in fraction of fasting hepatic DNL from baseline; the model will include change in fraction of fasting hepatic DNL from baseline as dependent variable, treatment group as independent variable, baseline fraction of fasting hepatic DNL and visit and interaction term of treatment and visit as covariate, and a random slope and intercept per subject. Model parameters will be estimated using REML. An unstructured covariance matrix will be used to estimate the intercept-slope covariance. In case of convergence problem, other covariance structure will be used in the order of compound symmetry and variance component. The LS mean and standard error and its corresponding 90% confidence intervals and p-values will be presented for each post-baseline visit. The LS mean difference between treatment and placebo will be presented along with its 90% confidence interval and the p-value for each post-baseline visit. Similar SAS code as described in Section 6.10.2.1 will be used.

Line plots of the fraction of fasting hepatic DNL (mean ± SD) will be plotted over time by treatment group for both pre-dose (C1D-11, C1D-7, and C1D1) and post-dose (C4D4, C4D8, C4D15, and C4D22); they will be overlaid to allow visual comparison.

6.10.3.2. Skin Surface Sebum Level Using Sebumeter®

Observed values and the change from baseline of total sebum production will be summarized by visit and treatment group.

6.10.3.3. Sebum FFA and Sebum DNL Using Sebutape®

Observed values and the change from baseline in FFA collected using Sebutape® will be summarized by visit and treatment.

Observed values and the change from baseline in the Sebum DNL collected using Sebutape® will be summarized by visit and treatment.

6.10.3.4. Circulating Biomarkers of Liver Injury and Fibrosis

Observed values and the change from baseline of circulating biomarkers of liver injury and fibrosis will be summarized by visit and treatment group.

6.10.3.5. Circulating Metabolic Parameters

Observed values and the change from baseline of circulating metabolic parameters will be summarized by visit and treatment group.

6.10.3.6. Steatosis (CAP) and Liver Stiffness (LSM) Determined by FibroScan®

Observed values and the change from baseline of CAP and LSM will be summarized by visit and treatment group.

6.10.3.7. Imaging Parameters Assessed by MRI-PDFF

Observed values and the change from baseline of liver volume and liver fat volume index will be summarized by visit and treatment group.

Liver fat volume index is calculated as PDFF(%) multiplied by Liver Volume (L).

6.11. Analysis of Safety Endpoints

The primary safety endpoints are:

- 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 parameters (HR, QT interval, PR interval, QRS interval, RR interval, and QTc [corrected] using the Fridericia correction

[QTcF = QT/cubic root of the R-R interval, where R-R is the duration of the entire cardiac cycle])

6.11.1. Analysis of Primary Safety and Tolerability Endpoints

6.11.1.1. Adverse Events

The latest version of the Medical Dictionary for Regulatory Activities (MedDRA version 22.0) will be used to code adverse events (and medical history). TEAEs will be summarized by treatment group. TEAE is defined as an adverse event with an onset that occurs after receiving the first dose of the study drug (AE start date ≥ first dose date) and within 30 days after receiving the last dose of the study drug (AE start date – last dose date ≤ 30). TEAEs will be tabulated including the following categories:

- TEAEs by System Organ Class and Preferred Term.
- Drug-related TEAEs by System Organ Class and Preferred Term. Related includes: Definitely Related, Possibly Related, or Probably Related; Unrelated includes: Not Related or Unlikely to be related. If drug relationship is missing, event will be considered related to the study drug.
- TEAEs Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term.
- Serious TEAEs by System Organ Class and Preferred Term.
- Drug-related Serious TEAEs by System Organ Class and Preferred Term.
- Serious TEAEs Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term.
- Severity of TEAEs by System Organ Class and Preferred Term. Severity of TEAEs will be presented using National Cancer Intuitional Common Toxicity Criteria for Adverse Events (CTCAE) grade. Subjects with same AE more than once will have the maximum CTCAE grade counted within system organ class and preferred term.

In each AE summary table above, subjects with same AE more than once will be counted only once within the same system organ class and preferred term.

An overall summary TEAE table will be also provided to present number and percentage of subjects who had any TEAE, drug-related TEAE, CTCAE grade 3 or higher AE, CTCAE grade 3 or higher drug-related TEAE, serious TEAE, drug-related serious TEAE, TEAE leading to drug discontinuation, TEAE leading to on-study death. On-study death is defined as death as the death that occurs between the first date of study drug and within 30 days after the last date of study drug.

6.11.1.2. Clinical Laboratory Abnormalities

All laboratory test values will be converted to international standardized units. If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier. Observed values and the change from baseline of clinical laboratory

assessments for hematology, chemistry, and urinalysis will be summarized by visit and cohort and treatment group. Shift table will be used to assess maximum increase and/or decrease in CTCAE grade during the study period in the following laboratory measurements:

- Hematology: Absolute lymphocyte count, absolute neutrophil count, hemoglobin, platelets, and white blood cell count.
- Clinical chemistry: creatinine, calcium, CO2, magnesium, potassium, and sodium.
- Liver Biochemistry Biomarkers: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma-glutamyl transferase (γGT), Alkaline phosphatase, and Total bilirubin.

6.11.1.3. Physical Examination Findings

Physical examination findings will only be listed.

6.11.1.4. Vital Signs

Observed values and the change from baseline in vital signs will be summarized by visit and cohort and treatment group.

6.11.1.5. 12-Lead Electrocardiogram Assessments

Observed values and the change from baseline in 12-lead ECG parameters will be summarized by visit and cohort and treatment group. In addition, a categorical analysis of QTcF interval will be performed for each time point. The number and percentage of subjects in each QTcF interval (≤450 msec, >450 - ≤480 msec, >480 - ≤500 msec, and >500 msec) will be summarized. Categories of changes in QTcF interval from baseline (≥30 msec and ≥60 msec) will be tabulated as well.

QTcF will be summarized using a shift from baseline table to worst post-baseline change based on the categories described above. ECG interpretation will be summarized using a shift from baseline table to worst post-baseline assessment based on the categories of normal, abnormal not clinically significant, abnormal clinically significant, and not done/missing.

6.12. Other Laboratory Assessments

Other laboratory assessments such as pregnancy tests (hCG and FSH) and serology (hepatitis B, hepatitis C, and HIV) will be summarized descriptively by visit and treatment group.

7. CHANGES TO THE PLANNED ANALYSIS IN THE PROTOCOL

Two-sample independent t-test will be carried out to compare liver fat (%) between FT-4101 treatment and the pooled placebo at 6 and 12 weeks as a supportive analysis, based on one-sided significance level of 0.05.

8. STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS® version 9.4.

9. APPENDIX

9.1. APPENDIX A – Schedule of Events (SOE)

ASSESSMENT	SCREEN	RUN-IN PERIOD			IN-HOUSE PERIOD		OUTPATIENT VISITS								IN-HOUSE PERIOD		OUTPATIENT	FOLLOW-UP
Study Visit 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	
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

ASSESSMENT	SCREEN	RUN-IN PERIOD			IN-HOUSE PERIOD		OUTPATIENT VISITS								IN-HOUSE PERIOD		OUTPATIENT	FOLLOW-UP
Study Visit 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)**
Deuterated Water Labeling Period (3 x 50 mL/day)[h]		C1D-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	
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-4101/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).
[l]Sampling for fasting circulating biomarker include metabolic parameter (Lipids, 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.

9.2. 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 hour post-dose	± 15 min
C1/D1	4 hour post-dose	± 15 min
C1/D1	6 hour post-dose	± 15 min
C1/D15	24 hour post-dose	± 4 hours
C2/D1	Pre-dose	± 15 min
C2/D15	24 hour post-dose	± 4 hours
C3/D15	24 hour 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 hour post-dose	± 15 min
	4 hour post-dose	± 15 min
	6 hour post-dose	± 15 min
	8 hour post-dose	± 30 min
	12 hour post-dose	± 60 min
	16 hour post-dose	± 60 min
C4/D15	24 hour post-dose	± 4 hours
	30 hour post-dose	± 4 hours