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STATISTICAL ANALYSIS PLAN (SAP)

Protocol Title:	A Phase 2 Dose Ranging, Randomized, Double Blind, and Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of EDP-305 in Subjects with Non-Alcoholic Steatohepatitis (NASH)
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LIST OF ABBREVIATIONS

The following abbreviations will be used within this SAP.

AE	adverse event(s)
ATC	anatomical therapeutic chemical
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
apo	apolipoproteins
APRI	AST to Platelet Ratio Index
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BA	bile acid
BMI	body mass index
C4	7α-OH-4-cholesten-3-one
CI	confidence interval
CK18	cytokeratin 18
C_{max}	maximum concentration
CRO	contract research organization
CSR	clinical study report
CV	cardiovascular
ECG	electrocardiogram
eCRF	electronic case report form
EENT	eyes/ears/nose/throat
ELF	enhanced liver fibrosis
EOS	end-of-study
EOT	End-of-treatment
FGF	fibroblast growth factor
FIB-4	Fibrosis-4
FSH	follicle stimulating hormone
FXR	farnesoid X receptor
GGT	Gamma Glutamyl Transferase
GLP-1	glucagon-like peptide-1
HbA1c	glycated hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	hepatitis C virus
HDL-C	high density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus

HOMA	homeostasis model assessment
ICF	informed consent form
ICH	International Conference on Harmonization
IL	interleukin
INR	international normalized ratio
IWRS	interactive web response system
LDH	Lactate Dehydrogenase
LDL-C	low density lipoprotein cholesterol
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCMC	Markov Chain Monte Carlo
MCV	Mean corpuscular volume
MI	Multiple Imputation
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging - proton density fat fraction
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NFS	NAFLD fibrosis score
PBO	placebo
PD	pharmacodynamics
PIIINP	procollagen III amino terminal peptide
PK	pharmacokinetics
PR	electrocardiographic interval occurring between the onset of the P wave and the QRS complex, representing time for atrial and ventricular depolarization, respectively
PRO C3	type 3 procollagen
PT	Prothrombin Time
PTT	Partial thromboplastin time
QD	once daily
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing the time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTcF	QT interval corrected by Fridericia's formula
RBC	Red Blood Cell
SAE	serious adverse event(s)

SAP	statistical analysis plan
SD	Standard Deviation
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TEAE	treatment emergent adverse event
TFLs	Tables, Figures and Listings
TG	triglyceride(s)
TIMP-1	tissue inhibitor of metalloproteinase 1
TNF	tumor necrosis factor
T_{max}	time to maximum concentration
ULN	upper limit of normal
US	United States
WBC	white blood cell (Count)
WHODDE	World Health Organization Drug Dictionary Enhanced
WTH	waist to hip ratio

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1 INTRODUCTION

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Enanta Pharmaceuticals, Inc. Protocol EDP 305-101 entitled "*A Phase 2 Dose Ranging, Randomized, Double Blind, and Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of EDP-305 in Subjects with Non-Alcoholic Steatohepatitis* (NASH)".

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol version 3.0 dated 21Feb2018 (Amendment 2.0) and CRF dated 2NOV2018. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Changes following approval of this SAP will be tracked in the SAP Change Log and a final amended version will be issued for Sponsor approval prior to database lock, and subsequent unblinding of treatment codes, efficacy lab and imaging data for final study results delivery.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analysis of the data may be conducted as deemed appropriate.

The preparation of this SAP has been based on International Conference on Harmonization (ICH) E9 guidelines. The table of contents and shells for the tables, figures and listings (TFLs) will be produced in a separate document. All data analyses and generation of TFLs will be performed using SAS 9.3® or higher.

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2 STUDY OBJECTIVES

2.1 Primary objective(s)

The primary objectives of the study are as follows:

- To evaluate change in alanine aminotransferase (ALT) levels
- To evaluate the safety and tolerability of EDP-305

2.2 Secondary objective(s)

The secondary objectives of the study are as follows:

- To evaluate the effect of EDP-305 on liver fat
- To evaluate the effect of EDP-305 on fibrosis ("liver stiffness")
- To evaluate the effect of EDP-305 on non-invasive liver fibrosis markers
- To evaluate the effects of EDP-305 on lipids
- To evaluate the effects of EDP-305 on glucose metabolism
- To evaluate the effects of EDP-305 on inflammatory markers
- To evaluate the pharmacokinetics (PK) of EDP-305 and its metabolites in plasma
- To evaluate the effect of EDP-305 on body weight
- To evaluate the effect of EDP-305 on waist to hip (WTH) ratio
- To evaluate the pharmacodynamics (PD) of EDP-305

3 STUDY DESIGN

3.1 General study design

This is a Phase 2 dose-ranging, randomized, double blind, and placebo-controlled study evaluating the safety, tolerability, PK and efficacy of EDP-305 in subjects with NASH.

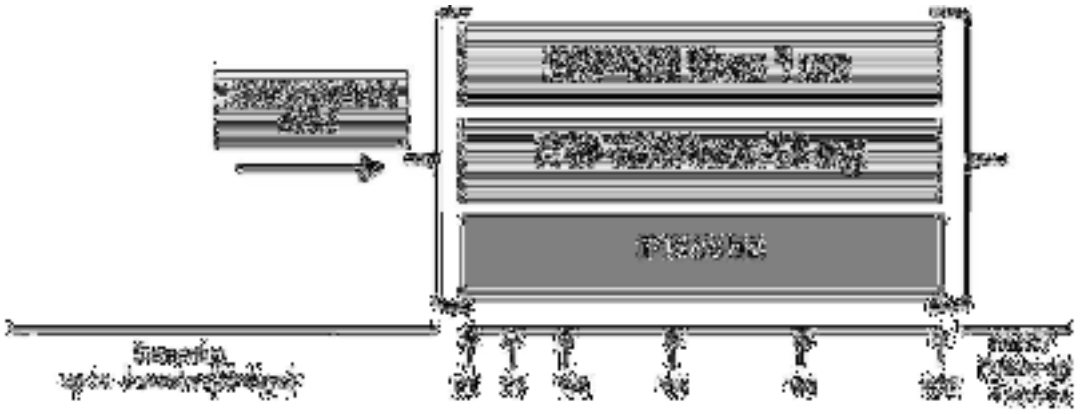
The study is composed of 3 phases or periods:

- Screening period which includes the Screening Visit and may occur over a period of 28 days prior to the first dose of study drug
- Treatment period which begins with the first dose of study drug on Day 1 and concludes with the End of Treatment (EOT) Visit on Day 84 (Week12)
- Safety Follow-up period which includes the End of Study (EOS) Visit on Day 112

This proposed study will evaluate EDP-305 in patients with NASH who will be randomized to one of three treatment groups: (1) 1 mg EDP-305, (2) 2.5 mg EDP-305, or (3) placebo in a 2:2:1 ratio. Approximately 125 subjects will be enrolled into the study. The study will be conducted at approximately 65 US and ex-US sites.

The Study Design is presented in Figure 1.

Figure 1: Study Flow Chart



Abbreviations: D=Day; W=Week

3.2 Randomization and blinding

3.2.1 Randomization

Subjects will be randomized to study treatment using an Interactive Web Response System (IWRS). Subjects will be stratified initially by prior liver biopsy vs no prior liver biopsy. Subjects will be randomized to the treatment groups shown below:

- Treatment Group 1 (N=50); EDP-305 1 mg orally for 12 weeks
- Treatment Group 2 (N=50); EDP-305 2.5 mg orally for 12 weeks

- Treatment Group 3 (N=25); Placebo (PBO) orally for 12 weeks

A minimum of 10 subjects per treatment group will be included in the PK/PD substudy. The randomization code will be produced by Enanta (or designee). The Enanta unblinded biostatistician or designee will review and approve the final randomization list.

During the Screening period, subjects will be identified by a unique screening number assigned by the clinical site. Subjects who have completed screening assessments and are eligible for participation in the study will be randomized before the first dose of study drug (Day −1 or Day 1) and assigned a unique subject number which will be used to identify the subject throughout the study.

3.2.2 Blinding

The study will be double-blinded meaning the subjects, Investigators, and site staff will be blinded to treatment assignment until the completion of the study.

All study personnel will be blinded to treatment assignment except for the following individuals:

- Unblinded Enanta/Clinical Research Organization (CRO) statistician for purpose of generating and monitoring the randomization list, working with the DSMB [redacted]
- Unblinded Drug Supply Chain personnel for the purpose of monitoring drug supplies
- Enanta/CRO Pharmacovigilance Group and Regulatory Affairs representatives when required to satisfy regulatory reporting requirements
- Bioanalytical Laboratory for the purpose of measuring drug concentrations

3.2.3 Unblinding

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The unblinding method will use the IWRS process.

Unblinding of individual subject treatment by the Investigator should be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, the Investigator should first attempt to contact the study medical monitor to discuss and agree to the need for unblinding. In situations in which Investigator have attempted and failed to contact the medical monitor, and/or the urgency of the case required immediate action, Investigators should use their best judgment, based on the nature and urgency of the clinical situation, and proceed with unblinding.

For unblinding, in the event the local [redacted] medical monitor cannot be reached, sites at all locations should call the following 24/7 global medical coverage hotline: [redacted]

Once a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor and study coordinator should be notified

within 24 hours of unblinding of the treatment. Information relating to unblinding (e.g., the reason, date) should be clearly recorded in the subject's study file. In addition, the Investigator should consider whether the clinical event that prompted unblinding should be considered a serious adverse event (SAE), according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report.

The Safety and Risk Management group will also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, Enanta may unblind individual subjects at any time for matters relating to safety concerns.

3.3 Study treatments and assessments

The maximum study duration from Screening period to end of the safety follow-up period is 20 weeks. The duration of treatment is 12 weeks.

EDP-305 will be supplied as 1 mg and 2.5 mg tablets for oral administration; doses administered will be 1 mg, 2.5 mg or placebo taken once daily (QD) for 12 weeks.

The subject will be instructed to take all study drug doses at home except when study drug will be administered in the clinic (i.e., at the Days 1 and 3, and Weeks 2, 4, 8 and 12 visits). The subject will be instructed to take the study drug approximately at the same time every day (i.e., orally in the morning after fasting overnight for a minimum of 8 hours). If a subject forgets to take their study drug at their scheduled time, the dose may be taken later that day following a minimum of 4 hours fast; however, no more than 1 dose should be taken on any calendar day and a minimum of 16 hours between doses should be maintained.

A detailed description of procedures and assessments to be conducted during this study is summarized in the Scheduled of Study Assessments in the table below.

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Table 2: Schedule of Study Assessments

Study Event	Screening[1]	Study Assessments per Planned Study Day						EOS
Visit Day	D-28 to -1	D1[2]	D3	D14±2	D28±2	D56±2	D84±3[3]	D112±2
Treatment Week[4]				W2	W4	W8	W12/EOT[5]	W16
ICF[6]; Demography; Medical History	x							
Inclusion/Exclusion	x							
FSH[7]; HIV, HCV, and HBV	x							
Pregnancy Test[8]	x	x			x	x	x	x
Height, Weight and BMI[9]	x	x					x	x
Physical Exam[10]	x	x	x	x	x	x	x	x
Vital Signs[11]	x	x	x	x	x	x	x	x
Oral Temperature	x	x						x
ECG	x	x	x		x		x	
Waist to Hip Ratio		x					x	
Safety Lab. Tests[12]	x	x	x	x	x	x	x	x
PT/PTT and INR	x							x
CV Markers[13]		x		x	x	x	x	x
MRI-PDFF, MRE	x						x	
ELF Panel, PRO C3, Inflammatory Markers[14, 15]		x					x	
APRI, FIB-4, and NFS		x					x	
FGF-19, C4, BA, and ALT[16]		x		x	x	x	x	
PK/PD sub study (PK, C4, FGF-19, BA, and ALT)[17]		x		x	x	x	x	
Population PK samples[18]		x		x	x	x	x	
CK-18 and GLP-1[15]		x		x	x	x	x	
Study Drug Dosing[19]		Daily Dosing						
Drug Accountability			x	x	x	x	x	
AE/SAE & Con Meds	x	x	x	x	x	x	x	x
Exploratory research samples[15]		x			x	x	x	

1. Screening assessments should be conducted within 28 days prior to the first dose of study drug (i.e., Study Days -28 to -1)
2. On Day 1, all samples are to be collected predose with the exception of post dose PK and PD samples

3. Subjects should discontinue drug on Day 84. Subjects who return for their EOT Visit after Day 84, should stop dosing on Day 84
4. For the treatment phase, indicates number of completed weeks of treatment
5. For the EOT visit for subjects who discontinue early, all procedures for the Week 12 visit will be conducted; however, an MRI /MRE will not be performed if the subject has discontinued study drug prior to Day 14 and only 1 PK sample will be obtained. Subjects who discontinue the study early should complete the EOT procedures as soon as possible and return 4 weeks later for the EOS visit. For subjects with persistent transaminase elevations and who discontinue study drug with evidence of liver injury, additional PK samples will be collected at each visit where safety labs are obtained
6. Informed consent must be obtained prior to conducting any study-specific procedures or assessments
7. For post-menopausal women only
8. Serum pregnancy test at Screening and Baseline, and urine pregnancy testing at Baseline and all other visits. If the urine pregnancy test is positive, a serum pregnancy test should be obtained as soon as possible to confirm.
9. Height to be assessed at Screening only
10. Full physical exam (PE) at screening and EOS Visit; subsequent PE should be targeted to review new signs and symptoms
11. Vital Signs include heart rate, respiratory rate, blood pressure, and will be measured once in the morning before the morning dose of study drug
12. Safety laboratory tests include chemistry (including liver function tests), hematology, and urinalysis and should be collected predose at all visits; See Table 2 for details. Creatinine clearance will be calculated based on serum creatinine value performed all visits. HbA1c will be obtained at Screening, Baseline, and Week 12 only
13. Lipids and CV risk markers to be collected are detailed in Table 2
14. Markers of inflammation include fibrinogen, CRP, IL6, IL1β, TNF-α, TNF-β, alpha2 macroglobulin and haptoglobin (See Table 2)
15. Samples will be collected from all subjects predose Additional samples may be collected to further assess safety events
16. Samples should be collected after a minimum 8 hr fast and before the subject takes the daily dose of study drug. All samples collected Day 1, Weeks 2, 4, 8 and 12 at predose and two samples post dose; with the first sample collected 1 to 3 hours postdose and the second sample collected at least 1 hour later
17. Collect PK/PD samples after a minimum 8 hr fast and before the daily dose of study drug. PK/PD samples on Days 1 and 84 (Week 12) collected predose and 2, 6, and 8 hr post dose; Weeks 2, 4 and 8 at predose and two samples post dose with the first sample collected 1 to 3 hours postdose and the second sample collected at least 1 hr late
18. PK predose samples should be collected after a minimum 8 hour fast before the daily dose of study drug. PK samples collected Day 1, Weeks 2, 4, 8 and 12 at predose and two samples post dose; the first sample collected 1 to 3 hours postdose and the second sample at least 1 hour later. For subjects with persistent transaminase or ALP elevations and have evidence of liver injury and who remain on study drug, additional PK samples will be collected at each visit where safety labs are obtained.
19. Study drug given in the clinic on days where subject is seen in the clinic

[redacted]

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4 STUDY ENDPOINTS

4.1 Primary efficacy endpoint(s)

The primary efficacy endpoint of the study is the change from Baseline in ALT levels at Week 12.

4.2 Secondary efficacy endpoint(s)

The secondary efficacy endpoints are as follows:

- Change from Baseline in percentage of fat in the liver as assessed by MRI-PDFF at Week 12
- Change from Baseline in liver stiffness as assessed by magnetic resonance elastography (MRE) at Week 12
- Change from Baseline of noninvasive liver fibrosis markers (ELF panel) and PRO C3 at Week 12
- Change from Baseline in NFS, APRI, and FIB-4 at Week 12
- Change from Baseline in TG, TC, HDL-C, LDL-C, adiponectin, and ApoA1, B, C3 at Week 12
- Change from Baseline in fasting glucose and insulin, HOMA index (in nondiabetic subjects) and HbA1c in subjects with T2DM at Week 12
- Change from Baseline in fibrinogen, CRP, IL6, IL1β, TNF-α, TNF-β, alpha2 macroglobulin and haptoglobin levels at Week 12
- Pharmacokinetic parameters of EDP-305 (and metabolites): C_{max}, T_{max}, and AUC_{last}
- Change from Baseline in body weight at Week 12
- Change in waist to hip WTH ratio at Week 12
- Pharmacodynamic parameters of EDP-305: FGF19, C4, and bile acid (BA) at Week 12

In addition, the percentage change from Baseline in the primary endpoint and all secondary endpoints will be summarized (as applicable).

4.3 Safety endpoint(s)

The primary safety endpoint of the study is the frequency of Adverse Events (AEs), Serious Adverse Events (SAEs), and AEs leading to discontinuation through Week 12

[redacted]

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5 SAMPLE SIZE AND POWER

Group sample sizes of 44 (in each dose group) and 22 placebo subjects achieves 80.438% power to reject the null hypothesis of equal means when the population mean difference in ALT is (−40.0) – (−10.0) = −30.0 with a standard deviation for both groups of 40.0 and with a significance level (alpha) of 0.050 using a two-sided two-sample equal-variance t-test. To account for a 10% discontinuation rate, 15 additional subjects will be enrolled to attempt to have at least 110 subjects who complete treatment bringing the total number of subjects enrolled to 125.

6 ANALYSIS POPULATIONS

6.1 Safety population

All subjects who receive at least one dose of study drug. Subjects will be included in the treatment group that corresponds to the study drug received during the study.

6.2 Efficacy population

All subjects who receive at least one dose of study drug. Subjects will be included in the randomized treatment group.

Subjects will be included in the analysis according to the treatment to which they were randomized.

6.3 Per protocol population

All subjects in the efficacy population who enter the study without a protocol violation and did not have a major (key) protocol deviation as defined below will be included in the per protocol population. This population will be reviewed and finalized prior to locking the database and unblinding the study.

6.4 Pharmacokinetic population

All subjects receiving active study drug and having any measurable plasma concentration of study drug at any timepoint.

Subjects will be included in the analysis according to the study drug received during the study.

6.5 Protocol deviations and exclusion from Per protocol analysis aet

Protocol deviations will be identified following the [redacted], and after review and validation of the Enanta study team prior to locking the database and unblinding the treatment codes. If necessary, a meeting will be held to discuss and adjudicate any deviations that need classification (major vs. minor). Deviations will be identified using data listings provided by [redacted] and from the deviation log maintained by [redacted].

The listing of protocol deviations will be reviewed by Enanta team with focus from Biometrics/Medical in order to define the Per Protocol population. Subjects with a protocol violation or a major protocol deviation will be thus identified for exclusion from the per protocol population.

[redacted]

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7 STATISTICAL CONSIDERATIONS AND ANALYSIS

7.1 Derived variables

The below table provides the list of derived variables for demographic and baseline characteristics, various duration derivations, drug compliance, baseline derivations and other important derivations applicable for this study.

Table 3.

Variables	Formula
Demographic and Baseline characteristics	
Age at informed consent (in years)	floor ((date of informed consent – date of birth + 1)/ 365.25)
Body mass index (BMI) (kg/m2)	weight (kg) / [height (m)]^2
Derivation of Duration	
Study day at any visit	Date of interest – date of first dose of study drug. One day is added if this difference is ≥ 0
Extent of Exposure (Days)	Date of last randomized study drug intake – Date of first randomized study medication intake + 1
Extent of Exposure (Weeks)	Extent of exposure (days)/7
Drug Compliance	
Compliance	100 × [1 - (Number of days of study drug interruption) / (Extent of exposure (days))]
Baseline Derivations	
Baseline (Average)	The average of the screening and the day 1 values.
Baseline (Last value pre-dose)	Last non-missing values collected prior to the first dose of study drug
Screening	The value obtained at screening.
Change from Baseline	Post Baseline value – Baseline
Percentage change from Baseline	[(Change from Baseline) / Baseline] * 100
Other Derivations	
Creatinine Clearance (Cockcroft-Gault)	CL_{Cr} (mL/min) = {((140−age [years]) × weight) / (72×S_{Cr})} × 0.85 (if female). S_{Cr} = serum creatinine
AST to Platelet Ratio Index (APRI)	APRI = ([AST (IU/L) / AST ULN (IU/L)] / [Platelets(10^9/L)]) × 100

	ULN = upper limit of normal
Fibrosis-4 score (FIB-4)	FIB-4 = [Age (years) × AST (IU/L)] / [Platelets (10^9/L) × (√ ALT (IU/L))
NAFLD fibrosis score (NFS)	NFS = -1.675 + 0.037 × Age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/Diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × Platelets (10^9/L) – 0.66 × Albumin (g/dL)

7.2 Definition and use of visit windows in reporting lab, vital signs

Note that Day 1 in the table below is taken as the first day of dosing with study drug. It may not be the same as the first study date which is the randomization date. Also note that Day 0 does not exist, so Day -1 is the day before Day 1. Also, the relative days (rel_day) from Day 1 are defined as the visit date minus first dosing date plus one. For treatment-free follow-up period, the rel_days is computed from the date of last dose. Unless otherwise specified in specific analyses, the analysis visit windows will follow the rules in the following table.

Table 4.

Analysis Visit No.	Analysis Visit Label	Target Day	Visit Window
1	Screening	N/A	-28≤rel_day≤-1
2	Baseline	1	Rel_day= 1*
3	Day 3	3	Rel_day= 3
4	Week 2	14	4<rel_day≤21
5	Week 4	28	22≤rel_day≤42
6	Week 8	56	43≤rel_day≤70
7	Week 12	84	71≤rel_day≤end of treatment+7
8	Follow-up Week 4	21**	End of treatment+7<=rel_day <end of study

* Baseline analysis visit window may be considered as Rel_day≤1 in some analyses (e.g., those involving change from Baseline). That is, in case that Day 1 observation is missing, the last non-missing observation before or on the first dosing date may be considered as

the Baseline. For Lab values, average of all values collected prior to the first dose of study drug will be considered Baseline.

** computed from the date of last dose.

7.3 Handling of missing data and outliers

7.3.1 Missing data analysis methods

In general, missing data for the primary endpoint and secondary endpoint are not imputed, with the exception being a secondary analysis on the primary endpoint. The extent and pattern of missing data for primary endpoints will be summarized by treatment group. All missing Week 12 values for the primary efficacy endpoint will be estimated by multiple imputation (MI). The Markov Chain Monte Carlo (MCMC) method (***Dong et al, 2013***) will be used to impute the missing Week 12 values. The least squares mean and standard error for the change from Baseline in Week 12 analysis values will also be derived from an analysis using the MCMC method of MI.

Multiple Imputation Method

MI handles missing data in three steps:

Step 1: Imputation using MCMC Method

For MI analysis first uses MCMC method to impute the missing data through SAS Proc MI. The goal of the imputation step is to draw random samples of missing data based on information contained in the observed data. Since the parameter (θ) of the data is also unknown, the imputation step actually draws random samples of both missing data and θ based on the observed data.

The MCMC method draws samples in two steps. At step one (I-Step), given the current estimate of $\theta(t)$ at the t^{th} iteration, a random sample Y_{miss}^{t+1} is drawn from the conditional predictive distribution of $P(Y_{mis}|Y_{obs}, 0^{t})$. At step two (P-step), given Y_{miss}^{t+1}, a random sample of $\theta^{(t+1)}$ is drawn from the distribution of $P(0IY_{obs}, Y_{mis}^{t+1})$. Starting with an initial value $\theta^{(0)}$ (usually an arbitrary guess), MCMC iterates between the I-step and the P-step, leading to a Markov Chain:

It can be shown that this Markov Chain converges in distribution to $P(\theta, Y_{mis}|Y_{obs})$. It follows that the sequence $\theta(1), \theta(2), \ldots, \theta(t), \ldots$ converges to $P(\theta|Y_{obs})$ and the sequence $Y_{mis}^{1}, Y_{mis}^{2}, \ldots, Y_{mis}^{t}, \ldots$ converges to $P(Y_{mis}|Y_{obs})$. Thus, after the Markov Chain converges,

m draws of Y_{mis} can form *m* imputations for the missing data. At the end of the first step in MI, missing data will be imputed m times to produce m sets of complete data.

Step 2: Statistical Analysis

The second step of MI analyzes the *m* sets of data separately using Proc Mixed to estimate the relevant standard errors and least square means. At the end of the second step, m sets of parameter estimates are obtained from separate analyses of m data sets.

Step 3: Combining Results

The third step of MI combines the m estimates into one using PROC MIANALYZE.

7.3.2 Handling of missing or incomplete dates

Imputation rules for missing or partial AE start dates are defined below:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date;
- Otherwise, impute the AE start day as 1.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing, then query site and leave as missing.

For missing and partial adverse event end dates, imputation will be performed as follows:

If only the day of the month is missing, the last day of the month will be used to replace the missing day. If the day and month are missing or a date is completely missing, it will be considered as missing.

Imputation rules for missing or partial medication start/stop dates are defined below:

If only Day of CM start date is missing:

If the CM start year and month are the same as that for the first dose date, then:

- If the full (or partial) CM end date is NOT before the first dose date or CM end date is missing, then impute the CM start day as the day of first dose date;
- Otherwise, impute the CM start day as 1.

If Day and Month of CM start date are missing:

If CM start year = first dose year, then:

- If the full (or partial) CM end date is NOT before the first dose date or CM end date is missing, then impute the CM start Month and Day as the Month and Day of first dose date
- Otherwise, impute the CM start MONTH as January and the DAY as 1.

If Year of CM start date is missing:

If the year of CM start is missing or CM start date is completely missing, then query site and leave as missing.

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8 STATISTICAL METHODS

8.1 General statistical conventions

All statistical procedures will be completed using SAS version 9.3 or higher.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. Two-sided 95 % confidence intervals (CI) will be provided when relevant. Any p-value below 0.05 will be displayed to 4 decimal places.

Any p-value less than 0.0001 will be displayed as <0.0001. Any p-value between 0.05 (inclusive) and 0.10 will be displayed to 3 decimal places and any p-value greater than 0.10 will be displayed to two decimal places. Any p-value greater than 0.9999 will be displayed as >0.9999.

All quantitative endpoints will be summarized using an 8-number summary (n, mean, standard deviation, median, 25th percentile, 75th percentile, minimum and maximum values). The mean and median and the percentiles will be rounded to one decimal place beyond the precision of the values being summarized, the standard deviation will be rounded to 2 additional decimal places beyond this precision and the minimum and maximum values will be displayed in the same precision. All qualitative endpoints will be summarized by the number of subjects meeting the endpoint and the percentage of subjects out of the appropriate population. The denominator will be displayed when needed and the percentage will be rounded to one decimal place

All subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within subject listings only. All listings will be sorted by investigational site, patient number, date/time and visit. The treatment group as well as patient's sex and age will be stated on each listing. Unless otherwise stated, data listings will be based on all subjects randomized.

Descriptive statistics in tables will include a pooled EDP-305 group (Combined EDP-305) except PK information. No inferential analysis will be performed using the combined group. No figures or listings will include the combined group. The overall (totals) will only be presented for study disposition.

8.2 Subject disposition

All subjects who provided informed consent will be included in a summary of subject accountability. The number and percentage of subjects screened, randomized, and treated, randomized and not treated, as well as the number and percentage of subjects in each analysis population (safety, efficacy, per protocol, and PK) will be summarized. The denominator for the calculation of percentages will be from the number of subjects randomized.

The following categories will also be summarized for subject disposition by treatment group and overall:

- Completed study drug per protocol

- Discontinued study drug early and the primary reason for discontinuation
- Completed the study
- Discontinued from the study early and the main reason for discontinuation

The denominator used for the calculation of percentages will be the number of subjects randomized.

In addition, the number of subjects excluded from Safety, Efficacy and PK analysis sets and reasons for exclusion will be summarized by treatment group and overall.

8.3 Protocol violations/deviations

All protocol deviations identified will be summarized by treatment group and overall, all protocol deviations will be listed.

Summaries will be conducted on all subjects that were randomized.

8.4 Demographics and baseline characteristics

No statistical testing will be performed for the comparison between treatment groups on demographics and Baseline characteristics.

8.4.1 Demographics

Subject demographics will be summarized by randomized treatment group for all subjects in the safety population. Age, height, weight and BMI at Baseline will be summarized using an 8-number summary (n, mean, standard deviation, median, 25th percentile, 75th percentile, minimum and maximum values). Qualitative variables such as gender, ethnicity and race will be summarized using count and percentage.

A by-subject listing will be provided.

8.4.2 Baseline and disease characteristics

The categorical Baseline characteristics such as Baseline ECG and other Baseline lab parameters will be summarized using frequency counts for the safety population. NASH relevant comorbidities, and concomitant medications in the past 6 months will also be summarized.

A summary of NASH diagnosis will be provided for the safety population.

The following are summarized using count and percentage:

- Liver Biopsy <= 24 mths of screening consistent with NASH **AND** Elevated ALT defined as 50 <= ALT (IU/L) <= 200 at Screening **AND** MRI-PDFF with >8% steatosis

OR

- Type II Diabetes Mellitus / Pre-Diabetes defined as Glucose >200mg/dL or fasting glucose >126mg/dL and HB1AC at least 6% **AND** Elevated ALT at Screening, where elevated ALT is defined as 50 <= ALT (IU/L) <= 200 **AND** MRI-PDFF with >8% steatosis.

Subjects will be considered diagnosed with NASH based on a liver biopsy within the last 24 months, prior to the present study. Otherwise, it will be assumed that subjects were diagnosed as having NASH by phenotype.

A by-subject listing will be provided.

8.4.3 Medical history

A summary of medical and surgical history will be presented by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Affairs® (MedDRA) Version 19.0 or higher for the safety population.

A by-subject listing will be provided.

8.4.4 Prior and concomitant medications

Medications used in this study will be coded by using the latest available version of the World Health Organization Drug Dictionary Enhanced (WHODDE).

Prior medications: are defined as those medications with a start date prior to the first dose of study drug.

Concomitant medications: are defined as those medications with a start date on or after the first dose of study drug and within 30 days after the last dose. A medication which started prior to dosing and continued after dosing will also be considered as concomitant medications.

Concomitant medications will be summarized descriptively using frequency tables by anatomical therapeutic chemical (ATC) class and preferred name by treatment group on the safety population. Concomitant diabetes medications will be summarized using the same format.

A by-subject listing will be provided for prior and concomitant medications.

Details for imputing missing or partial start and/or stop dates of medication are described in Section 7.2.2.

8.5 Extent of exposure

8.5.1 Treatment duration

Duration of study drug (in days) will be calculated as: last dose date – first dose date + 1 day, regardless of study drug interruption.

Study drug exposure will be summarised by treatment group on the Safety Population using descriptive statistics. A categorical (0-2 Weeks, 2-4 Weeks, 4-6 Weeks, 6-8 Weeks, 8-10 Weeks, 10-12 Weeks 12-16) summary will be provided.

8.5.2 Treatment compliance

Study drug compliance based on the number of tablets taken will be calculated as:
100 x [(total number of tablets dispensed) – (total number of tablets returned)]/ (total number of tablets planned to be taken per day x duration of study drug exposure in days).
The maximum percentage of tablets taken will be 100%.

Study drug compliance based on study drug exposure will be calculated as:
100 x [1 − (total number of days of any study drug interruption) / (duration of study drug exposure in days)].

Study drug compliance will be summarized by treatment group using 8-number summary. They will also be summarized in categories "<80%, 80% - <90%, 90% - <100% and "≥100% compliant" using frequency tables.

Study drug compliance summaries will be based on the Safety Population.

8.6 Efficacy analyses

This section addresses separately the analyses to be conducted on the primary, secondary, and additional efficacy variables. All the efficacy analyses will be performed using efficacy population as primary analysis.

8.6.1 Analysis methods

Analysis of Covariance (ANCOVA) Model for Change from Baseline

In summaries of efficacy endpoints examining changes from Baseline at Week 12, ANCOVA of the differences between post-Baseline and Baseline measurements will be performed, with treatment group as fixed effects and the Baseline measurement as a covariate.

The model will be used to derive least squares estimates of the treatment differences (each active treatment group versus placebo) in mean change and two-sided 95% confidence intervals. Where applicable, t-statistics corresponding to the type III sums of squares for the differences in the least squares means will be used to obtain p-values for treatment group comparisons (each active treatment group versus placebo). Moreover, two-sided 95% confidence intervals for the mean change within each treatment group will be calculated.

8.6.1.1 Multiplicity

No adjustment will be made for multiple comparisons.

8.6.1.2 Treatment by center interaction analysis (multi-center study)

No analysis will be made to assess the treatment-by-center interaction.

8.6.2 Analysis of primary efficacy endpoint(s)

The primary efficacy endpoint of the study is the change from Baseline in ALT at Week 12. All subjects in the efficacy population will be included, with a secondary analysis

performed on the per protocol population.

Baseline in ALT will be derived based on three different methods (see Table 3): Baseline (Average), Baseline (Last value pre-dose), and Baseline (Screening).

A descriptive summary table will be presented for ALT values, change from Baseline and percentage change from Baseline in ALT by treatment group and visit using the 8-number summary. Percent change from baseline will be analyzed similarly as the change results.

Change from Baseline in ALT at Week 12 will be analysed using an ANCOVA model with treatment as a fixed effect and the associated Baseline value as a covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$. As an additional analysis, the primary endpoint will be analysed using the Multiple Imputation method as described in section 7.2.1.

A by-subject listing will be provided for observed and derived variables.

8.6.3 Analysis of secondary efficacy endpoint(s)

All analysis of secondary efficacy endpoints will be performed on the efficacy population. Additional analyses will be performed on the per protocol population. All secondary endpoint related to PK data will be analysed using subjects in the PK population. Endpoints related to PD data will be analyzed using subjects in the efficacy population unless otherwise specified.

8.6.3.1 Change from baseline and percentage change from baseline in percentage of fat in the liver as assessed by MRI-PDFF at week 12

Percentage of fat in the liver assessed by MRI-PDFF at Screening and Week 12, change from Baseline and percentage change from Baseline will be summarized using an 8-number summary by visit and treatment group.

The screening visit will be considered the Baseline value for this endpoint.

Change from Baseline and percentage change from Baseline in percentage of fat in the liver at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

In addition, the proportion of subjects who show at least a 30% reduction versus those less than a 30% reduction from Baseline in liver fat assessed by MRI-PDFF at Week 12 will be summarized (***Loomba et.al, 2018***). Inferential testing will be performed using a Fisher's Exact test to compare each of the active arms to the placebo arm. All subjects in the efficacy population will be included in this analysis, with those subjects with missing Week 12 MRI-PDFF results included in the denominator (i.e., Missing=failure). The ALT value change from Baseline in ALT and percentage change from Baseline in ALT at week

12 will be summarized by treatment and liver fat response rate. The ANCOVA model will be repeated as described above, adding in the subgroup as a fixed effect.

A by-subject listing will be provided for observed and derived variables.

8.6.3.2 Change from baseline and percentage change from baseline in liver stiffness as assessed by MRE at week 12

The liver stiffness as assessed by MRE at the Screening visit and Week 12, change from Baseline and percentage change from Baseline will be summarized using an 8-number summary by visit and treatment group.

The screening visit will be considered the Baseline value for this endpoint.

Change from Baseline and percentage change from Baseline in liver stiffness at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

In addition, the proportion of subjects who show at least a 15% reduction versus those less than a 15% reduction from Baseline in liver stiffness will be summarized by visit and treatment group (***Loomba et.al, 2018***). Inferential testing will be performed using a Fisher's Exact test to compare each of the active arms to the placebo arm. The ALT value change from Baseline in ALT and percentage change from Baseline in ALT will be summarized by treatment and liver stiffness response rate.

By-subject listing will be provided for observed and derived variables.

8.6.3.3 Change from baseline and percentage change from baseline of noninvasive liver fibrosis markers (ELF panel) and PRO C3 at week 12

ELF Panel at Week 12

The ELF panel combines 3 biomarkers that have been shown to correlate with the level of liver fibrosis assessed by a liver biopsy. These biomarkers include HA, PIIINP, and TIMP-1.

A descriptive summary will be provided for noninvasive liver fibrosis markers (ELF panel) values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline of noninvasive liver fibrosis markers (ELF panel) at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

PRO C3 at Week 12

A descriptive summary will be provided for PRO C3 values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline PRO C3 at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

8.6.3.4 Change from baseline and percentage change from baseline in fibrosis at week 12

Fibrosis will be estimated using the APRI, the fibrosis 4 (FIB-4) formulae, and the NAFLD fibrosis score (NFS).

NFS at Week 12

The NFS will be calculated by the central laboratory using the following formula:

$-1.675 + 0.037 \times$ Age (years) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ IFG/Diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ Platelets (10^9/L) $- 0.66 \times$ Albumin (g/dL)

NFS online calculator reference:

https://www.mdcalc.com/nafld-non-alcoholic-fatty-liver-disease-fibrosis-score

A descriptive summary will be provided for NFS values, change from Baseline and the percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in NFS at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

APRI at Week 12

The APRI will be calculated by the central laboratory using the following formula:

([AST IU/L / AST ULN] / [Platelet count 109/L]) $\times$ 100 = APRI

Online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri

A descriptive summary will be provided for APRI, change from Baseline and the percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in APRI at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

FIB-4 at Week 12

The FIB-4 score will be calculated using the following formula:

[Age (years) × AST (IU/L)] / [Platelets (10^9/L) × (√ ALT (IU/L)))]

FIB-4 online calculator reference: http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

A descriptive summary will be provided for FIB-4 values, change from Baseline and the percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in FIB-4 at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

8.6.3.5 Change from baseline and percentage change from baseline in lipids by visit and at week 12

Lipids will be evaluated using the regular lipid panel obtained in the biochemistry panel from the standard blood draw. In addition, a special LIPO Profile assay will be used to further evaluate the number of particles in each of the lipid parameters. This section will describe the parameters obtained from this standard lipid profile and from the LIPO profile, where applicable.

Triglycerides by Visit and at Week 12

Triglycerides are captured in the general lab biochemistry panel and also in the LIPO profile panel. Both measurements of triglycerides will be summarized separately.

A descriptive summary will be provided for triglyceride values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in triglycerides at each visit, with Week 12 as the visit of primary interest, will be analysed using an ANCOVA model

with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

Total Cholesterol by Visit and at Week 12

Total cholesterol is captured in the general lab biochemistry panel and also in the LIPO profile panel. Both measurements of total cholesterol will be summarized separately.

A descriptive summary will be provided for total cholesterol values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in total cholesterol at each visit, with Week 12 as the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

HDL by Visit and at Week 12

HDL is captured in the general lab biochemistry panel and also in the LIPO profile panel (as HDL-C). Both measurements of HDL will be summarized separately.

A descriptive summary will be provided for HDL values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in HDL at each visit, with the Week 12 being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

LDL by Visit and at Week 12

LDL is captured in the general lab biochemistry panel and also in the LIPO profile panel (as LDL-C). Both measurements of LDL will be summarized separately.

A descriptive summary will be provided for LDL values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in LDL at each visit, with the Week 12 being the primary visit of interest, will be analysed using an ANCOVA model

with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

Total/HDL Cholesterol (CT) Ratio by Visit and at Week 12

A descriptive summary will be provided for total cholesterol/HDL Ratio values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group. Ratio will be also obtained from LIPO profile.

Change from Baseline and percentage change from Baseline in total cholesterol/HDL ratio at each visit, with Week 12 as the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

Adiponectin by Visit and Week 12

A descriptive summary will be provided for adiponectin values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in adiponectin values by visit, with the Week 12 being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

ApoA-1 by Visit and at Week 12

A descriptive summary will be provided for ApoA-1 values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in ApoA-1 by visit, with the Week 12 being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

ApoB by Visit and at Week 12

A descriptive summary will be provided for ApoB values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in ApoB by visit, with the Week 12 being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

ApoC3 by Visit and at Week 12

A descriptive summary will be provided for ApoC3 values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in ApoC3 by visit, with the Week 12 being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

ApoB/A-1 Ratio by Visit and at Week 12

A descriptive summary will be provided for ApoB/A-1 ratio values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in ApoB/A-1 ratio by visit, with the Week 12 being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

8.6.3.6 Change from baseline and percentage change from baseline in parameters of glucose metabolism by visit and at week 12

Fasting Glucose by Visit and at Week 12

A descriptive summary will be provided for fasting glucose, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline will be analysed by visit, with

the Week 12 visit being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

Fasting Insulin by Visit and at Week 12

A descriptive summary will be provided for fasting insulin, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline will be analysed by visit, with the Week 12 visit being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

HOMA Index for Non-Diabetic Subjects by Visit and at Week 12

Subjects who are **not considered** having type 2 diabetes will be identified using the NASH history page in the CRF. A descriptive summary will be provided for HOMA index for the non-diabetic subjects, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline will be analysed by visit, with the Week 12 visit being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

HOMA Index for Diabetic Subjects by Visit and at Week 12

Subjects who are considered as having type 2 diabetes will be identified using the NASH history page in the CRF.

A descriptive summary will be provided for HOMA index for the diabetic subjects, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline will be analyzed by visit, with the week 12 visit being the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided

95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

HbA1C for Subjects with Type 2 Diabetes by Visit and at Week 12

Subjects who are considered as having type 2 diabetes will be identified using the NASH history page in the CRF.

A descriptive summary will be provided for HbA1c for subjects with type 2 diabetes, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline will be analysed by visit, with the Week 12 visit being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

8.6.3.7 Change from baseline and percentage change from baseline in laboratory Inflammation parameter levels by visit and at week 12

Fibrinogen by Visit and at Week 12

A descriptive summary will be provided for fibrinogen levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in fibrinogen levels by visit, with the Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

CRP (hs-CRP) by Visit and at Week12

A descriptive summary will be provided for CRP (hs-CRP) levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in CRP (hs-CRP) levels at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-

squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

IL6 by Visit and at Week 12

A descriptive summary will be provided for IL6 levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in IL6 levels at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

IL1β by Visit and at Week 12

A descriptive summary will be provided for IL1β levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in IL1β levels at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

TNF-α by Visit and at Week 12

A descriptive summary will be provided for TNF-α levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in TNF-α levels at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

TNF-β by Visit and at Week 12

A descriptive summary will be provided for TNF-β levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in TNF-β levels at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the

associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

Haptoglobin by Visit and at Week 12

A descriptive summary will be provided for haptoglobin levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in haptoglobin levels at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

Alpha2 Macroglobulin by Visit and at Week 12

A descriptive summary will be provided for alpha2 macroglobulin levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in alpha2 macroglobulin levels at Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

8.6.3.8 Change from baseline and percentage change from baseline in body weight by visit and at week

A descriptive summary will be provided for body weight, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in body weight by visit, with the Week 12 visit as the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

8.6.3.9 Change from baseline and percentage change from baseline in waist to hip (WTH) ratio by visit and at week 12

A descriptive summary will be provided for Waist Circumference, Hip Circumference, and WTH ratio using 8-nummer summary by visit and treatment group. In addition, change from Baseline and percentage change from Baseline in WTH ratio will be summarized.

Change from Baseline and percentage change from Baseline in waist to hip WTH ratio by visit, with the Week 12 visit as the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

8.6.3.1 Change from Baseline and percentage change from Baseline in NASH biomarker by Visit and at Week 12

Cytokeratin (CK) 18 by Visit and at Week 12

A descriptive summary will be provided for CK18 levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in CK18 levels by visit, with the Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

GLP-1 by Visit and at Week 12

A descriptive summary will be provided for GLP-1 levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in GLP-1 levels by visit, with the Week 12 will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

8.6.4 Additional Analyses (Liver Tests)

8.6.4.1 Change from Baseline and Percentage Change from Baseline in Additional

Liver Parameters

AST by Visit and at Week 12

A descriptive summary will be provided for AST values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in AST at each visit, with the Week 12 being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares mean and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

Total Bilirubin by Visit and at Week 12

A descriptive summary will be provided for Total Bilirubin values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in Total Bilirubin at each visit, with the Week 12 being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

GGT by Visit and at Week 12

A descriptive summary will be provided for GGT values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in GGT at each visit, with the Week 12 being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

Alkaline Phosphatase by Visit and at Week 12

A descriptive summary will be provided for alkaline phosphatase values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in alkaline phosphatase at

each visit, with the Week 12 being the primary visit of interest, will be analysed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

8.6.4.2 Subgroup Analyses

Subgroup analyses will be performed on selected outcomes in subgroups of interest. All subgroup analyses will be exploratory in nature. As the interest will be on how different treatment regimens work in a specific subgroup, instead of whether the treatment differences are the same across different subgroups, the subgroup analyses will be performed by analyzing the outcome data in different subgroups, instead of analyzing the outcome data in the whole population with subgroup factors included in the analyses model.

Subgroup analyses will be performed for the primary endpoint and the secondary endpoints to determine whether significant differences exist in primary and secondary endpoint results between subgroups.

These subgroup analyses will be carried out using the subjects from the efficacy population.

The list of potential subgroups (with applicable definitions in parentheses) includes the following:

- MRE Week 12 response: (<15% reduction vs ⩾15% reduction in percentage of change from baseline)
- MRI-PDFF Week 12 response: (<30% reduction vs ⩾30% reduction in percentage of change from baseline)
- Both MRE Week 12 response (⩾15% reduction in percentage of change from baseline) and MRI-PDFF Week 12 response (⩾30% reduction in percentage of change from baseline) vs non-response
- NASH Diagnosis (biopsy vs phenotype)
- ALT Week 12 Category (>=0 change from baseline
  (0--10] change from baseline
  (-10--20] change from baseline
  (-20--30] change from baseline
  (-30--40] change from baseline
  <-40 change from baseline) AND same ALT categories for percent change from baseline

8.6.4.3 Exploring Relationships between Endpoints

Relationships between the endpoints will be evaluated as follows:

- Comparing the percentage change in ALT to the proportion of subjects with at least a 30% reduction in the percentage change from baseline in the MRI-PDFF score
- Comparing the percentage change in the WTH ratio to the proportion of subjects with at least a 30% reduction in the percentage change from baseline the MRI-PDFF at Week 12
- Comparing the percentage change in PRO-C3 to the proportion of subjects with at least a 30% reduction in the percentage change from baseline the MRI-PDFF at Week 12
- Comparing the percentage change in ALT to the proportion of subjects with at least a 15% reduction in the percentage change from baseline in the MRE at Week 12
- Comparing the percentage change in the WTH ratio to the proportion of subjects with at least a 15% reduction in the percentage change from baseline the MRE at Week 12
- Comparing the percentage change in PRO-C3 to the proportion of subjects with at least a 30 point reduction in ALT at Week 12
- Comparing the percentage change in body weight to the proportion of subjects with at least a 30 point reduction in ALT at Week 12
- Comparing the percentage change in PRO-C3 to the proportion of subjects with at least a 20 percent reduction in ALT at Week 12
- Comparing the percentage change in body weight to the proportion of subjects with at least a 20 percent reduction in ALT at Week 12
- Comparing the percentage change in body weight to the proportion of subjects with at least a 30% reduction in the percentage change from baseline in MRI-PDFF at Week 12
- Comparing the percentage change in body weight to the proportion of subjects with at least a 15% reduction in the percentage change from baseline in MRE at Week 12

In addition, relationships between the primary and secondary endpoints will be explored using scatterplots (and correlation coefficients) using various change and percent change from baseline. All data points will be included for all visits on a single plot, with separate color for each treatment group.

8.7 Safety analyzes

All safety analyzes will be based on the Safety population and will be performed for all safety variables specified below.

No statistical tests will be performed.

8.7.1 Adverse events

The primary safety endpoint of the study is the frequency of AEs, SAEs, and AEs leading to discontinuation through Week 12.

All Adverse Events (AEs) will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0 or higher. All subjects in the safety analysis set will be included in the summaries.

AEs will be classified as pre-treatment AEs and treatment emergent adverse events (TEAEs) and are defined as follows:

Pre-treatment AE: A pre-treatment event is any event that meets the criteria for an AE/SAE and occurs after the subject signs the ICF but before receiving the first administration of study drug.

TEAE: A TEAE is defined as an AE occurring or worsening on or after the first dose of study drug within 7 days after the last dose of study drug.

Post-treatment AE: any AE that was newly developed after the last dose date + 7 days.

Treatment-Related AEs: AE will be defined as related if causality is either probable or possible. AEs where the causality is missing will be assumed to have "Reasonable possibility of relatedness.

Grade AEs:

Grade AEs (serious and non-serious) in accordance with the NCI/CTCAE scale (available at

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf) as presented below:

- **Mild** (Grade 1) asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Moderate** (Grade 2) minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- **Severe** (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
- **Life-threatening** (Grade 4) Life-threatening consequences; urgent intervention indicated
- **Death** (Grade 5) Death related to the AE.

Details for imputing missing or partial start dates of adverse events are described in Section 7.2.2. Imputed Adverse Event dates will be used for determining treatment-emergence.

Summaries of AEs will include the following:

- Treatment-emergent AEs
- Treatment-emergent AEs by severity
- Treatment-emergent treatment-related AEs
- Treatment-emergent AEs leading to study drug discontinuation
- SAEs
- Treatment-related SAEs
- AEs leading to death

All TEAEs will be summarized by SOC, PT and treatment group using frequency counts and percentages. In addition, an overall summary for the categories above will be prepared by treatment group and overall. On-treatment AEs will be summarized separately from those events that occurred during treatment-free follow-up. Those events that occurred during treatment-free follow-up will be summarized by randomized treatment group. The denominator for these events will be only those subjects who entered into the 4 week treatment free follow-up period.

Where a subject has the same adverse event, based on preferred terminology, reported multiple times in the treatment period, the subject will only be counted once at the preferred terminology level in adverse event frequency tables.

Where a subject has multiple adverse events within the same system organ class in the treatment period, the subject will only be counted once at the system organ class level in adverse event frequency tables.

When reporting adverse events by severity, in addition to providing a summary table based on the event selection criteria detailed above, summary table will also be provided based on the most severe event during the treatment period - independent of relationship to study treatment.

8.7.2 Stopping Rules

Summaries will be provided using counts and percentages for subjects who meets the stopping rules as described below:

- ALT or AST > 5 x Baseline
- ALT or AST > 2 x Baseline AND concomitant total bilirubin > 2 x Baseline OR Concomitant INR > 0.2 from Baseline
- ALT or AST > Baseline AND Right Upper Quadrant Abdominal Pain, Anorexia, Nausea, Vomiting, Fever, Eosinophilia, and/or Rash

8.7.2.1 Close Monitoring for Drug Discontinuation due to Elevated ALT/AST

The following close observation guidelines applies to subjects that repeat assessments show persistent elevations of transaminases, but who do not meet drug discontinuation criteria, and for subjects who discontinue study drug due to ALT/AST elevations.

A listing will be used to track and evaluate subjects that are part of the close observation guidelines. Monitoring of these subjects will be ongoing throughout the study.

8.7.3 Clinical laboratory evaluations

Summaries of clinical laboratory results will be performed using an 8-number summary by visit and treatment. All subjects in the safety population will be included in these summaries. Baseline is defined as the last value collected prior to first dose of study drug.

The number and percentage of subjects with treatment-emergent laboratory abnormalities within 7 days of last dose of study drug will be summarized by treatment group. In addition, shift from Baseline tables will be generated by visit and treatment group. All summary tables will be repeated for abnormalities that occur during the treatment-free follow-up which is defined as occurring more than 7 days after the date of last dose. The denominator for these will include any subject who entered into the 4 week treatment-free follow-up phase.

All laboratory data will be included in the data listings and all test values outside the normal range will be flagged.

Pregnancy test and FSH will be listed separately.

The laboratory parameters listed in Table 2 on the following page will be assessed for each patient.

Creatinine clearance will be calculated by the central laboratory using the Cockcroft Gault equation and actual body weight:

CLCr (mL/min) = {((140 − Age [years]) × weight[kg]) / (72 × SCr[mg/dL])} × 0.85 (if female).

where SCr =serum creatinine

Online calculator can be found at:

https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc

8.7.4 Vital signs

Vital signs will include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths/min), heart rate (beats/min), and oral temperature (°C). Vital signs data will be summarized using an 8-number summary by visit and treatment. In addition, the number and percentage of subjects with significant changes in vital signs from Baseline will be summarized by treatment. No statistical testing will be performed. Baseline is defined as the last value collected prior to first dose of study drug.

Criteria for clinically significant changes in vital signs parameters.

Pulse Rate

- < 50 bpm
- >120 bpm
- 30 bpm increase from Baseline
- 30 bpm decrease from Baseline

Blood Pressure

- SBP > 150 mmHg or DBP > 100 mmHg
- SBP > 200 mmHg or DBP > 110 mmHg

Respiration Rate

- < 8 breaths/min
- 40 breaths/min

Temperature

- 38.3°C
- 1.1°C increase from Baseline (Baseline > 36.8°C)

Change in Weight

- 5% increase from Baseline
- 5% decrease from Baseline

A by-subject listing will be provided.

8.7.5 Physical examinations

A full physical examination will be conducted at Screening and EOS as indicated in the Schedule of Assessments and will include a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; chest, lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated.

Physical examination data will be provided in data listings.

8.7.6 Electrocardiograms (ECG)

12-lead ECG measurements include (Heart Rate (bpm), QRS Duration (msec), PR Interval (msec), QT Interval (msec) and QTcF (msec)) and will be summarized using an 8-number summary by visit and treatment for all safety subjects for observed values and changes from Baseline. The overall ECG interpretation (Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant) will be summarized by presenting the number and percentage of subjects for each treatment group and time-point. In addition,

the number and percentage of subjects with significant changes in ECG parameters will be summarized by treatment. Change from Baseline in QTcF > 60 msec or a QTcF interval > 500 msec and QTcF > 450 msec for males and 470 msec for females at either screening or Baseline are considered as significant changes in ECG parameters.

Baseline is defined as the last value collected prior to first dose of study drug.

No statistical testing will be performed.

A by-subject listing will be provided.

8.8 Pharmacokinetics (PK) and Pharmacokinetics/Pharmacodynamics (PK/PD) Analysis

During the study, PK samples and PD samples for FGF19, C4, bile acid, and ALT will be collected according to one of two schedules on Days 1 and 84. Subjects agreeing to participate in the PK/PD substudy will have samples collected at four discrete times: predose and 2, 6, and 8 hours after administration of EDP-305 on Days 1 and 84. This scheme will be referred to as "intensive" sampling in this SAP. On Days 1 and 84, all other subjects will have a sample collected predose, a second sample collected 1 to 3 hours after administration of EDP-305, and a third sample collected at least 1 hour after the second sample. This scheme will be referred to as "sparse" sampling. Additionally, all subjects will have PK, FGF19, C4, bile acid, and ALT samples collected according to the sparse scheme on Weeks 2, 4, and 8.

For the sparse sampling scheme, the nominal window for the first post-dose sample is defined relative to the time of EDP-305 administration while the nominal window for the second post-dose sample is defined relative to the time of collection of the first post-dose sample. As a consequence, actual sampling times for the second post-dose sample may fall within the 1- to 3-hour window described for the first post-dose sample. For example, if the first post-dose sample is collected 1 hour after EDP-305 administration and the second post-dose sample is collected 1 hour later, then the both samples would fall within the 1- to 3-hour window. In addition, actual sampling times relative to EDP-305 administration for post-dose samples collected according to the sparse scheme may vary between subjects and study visits. To permit more meaningful summarization, post-dose samples collected according to the sparse scheme will be binned by actual elapsed time since the time of the reference dose of EDP-305 for each visit. Bins for sparse post-dose samples are described in Table 3. Bins may be modified based on the distribution of the data.

Table 3: Bin Time for Post-Dose Sparse Samples

Bin Time Midpoint (hr)	Range for actual post-dose sample time (relative to time of EDP-305 dose)
0.5	0 to < 1 h
2.0	≥ 1 to < 3 h

4.0	≥ 3 to < 5 h
6.0	≥ 5 to < 7 h
8.0	≥ 7 to < 9 h

For plotting purposes, sparse predose samples collected prior to administration of the reference dose of EDP-305 at each study visit will be assigned to a 0-hour bin. In the event that a predose sample is collected after administration of the reference dose of EDP-305 at a particular study visit, this sample will be assigned to a bin in the same manner as described above for sparse post-dose samples.

8.8.1 Pharmacokinetic (PK) Analysis

The PK analysis will use the pharmacokinetic population and will include only subjects in active treatment arms.

8.8.1.1 Analysis of Sparse PK Samples

The concentration data for EDP-305 and each metabolite collected according to the sparse sampling scheme will be summarized by active treatment arm, visit, and bin time midpoint. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. If more than 50% of subjects have postdose concentration values below BLQ, descriptive statistics will not be presented except for maximum and BLQ will be displayed for mean and minimum. The number of observations, arithmetic mean, standard deviation (SD), % coefficient of variation (%CV), median, minimum, maximum, geometric mean, and %CV of the geometric mean (%GCV) will be displayed. Linear and semi-log plots of the arithmetic mean concentration versus bin time will be created. The linear plots of mean concentrations will include the SD (±) for each mean. Composite (i.e. "spaghetti") plots of individual subject EDP-305 and metabolite plasma concentrations versus time data will be created on both the linear and semi-logarithmic scales. A summary plot of the means and SD of the pre-dose concentrations at each visit will be provided by treatment.

Individual data will be presented in listing.

8.8.1.2 Analysis of Intensive PK samples

The concentration data for EDP-305 and each metabolite collected according to the intensive sampling scheme will be summarized by active treatment arm, visit and nominal time since the reference dose. Concentrations that are BLQ will be treated as zero for the computation of descriptive statistics. If more than 50% of subjects have postdose concentration values below BLQ, descriptive statistics will not be presented except for maximum and BLQ will be displayed for mean and minimum. The number of observations, arithmetic mean, SD, %CV, median, minimum, maximum, geometric mean, and %GCV values will be displayed. Linear and semi-log plots of the arithmetic mean concentration versus nominal sampling time will be created. The linear plots of mean

concentrations will include the SD (±) for each mean. Composite (i.e. "spaghetti") plots of individual subject EDP-305 and metabolite plasma concentrations versus time will be created on both the linear and semi-logarithmic scales. Predose samples collected under to the intensive sampling scheme will be pooled with those collected under the sparse sampling scheme for the purpose of creating the longitudinal summary plot of the means and standard deviations of the pre-dose concentrations (See Section 8.8.1.1). Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by subject (one subject per page, Day 1 and Day 84 on same plot).

The PK parameters listed in Table 6 will be calculated as indicated for plasma EDP-305 and its metabolites, as applicable. PK parameters will be calculated by noncompartmental methods (only on Day 1 and Day 84).

Table 6: PK/PD Parameters for Subjects with Intensive Samples

PK Parameter	Description
AUC_{last}	The area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration computed using the linear up/log down trapezoidal rule.
C_{max}	Maximum observed concentration.
T_{last}	Time to last quantifiable concentration.
T_{max}	Time to reach C_{max}. If the maximum value occurs at more than one timepoint, T_{max} is defined as the first time point with this value.

Plasma PK parameters for each dose level will be calculated from the concentrations of EDP-305 and its metabolites measured in predose and post-dose plasma samples. For each EDP-305 dose level, descriptive statistics of AUC_{last} and C_{max} (sample size, arithmetic means, geometric means, standard deviation (SD), %CV, minimum, median, maximum, and %GCV) will be presented. Only the minimum, median, and maximum will be presented for T_{max}. T_{last} will be presented as a diagnostic parameter in the listing of individual PK parameters, but will not be included in summary tables with other PK parameters.

Individual data will be presented in listing.

8.8.2 Pharmacodynamic (PD) Analysis

The PD analysis will use the efficacy population and will include all treatment arms (active and placebo).

8.8.2.1 Analysis of Sparse PD Samples

A descriptive summary will be provided for the FGF19, C4, and bile acid endpoints including measured concentrations, change from baseline, and percentage change from baseline using the 8-number summary by visit, treatment group, and bin time midpoint.

Change from baseline and percentage change from baseline in the FGF19, C4, and bile acid concentrations for each bin time midpoint by visit will be analysed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate with the Week 12 visit being considered the primary visit of interest. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

8.8.2.2 Analysis of Intensive PD Samples

A descriptive summary will be provided for the FGF19, C4, and bile acid endpoints including measured concentrations, change from baseline, and percentage change from baseline using 8-number summary by visit, treatment group, and nominal time. For Days 1 and 84 (overlaid), linear plots of the arithmetic mean concentration (±SD) versus nominal sampling time figures will be created for FGF19, C4, and bile acid endpoints.

Change from baseline and the percentage change from baseline in the FGF19, C4, and bile acid concentrations for each nominal time by visit will be analysed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate with the Week 12 visit being considered the primary visit of interest. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

The area under the curve from 0 to 8 hours (AUC_{0-8}) and from 2 to 8 hours (AUC_{2-8}) will be computed for FGF19 and C4 at Days 1 and 84 using the linear trapezoidal rule. Descriptive summaries of AUC_{0-8} and AUC_{2-8} (sample size, arithmetic means, geometric means, standard deviation (SD), %CV, minimum, median, maximum, and %GCV) for FGF19 and C4 will be presented by visit and treatment group.

The change from baseline and percent change from baseline for AUC_{0-8} and AUC_{2-8} will be computed for Day 84 using the parameter value at Day 1 as the baseline value.

Change from baseline and the percentage change from baseline in the AUC_{0-8} and the AUC_{2-8} for FGF19 and C4 at Day 84 will be analysed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables. Composite (i.e.

"spaghetti") plots of individual subject FGF19, C4, and bile acid concentrations versus time will be created on the linear scale.

8.8.2.3 PK/PD Analysis at Week 12 for Subjects with Intensive Samples

Correlation and PK/PD plots will be created using all subjects in the PK population. Correlation and other PD plots will be created using all subjects in the efficacy population, including placebo, as applicable. The following scatterplots will be generated:

- AUC_{0-8} in FGF19 with EDP-305 AUC_{last} for Day 1 and Day 84 (Week 12)
- AUC_{2-8} in FGF19 with EDP-305 AUC_{last} for Day 1 and Day 84 (Week 12)
- AUC_{0-8} in C4 with EDP-305 AUC_{last} for (Day 1 and Day 84 [Week 12])
- AUC_{2-8} in C4 with EDP-305 AUC_{last} for (Day 1 and Day 84 [Week 12])
- Percentage change from Baseline in AUC_{0-8} FGF19 with EDP-305 AUC_{last} (Week 12)
- Percentage change from Baseline in AUC_{2-8} FGF19 with EDP-305 AUC_{last} (Week 12)
- Percentage change from Baseline in AUC_{0-8} C4 with EDP-305 AUC_{last} (Week 12)
- Percentage change from Baseline in AUC_{2-8} C4 with EDP-305 AUC_{last} (Week 12)
- Percentage change from Baseline in Bile Acid (predose) with EDP-305 AUC_{last} (Week 12)
- Percentage change from Baseline in ALT (predose Week 12) with percentage change from Baseline in AUC_{0-8} FGF19 (Week 12)
- Percentage change from Baseline in ALT (predose Week 12) with percentage change from Baseline in AUC_{2-8} FGF19 (Week 12)
- Percentage change from Baseline in ALT (predose Week 12) with percentage change from Baseline in AUC_{0-8} C4 (Week 12)
- Percentage change from Baseline in ALT (predose Week 12) with percentage change from Baseline in AUC_{2-8} C4 (Week 12)
- Percentage change from Baseline in ALT (predose Week 12) with EDP-305 AUC_{last} (Week 12)
- Percentage change from Baseline in FGF19 (predose) with EDP-305 C_{max} (Week 12)
- Percentage change from Baseline in C4 (predose) with EDP-305 C_{max} (Week 12)
- Percentage change from Baseline in Bile Acid (predose) with EDP-305 C_{max} (Week 12)

8.8.2.4 PK/PD Analysis at Week 12 for All Subjects

Correlation and PK/PD plots will be created using all subjects in the PK population. Correlation and other PD plots will be created using all subjects in the efficacy population, including placebo, as applicable. The following scatterplots will be generated:

- Percentage change from Baseline in ALT with the percentage change from Baseline in FGF19 (Predose Week 12)
- Percentage change from Baseline in ALT with the percentage change from Baseline in C4 (Predose Week 12)
- Percentage change from Baseline in ALT with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in ALT with EDP-305 concentration value (predose at Week 12)
- Percentage change from Baseline in AST with the percentage change from Baseline in FGF19 (Predose Week 12)
- Percentage change from Baseline in AST with the percentage change from Baseline in C4 (Predose Week 12)
- Percentage change from Baseline in AST with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in AST with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in GGT with the percentage change from Baseline in FGF19 (Predose Week 12)
- Percentage change from Baseline in GGT with the percentage change from Baseline in C4 (Predose Week 12)
- Percentage change from Baseline in GGT with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in GGT with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in Total Bilirubin with the percentage change from Baseline in FGF19 (Predose Week 12)
- Percentage change from Baseline in Total Bilirubin with the percentage change from Baseline in C4 (Predose Week 12)

- Percentage change from Baseline in Total Bilirubin with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in Total Bilirubin with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in Alkaline Phosphatase with the percentage change from Baseline in FGF19 (Predose Week 12)
- Percentage change from Baseline in Alkaline Phosphatase with the percentage change from Baseline in C4 (Predose Week 12)
- Percentage change from Baseline in Alkaline Phosphatase with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in Alkaline Phosphatase with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in FGF19 with the percentage change from Baseline in C4 (Predose Week 12)
- Percentage change from Baseline in FGF19 with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in FGF19 with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in C4 with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in C4 with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in Bile Acid with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in Cholesterol with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in HDL with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in LDL with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in triglycerides with EDP-305 concentration value (Predose Week 12)

- Box plot of EDP-305 and EP-022679 concentration (last predose) for subjects with adverse events occurring in at least 5% of the combined active subjects.

[redacted]

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9 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

[redacted]

PK and pruritus:

- Summary of plasma concentration of EDP-305 and EP-022679 per time point and treatment group by visit for subjects with and without pruritus
- Summary of PK parameters by treatment group by visit for subjects with and without pruritus
- Mean plasma concentrations (±SD) of EDP-305 and EP-022679 versus time profile by treatment group and visit for subjects with and without Pruritus (linear and semi-log scale)
- Boxplot of AUC_{last} and C_{max} for EDP-305 and EP-022679 by treatment group and visit for subjects with and without pruritus
- Boxplot of predose concentration at Week 2,4,8 and 12 for EDP-305 and EP-022679 by treatment group for subjects with and without pruritus
- Listing of EDP-305 and EP-022679 concentration value for subjects with pruritus

C4 and pruritus:

- Summary of C4, change from baseline and percentage change from baseline by hour by visit for subjects with and without pruritus
- Summary of AUC_{0-8} and AUC_{2-8} for C4, change from baseline and percentage change from baseline at Week 12 for subjects with and without pruritus
- Mean C4 (±SD) versus time profile by treatment group and visit for subjects with and without pruritus (linear and semi-log scale)
- Boxplot of percentage change from baseline in C4 for AUC_{0-8} and AUC_{2-8} at Week 12 by treatment group

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