MAIN STUDY STATISTICAL ANALYSIS PLAN

Protocol Title:	A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND EFFICACY OF EFRUXIFERMIN IN SUBJECTS WITH COMPENSATED CIRRHOSIS DUE TO NONALCOHOLIC STEATOHEPATITIS (NASH)
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Investigational Product:	Efruxifermin (EFX)
Sponsor:	Akero Therapeutics, Inc 601 Gateway Blvd., Suite 350 South San Francisco, CA 94080
SAP Version/Date:	Version 2.0 / 16 December 2024

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SIGNATURE PAGE

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Protocol Number:	AK-US-001-0103
SAP Version/Date:	Version 2.0 / 16 December 2024

We, the undersigned, have reviewed and approved this Statistical Analysis Plan

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VERSION HISTORY

Version	Version Date	Description
1.0		Original signed version
2.0		After the Week 36 primary endpoint analysis and unblinding of select Akero team members in accordance with the unblinding plan procedures, the following additional descriptive and sensitivity analyses were specified for the Week 96 analysis: Added descriptive shift tables presenting the bivariate response at Week 36 and Week 96 for histology endpoints to characterize the durability of responses between Week 36 and Week 96 and proportion of non-responders at Week 36 that became responders at Week 96, as well as changes in fibrosis from Week 36 to Week 96 Additional categories added to baseline characteristics summaries in Section 3.3.4 and concomitant insulin usage in Section 3.3.6 Additional subgroup analyses for histology endpoints in Section 3.4.1: • FibroScan® Liver stiffness > 20 vs ≤20, • GLP-1 RA based therapies at baseline (Yes, No) Added risk ratio estimate and 95% CI for histology endpoints and correlation analysis at Week 96 for fibrosis improvement with no worsening of NAS Additional sensitivity analysis was specified in Section 3.4.1 for week 96 fibrosis improvement with no worsening of NAS endpoint using all available biopsy data Additional sensitivity analysis was specified in Section 3.4.2 detailing analysis of liver stiffness parameter with exclusion of certain assessments not meeting quality criteria Descriptive summary of EFS was updated to include pointwise estimate and 95% confidence interval at Week 36 and Week 96 in Section 3.4.3 Descriptive summary of drug-related treatment-emergent adverse events leading to discontinuation of treatment, and common drug-related adverse events in Section 3.5.1, and AESIs summary updated to include the AESI category Minor updates throughout the document List of signatories for Week 96 analysis was updated

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase (serum glutamate pyruvate transaminase)
ANCOVA	Analysis of Covariance
AST	aspartate aminotransferase (serum glutamate oxaloacetate transaminase)
AUC	area under receiver operating characteristic curve
BLQ	below the limit of quantification
BMD	bone mineral density
BMI	body-mass index
BSAP	bone specific alkaline phosphatase
C3M	type III collagen
CLDQ-NASH	chronic liver disease questionnaire-nonalcoholic steatohepatitis
CMH	cochran-mantel-haenszel
CRF	case report form
CRN	clinical research network
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CTX-1	c-telopeptide of type I collagen
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DXA	dual-energy x-ray absorptiometry
DAS	dual-energy x-ray absorptiometry analysis set
ECG	electrocardiogram
EDC	electronic data capture
EFS	event-free survival
EFX	efruxifermin
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
FAS	full analysis set
FAST	fibroscan® aspartate aminotransferase score
GGT	gamma glutamyl transferase
GLP-1	glucagon-like peptide-1 (agonist)
HA	hyaluronic acid
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	homeostasis model assessment of insulin resistance
INR	international normalized ratio
IQR/M	interquartile range/median value
IRT	Interactive response technology
kPa	kilopascals

Abbreviation	Definition
LBAS	liver biopsy analysis set
LDL-C	low-density lipoprotein cholesterol
LS	least-squares
LSM	liver stiffness measurement
MedDRA	medical dictionary for regulatory activities
MELD	model for end-stage liver disease
ML	Machine learning
MMRM	mixed-model repeated-measures
MRE	magnetic resonance elastography
MAS	magnetic resonance elastography analysis set
NAFLD	non-alcoholic fatty liver disease
Nab	neutralizing antibody
NAS	non-alcoholic fatty liver disease activity score
NASH	nonalcoholic steatohepatitis
P1NP	procollagen type 1 N pro-peptide
PBMC	peripheral blood mononuclear cell
PIIINP	amino-terminal propeptide of type III procollagen
PK	pharmacokinetics
PP	per protocol
Pro-C3	pro-peptide of type 3 procollagen
PT	preferred term
PTH	parathyroid hormone
QTcF	QT interval corrected using Fridericia's formula
QW	once weekly
SAP	statistical analysis plan
SAS®	statistical analysis system®
SOC	system organ class
T2D	type 2 diabetes
TB	total bilirubin
TEAEs	treatment-emergent adverse events
TESAEs	treatment-emergent serious adverse events
TG	triglyceride
TIMP-1	tissue inhibitor of metalloproteinase-1
UFC	urinary free cortisol
ULN	upper-limit of normal
VLDL-C	very low-density lipoprotein cholesterol
WHO	World Health Organization
WPAI-NASH	work productivity and activity impairment for nonalcoholic steatohepatitis

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of the Main Study data from Akero Therapeutics, Inc. Protocol AK-US-001-0103. A separate SAP will be provided for the analysis of Cohort D data from Akero Therapeutics, Inc. Protocol AK-US-001-0103. The SAP will be finalized prior to unblinding of the database. Any deviations from the SAP after database unblinding will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is:

- To evaluate the effect of EFX compared to placebo on fibrosis regression in subjects with compensated cirrhosis due to NASH at Week 36

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the effect of EFX compared to placebo on achieving NASH resolution in subjects with compensated cirrhosis due to NASH at Week 36 and Week 96
- To evaluate the effect of EFX compared to placebo on achieving NASH resolution and improvement in fibrosis at Week 36 and Week 96
- To evaluate the effect of EFX compared to placebo on fibrosis regression in subjects with compensated cirrhosis due to NASH at Week 96
- To evaluate the effect of EFX compared to placebo on fibrosis regression in subjects with compensated cirrhosis due to NASH at Week 36 and Week 96
- To evaluate the effect of EFX compared to placebo on non-invasive markers of fibrosis
- To evaluate the effect of EFX compared to placebo on lipoproteins
- To evaluate the effect of EFX compared to placebo on markers of insulin sensitivity and glycemic control
- To evaluate the effect of EFX compared to placebo on weight change
- To assess the immunogenicity of EFX
- To assess the safety and tolerability of EFX

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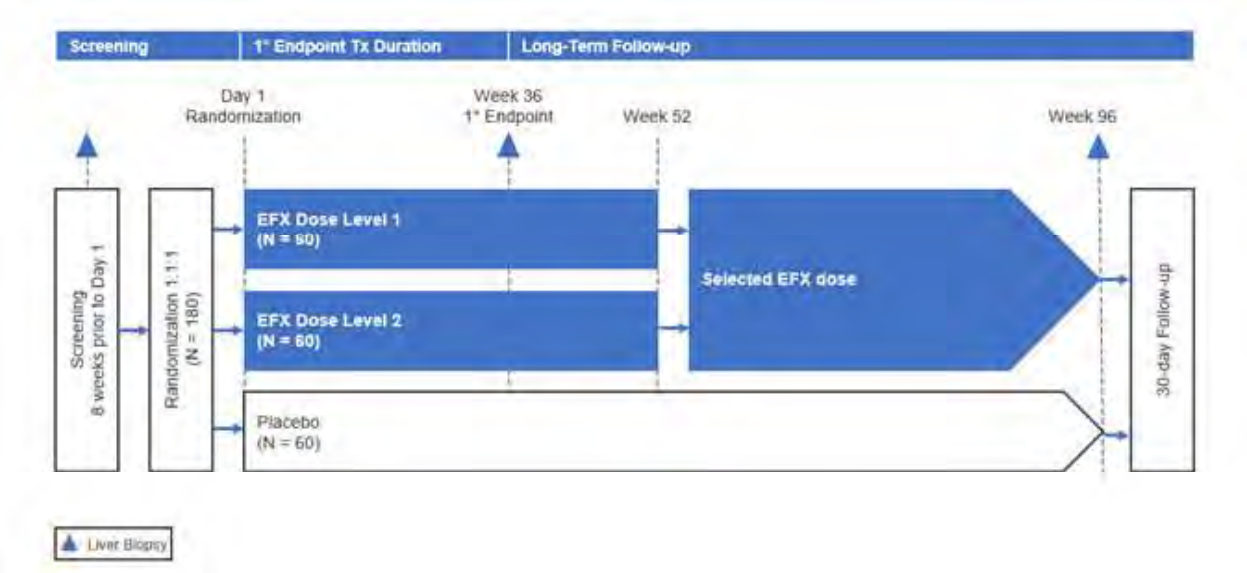
2.2 Study Design

2.2.1 Overview

This is a Phase 2b, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of EFX in subjects with compensated cirrhosis due to NASH. Subjects will have fibrosis stage 4 without any history of decompensation and will be dosed once weekly (QW) with EFX 50 mg, EFX 28 mg, or placebo for up to 96 weeks.

After all subjects have completed the Primary Endpoint Treatment Duration (i.e., completed 36 weeks of treatment or permanently discontinued the study prior to the Week 36 visit), the primary endpoint analysis will be performed to select a single dose of EFX (50 mg or 28 mg) for further evaluation. The Sponsor will seek alignment from the applicable regulatory authorities on the dose selected prior to clinical use.

Subjects receiving EFX 50 mg or EFX 28 mg may be eligible to receive the selected dose of EFX. Roll over to the selected dose of EFX will occur only after all active subjects have completed 52 weeks of treatment and dose selection is confirmed. Subjects assigned to the placebo group will continue to receive placebo but may be offered open label EFX in a separate roll over study after completing 96 weeks of treatment.



Study participation may last up to 108 weeks, including an 8 week screening period, 96 week treatment period, and a 30-day Follow-up visit.

Note that after the Week 36 analysis, all subjects remained on their originally assigned EFX dose for the remainder of the study.

2.2.2 Randomization and Blinding

On Day 1, eligible subjects will be randomized in a blinded fashion in a 1:1:1 ratio to 1 of 3 treatment groups. Randomization will be stratified by type 2 diabetes (T2D) status (Yes vs No) and diagnosis of cryptogenic cirrhosis presumed secondary to NASH (Yes vs No) at baseline.

Treatment Group	Study Drug Assignment
EFX 50 mg (N = 60)	EFX 50 mg, subcutaneous injection, once weekly
EFX 28 mg (N = 60)	EFX 28 mg, subcutaneous injection, once weekly
Placebo (N = 60)	Placebo, subcutaneous injection, once weekly

An Interactive Response Technology (IRT) system will be used for centralized randomization and treatment assignment. Investigative site personnel will obtain the treatment assignment from the IRT system. Subjects and all personnel directly involved in the conduct of the study will be blinded to treatment assignments. Study drugs will be dispensed in a blinded fashion to the subjects.

2.2.3 Study Drug Description

Efruxifermin is an IgG1Fc-fibroblast growth factor 21 (FGF21) fusion protein.

Efruxifermin 50 mg, EFX 28 mg, and placebo will be provided as a frozen liquid formulation and will be administered as a subcutaneous (SC) injection in the abdomen as follows:

- EFX 50 mg, QW
- EFX 28 mg, QW
- Placebo, QW

2.2.4 Sample Size Determination

The primary endpoint is the proportion of subjects who achieve ≥ 1 stage improvement in fibrosis and no worsening of steatohepatitis at Week 36. Based on results of published studies in NASH with compensated cirrhosis and results of Cohort C in the Phase 2a BALANCED study of EFX, it is estimated that approximately 12% of subjects on placebo and 42% of subjects on EFX will reach this endpoint.

With a two-sided Cochran-Mantel-Haenszel (CMH) test for proportion difference, at a significance level of 0.05, 45 completed subjects per group will provide at least 90% power. Sample size calculations are for testing 2 proportions using a CMH test and were computed using the normal approximation method. Factoring in dropouts, the study plans to randomize at least 150 subjects in total.

2.2.5 Primary Efficacy Endpoint

The primary endpoint is the proportion of subjects who achieve ≥ 1 stage improvement in fibrosis (based on NASH Clinical Research Network [CRN] fibrosis score) and no worsening of steatohepatitis at Week 36.

2.2.6 Secondary Efficacy Endpoints

The secondary endpoints are:

- Proportion of subjects who achieve NASH resolution (defined as a non-alcoholic fatty liver disease activity score [NAS] of 0-1 for inflammation and 0 for ballooning) as determined by the NASH CRN criteria at Week 36 and Week 96
- Proportion of subjects who achieve ≥ 1 stage improvement in fibrosis (based on NASH CRN fibrosis score) and no worsening of steatohepatitis at Week 96
- Proportion of subjects who achieve ≥ 1 stage improvement in fibrosis (based on NASH CRN fibrosis score) at Week 36 and Week 96
- Proportion of subjects who achieve NASH resolution (defined as a NAS of 0-1 for inflammation and 0 for ballooning) and ≥ 1 stage improvement in fibrosis (based on NASH CRN fibrosis score) at Week 36 and Week 96
- Change from baseline in enhanced liver fibrosis (ELF) score, three components of ELF including Amino-terminal propeptide of type III procollagen (PIIINP), hyaluronic acid (HA) and tissue inhibitor of metalloproteinase-1 (TIMP-1), pro-peptide of type 3 collagen (Pro-C3), liver stiffness assessed by FibroScan® and FibroScan® -AST (FAST) score
- Change from baseline in triglyceride (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and low density lipoprotein cholesterol (LDL-C)
- Change from baseline in Hemoglobin A1c (HbA1c), C-peptide, adiponectin, insulin, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)
- Change from baseline in body weight

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2.2.8 *Safety Endpoints*

- Safety and tolerability will be assessed through the reporting of extent of exposure, adverse events (AEs), clinical laboratory tests, electrocardiograms (ECGs), ultrasounds, vital sign assessments, and concomitant medication usage
- Detect and measure anti-drug antibodies (ADA), including neutralizing antibody (NAb), against EFX

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 *Analysis Day*

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0, in alignment with international data standards for clinical trials. Analysis day will be calculated as (date of clinical event – date of first dose of study drug) + 1 if the date of the event is on or after the date of first dose and as (date of clinical event – date of first dose of study drug) if the date of event is before the date of first dose.

3.1.2 *Analysis Visits*

Scheduled visits will be assigned to analysis visits as recorded on the Case Report Form (CRF).

Unscheduled visits and early termination visits for the liver biopsy and MRE will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 36	253	113	463
Week 96	673	464	EOS

Unscheduled visits and early termination visits for fibrosis biomarkers (ELF, Pro-C3 and C3M) will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 12	85	43	127
Week 24	169	128	211
Week 36	253	212	295
Week 48	337	296	421

Week 72	505	422	589
Week 96	673	590	EOS

Unscheduled and early termination visits for lipoproteins (Lipoprotein(a), TG, total cholesterol, HDL-C, non-HDL-C, LDL-C, and VLDL-C), markers of liver injury and function (ALT, AST, ALP, GGT, TB, direct bilirubin, INR, albumin, platelets, uric acid, and MELD score), eGFR, high-sensitivity C-reactive protein, and HbA1c will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 1	8	2	15
Week 4	29	16	43
Week 8	57	44	71
Week 12	85	72	99
Week 16	113	100	127
Week 20	141	128	155
Week 24	169	156	183
Week 28	197	184	211
Week 32	225	212	239
Week 36	253	240	267
Week 40	281	268	295
Week 44	309	296	313
Week 48	337	314	351
Week 52	365	352	379
Week 56	393	380	421
Week 64	449	422	477
Week 72	505	478	533
Week 80	561	534	589
Week 88	617	590	645
Week 96	673	646	EOS

Unscheduled and early termination visits for bone biomarkers (P1NP, CTX-1, BSAP, Vitamin D, and PTH), lipid metabolism biomarkers (apolipoprotein B and apolipoprotein C3), and insulin sensitivity and glycemic control biomarkers (C-peptide, adiponectin, insulin, and HOMA-IR) will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 4	29	16	57
Week 12	85	58	127
Week 24	169	128	211
Week 36	253	212	295
Week 48	337	296	421
Week 72	505	422	589
Week 96	673	590	EOS

Unscheduled and early termination visits for ADA and NAb will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 8	57	29	85
Week 16	113	86	141

Week 24	169	142	197
Week 32	225	198	239
Week 36	253	240	295
Week 48	337	296	365
Week 56	393	366	421
Week 64	449	422	477
Week 72	505	478	533
Week 80	561	534	589
Week 88	617	590	645
Week 96	673	646	EOS

Unscheduled and early termination visits for salivary cortisol will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 8	57	29	85
Week 16	113	86	141
Week 24	169	142	197
Week 32	225	198	253
Week 40	281	254	309
Week 48	337	310	365
Week 56	393	366	421
Week 64	449	422	477
Week 72	505	478	533
Week 80	561	534	589
Week 88	617	590	645
Week 96	673	646	EOS

Unscheduled and early termination visits for UFC, UFC per 24h, UFC per volume and UFC to creatinine ratio will be assigned analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 8	57	1	EOS

Unscheduled and early termination visits for IGF-1, free T4 and TSH will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 12	85	43	127
Week 24	169	128	211
Week 36	253	212	295
Week 48	337	296	365
Week 56	393	366	449
Week 72	505	450	561
Week 88	617	562	645
Week 96	673	646	EOS

Unscheduled and early termination visits for FibroScan® will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 24	169	85	211

Week 36	253	212	295
Week 48	337	296	421
Week 72	505	422	589
Week 96	673	590	EOS

Unscheduled and early termination visits for body weight, blood pressure and heart rate will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 1	8	2	11
Week 2	15	12	18
Week 3	22	19	25
Week 4	29	26	43
Week 8	57	44	71
Week 12	85	72	99
Week 16	113	100	127
Week 20	141	128	155
Week 24	169	156	183
Week 28	197	184	211
Week 32	225	212	239
Week 36	253	240	267
Week 40	281	268	295
Week 44	309	296	313
Week 48	337	314	351
Week 52	365	352	379
Week 56	393	380	421
Week 64	449	422	477
Week 72	505	478	533
Week 80	561	534	589
Week 88	617	590	645
Week 96	673	646	EOS

Unscheduled and early termination visits for DXA scan will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 36	253	113	295
Week 48	337	296	505
Week 96	673	506	EOS

Unscheduled and early termination visits for Child-Pugh score will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 12	85	43	169
Week 36	253	170	295
Week 48	337	296	421
Week 72	505	422	589
Week 96	673	590	EOS

Unscheduled and early termination visits for CLDQ-NASH and WPAI-NASH will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 12	85	43	127
Week 24	169	128	211
Week 36	253	212	267
Week 40	281	268	295
Week 44	309	296	313
Week 48	337	314	351
Week 52	365	352	435
Week 72	505	436	589
Week 96	673	590	EOS

Within an analysis visit window, the measurement from the scheduled visits will be used if available. If no scheduled visit occurs, the measurement from the visit closest to the defined target analysis day within the window will be used. If there is more than one measurement with equal distance to the defined target analysis day, the latter will be used. If no visits occur within a visit window, the measurement for this visit will be treated as missing.

For PK concentration summaries, a concentration that is intended as pre-dose will be excluded from analysis if it is >24 hours before a dose or after the current dose. Beyond this rule, PK concentrations must be within the visit window to be included in summary statistics of PK.

3.1.3 Definition of Baseline

For all variables except as specified, pre-dose measurements on Baseline visit (Day 1) will be considered the baseline values. If the measurement at this visit is not available, the last measurement prior to the first dose of study drug may be used as the baseline value unless it is stated otherwise. For height, abdominal ultrasound, FibroScan®, DXA, Liver Biopsy, and MRE , the scheduled baseline visit is Screening. If there is > 1 measurement at Screening or prior to Day 1, the last measurement prior to the first dose of study drug will be used as baseline.

Baseline ALT, AST, ALP, GGT, TB, direct bilirubin, HbA1c, and uric acid as well as lipid variables including TG, Total Cholesterol, HDL-C, non-HDL-C, LDL-C, VLDL-C and Lipoprotein (a) will be the average of available pre-dose measurements from screening to Day 1. If one is missing, the available one will be used.

Baseline blood pressure will be the average of Screening, Pre-Baseline, and Baseline visit (Day 1) values. If one value is missing, the average of the two available values will be used. If two values are missing, the available one will be used.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum. For certain continuous data, it will be summarized with descriptive statistics including n (number of non-missing values), arithmetic mean, arithmetic standard deviation, geometric mean, geometric coefficient of variation, median, minimum, and maximum. PK concentrations will be summarized with the set of continuous parameters including geometric mean and will add the statistic of number of samples below the limit of quantification (BLQ).

All individual subject data will be listed as measured.

3.1.5 Hypothesis Testing

The statistical hypotheses will be tested at the 2-sided, 0.05 significance for the parameters with neutral direction other than specified. Each treatment will be compared to placebo, and no adjustments for multiplicity will be performed.

3.1.6 Handling of Dropouts and Missing Data

Missing data for primary endpoint may be the result of intercurrent events. The handling of these cases for analysis of the primary endpoint and all secondary histological endpoints is discussed in Estimands. With these exceptions, values for missing data will not be imputed unless specified.

Where appropriate, safety data for subjects that did not complete the study will be included in summary statistics. For example, if a subject received study drug, the subject will be included in a summary of AEs according to the treatment received; otherwise, if the subject is not dosed then they will be excluded from the summary. If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point. If the subject is missing a baseline value, then the subject will be excluded from the calculation of summary statistics for the baseline value and the change from baseline values.

Values for missing safety laboratory data will not be imputed; however, a missing baseline result will be replaced with a last pre-dose result, if available. If no pre-dose laboratory value is available, the baseline value will be assumed to be normal (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities.

Values for missing vital signs data will not be imputed; however, a missing baseline result will be replaced with last pre-dose result, if available.

If needed, completely or partially missing start date for medical history events will be imputed in a conservative fashion as follows:

Date	Type of Missing Date	Handling of Missing Date
Event Start Date (e.g., YYYY-MM-DD)	Completely missing	No imputation will be applied
	Only YYYY is available	Use the first day of YYYY to impute the missing month and date parts of the start date
	YYYY and MM are available, but DD is missing	Use the first day of MM to impute the missing date part of the start date

BLQ PK concentration at pre-dose at Baseline will be imputed as zero and the other pre-dose BLQ PK concentrations will be imputed as half of the low limit of quantification (0.5*LLOQ).

3.2 Analysis Populations

3.2.1 Full Analysis Set (FAS)

The FAS will include all subjects who were randomized and received at least one dose of study drug.

Subjects who receive a dose of study drug other than that to which they were randomized for the entire duration of treatment will be analyzed according to treatment group to which they were randomized.

3.2.2 Per Protocol (PP) Analysis Set

The 36-Week PP Analysis Set will be a subset of the FAS and will include subjects who finish scheduled visits with applicable assessments and do not have major protocol deviations.

The following criteria are evaluated for compliance to the protocol,

- Completed scheduled visits with applicable efficacy assessments (i.e., liver biopsy assessment at baseline and Week 36)
- ≥ 80% of overall treatment compliance
- Treatment duration ≥ 28 weeks
- No major protocol deviations that are likely to affect the primary endpoint

A major protocol deviation is defined as any CSR reportable or non-reportable protocol deviation likely to affect the primary endpoint, which includes, but is not limited to the following:

  - Violations of inclusion/exclusion criteria;
  - Received the wrong treatment;
  - Unscheduled and/or unintended unblinding occurred; and
  - Received a prohibited medication or had a restricted concomitant medication change that is likely to affect the primary endpoint

The 96-Week PP Analysis Set will be a subset of the FAS and will include subjects who finish scheduled visits with applicable assessments and do not have major protocol deviations.

The following criteria are evaluated for compliance to the protocol,

- Completed scheduled visits with applicable efficacy assessments (i.e., liver biopsy assessment at baseline and Week 96)
- ≥ 80% of overall treatment compliance
- Treatment duration ≥ 76 weeks
- No major protocol deviations that are likely to affect the primary endpoint

A major protocol deviation is defined as any CSR reportable or non-reportable protocol deviation likely to affect the primary endpoint, which includes, but is not limited to the following:

  - Violations of inclusion/exclusion criteria;
  - Received the wrong treatment;
  - Unscheduled and/or unintended unblinding occurred; and
  - Received a prohibited medication or had a restricted concomitant medication change that is likely to affect the primary endpoint

3.2.3 Safety Analysis Set

The Safety Analysis Set will include all subjects who received at least one dose of study drug. The Safety Analysis Set will be the analysis set for safety analyses. Subjects in this analysis set will be summarized according to the actual treatment received.

3.2.4 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set will include all randomized subjects who took at least one dose of study drug and for whom concentration data of EFX is available. Subjects in this analysis set will be summarized according to the actual treatment received.

3.2.5 Liver Biopsy Analysis Set (LBAS)

The 36-Week LBAS will be a subset of the FAS and will include all FAS subjects who have Baseline and Week 36 liver biopsy results. It will be the analysis set for histological efficacy analyses at Week 36 including the primary endpoint. The Week 36 liver biopsy includes scheduled Week 36 liver biopsy and unscheduled liver biopsy within the analysis window, analysis day from 113 to 463.

The 96-Week LBAS will be a subset of the FAS and will include all FAS subjects who have Baseline and Week 96 liver biopsy results. It will be the analysis set for histological efficacy analyses at Week 96. The Week 96 liver biopsy includes scheduled Week 96 liver biopsy and unscheduled liver biopsy within the analysis window, analysis day from 464 to EOS.

3.2.6 DXA Analysis Set (DAS)

DAS will be a subset of the FAS. It will include all FAS subjects who have Screening and on-study DXA results. It will be the analysis set for DXA endpoints analyses.

3.2.7 MRE Analysis Set (MAS)

MAS will be a subset of the FAS. It will include all FAS subjects who have Screening and on-study MRE results. It will be the analysis set for liver stiffness by MRE endpoints analyses.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of subjects who were screened (signed informed consent), discontinued early during screening (screen failures), and randomized will be summarized in total based on all screened subjects. Reasons for early discontinuation will also be summarized.

Counts and percentages of subjects in each of the following disposition categories will be presented by treatment and in total based on all randomized subjects:

- Subjects who were randomized
- Subjects who started study drug
- Subjects who completed dosing through Week 36
- Subjects who completed dosing through Week 96
- Subjects who withdrew from the treatment prior to Week 36
- Subjects who withdrew from treatment after Week 36
- Subjects who completed the study
- Subjects who withdrew from the study

For randomized subjects who withdraw from the treatment and withdraw from the study, the primary reason including COVID-19 contributed or the withdrawal will be summarized.

3.3.2 Protocol Deviations

Protocol deviations will be defined in the Protocol Deviation Plan. Counts and percentages of subjects with CSR reportable protocol deviations by deviation category will be summarized by treatment and in total based on all randomized subjects.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarized by treatment and in total based on all randomized subjects.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 , ≥75 years)
- Sex
- Race
- Ethnicity
- Height (cm) at Baseline
- Weight (kg) at Baseline
- Body mass index (BMI) (kg/m^2) at Baseline
- BMI categories at Baseline (<30 kg/m^2, ≥30 kg/m^2)
- Type 2 diabetes status at Baseline from electronic data capture (EDC)
- Statin use at Baseline
- Vitamin E/ Thiazolidinedione use at Baseline
- Diagnosis of Cryptogenic Cirrhosis presumed secondary to NASH at Baseline from EDC
- Definitive NASH at Baseline
- NAS at Baseline including Total NAS, Steatosis, Ballooning and Lobular Inflammation
- Total NAS category (≤3 vs >3) at Baseline
- Pro-C3 (Gen 2 ELISA) , corrected Pro-C3, corrected Pro-C3 /C3M, and ELF score and ELF categories (<11.3, ≥ 11.3) at Baseline
- Liver stiffness (kPa, IQR/M) and CAP (dB/m) by FibroScan®
- FAST Score at baseline
- Liver stiffness by MRE (kPa)
- TG (mg/dL), Total Cholesterol (mg/dL), LDL-C (mg/dL), HDL-C (mg/dL), and non-HDL-C (mg/dL) at Baseline
- HbA1c (%), Adiponectin, Insulin (IU/L), and HOMA-IR at Baseline
- HbAc1 category (<6.5% vs ≥6.5%)
- Baseline HbAc1 in subjects with type 2 diabetes at Baseline from EDC
- Baseline blood pressure (SBP and DBP)
- Baseline SBP category (<130 vs ≥130)
- ALT, AST, ALP, GGT, TB, direct bilirubin, INR, Albumin, Platelets, Uric Acid, Child-Pugh, and MELD at Baseline
- ALT and AST categories at Baseline (≤ULN, >ULN)
- P1NP and CTX-1 at Baseline

- Vitamin D level at Baseline
- GLP-1 usage at Baseline (Yes, No)

GLP-1 RA based therapies use at baseline will include subjects that had a concomitant medication in the preferred terms Semaglutide, Dulaglutide, Liraglutide, Exenatide, or Tirzepatide starting prior to first dose and medication end date is on or after first dose.

For other medication usage at baseline, it is defined as the start date of medication prior to the first dose of study drug.

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total for all randomized subjects and each defined analysis population if the analysis population composition is different than all randomized subjects.

All demographic and baseline characteristics data will be listed by subject.

3.3.5 Medical History

Medical history will be coded to system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. Counts and percentages of subjects with medical history by reported term will be summarized by treatment and in total based on all randomized subjects.

Listing will present SOC, preferred term, and verbatim text by subject.

3.3.6 Prior and Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the World Health Organization (WHO) Drug Dictionary version B3 Global, March 2021. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time on or after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

Counts and percentages of subjects taking concomitant medications by ATC class and preferred term will be summarized by treatment and in total based on the Safety Analysis Set. The use of any prior medication or concomitant medication will be listed for all randomized subjects.

Concomitant insulin usage (Yes, or No) will be summarized. Concomitant insulin usage includes subjects that had a concomitant medication in the ATCs, Insulins and analogues for injection, intermediate-or long-acting combined with fast-acting; insulins and analogues for injection, intermediate-acting; insulins and analogues for injection, fast-acting; insulins and analogues for injection, long-acting.

3.3.7 Study Drug Exposure and Compliance

Weeks of exposure to study drug will be calculated as:

(date of last dose of study drug - date of first dose of study drug + 7) / 7

Weeks of exposure to study drug will be summarized by treatment based on the Safety Analysis Set with descriptive statistics and with counts and percentages of subjects with exposure in the following categories:

- > 0 to ≤ 12 weeks
- > 12 to ≤ 24 weeks
- > 24 to ≤ 36 weeks
- > 36 to ≤ 48 weeks
- > 48 to ≤ 52 weeks
- > 52 to < 96 weeks
- ≥ 96 weeks

The total number of injections administered will be calculated for each subject. A contingency table will be provided to display the number and percentage of subjects in each treatment group with the following above drug exposure weeks.

Study drug compliance will be calculated as:

$$\text{Compliance rate for each patient} = \frac{\text{Number of injections administered}}{\text{Number of injections expected}} * 100$$

where number of injections expected is the weeks of exposure to study drug.

Descriptive statistics for study drug compliance will be presented by treatment group. In addition, the number and percentage of subjects with treatment compliance of the following categories will be summarized by treatment group:

- <80%,
- ≥80% to ≤100% and
- >100%.

Subjects that receive less than 80% of the planned doses of study drug are considered noncompliant. The frequency and percentage of subjects who are compliant and noncompliant will be summarized by treatment group.

3.4 Efficacy Assessment

The primary efficacy endpoint and all other histological efficacy data will be summarized and analyzed by randomized treatment in the LBAS. Efficacy analysis will be performed by treatment group. In addition, all EFX subjects will be combined as "All EFX" group in all histology analyses and for other efficacy parameters as appropriate.

Non-histological efficacy data will be summarized and analyzed by randomized treatment in the FAS, without imputing missing data.

3.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the proportion of subjects who achieve ≥ 1 stage improvement in fibrosis (based on NASH CRN fibrosis score) and no worsening of steatohepatitis at Week 36 in the LBAS.

Evaluation of fibrosis stage will be based on NASH CRN Fibrosis Staging System described in live biopsy management manual Table 1. For analysis purposes, NASH CRN fibrosis stages 1, 1A, 1B, and 1C will all be considered as stage 1. No worsening of steatohepatitis is defined as

no increase in score for any of the 3 components of NAS. The evaluation of the NAS endpoint will be calculated using the following 3 categorical features: steatosis [0-3], lobular inflammation [0-3], and hepatocellular ballooning [0-2]. In this study, NAS will be derived as the unweighted sum of steatosis, lobular inflammation, and hepatocellular ballooning scores. The scores will be assigned as defined in live biopsy management manual Table 1.

3.4.1.1 Primary Estimand

The estimand for the primary histological endpoint of this study is defined as follows:

1. Treatment: EFX 28 mg, EFX 50 mg, and placebo.
2. Population: subjects with compensated cirrhosis due to NASH as defined by the inclusion/exclusion criteria.
3. Endpoint: the proportion of subjects who achieve ≥ 1 stage improvement in fibrosis (based on NASH CRN fibrosis score) and no worsening of steatohepatitis at Week 36.
4. Inter-current events and their corresponding approaches: the following intercurrent events will be handled using the composite variable strategy,

Intercurrent Event	Status
Liver Transplant	Subject defined as a non-responder (even if a post-treatment biopsy is available)
Adjudicated MELD score ≥ 15	
Adjudicated Hepatic decompensation event	
Bariatric surgery (e.g. gastroplasty, Roux-en-Y gastric bypass) performed prior to biopsy at Week 36	Subject defined as a non-responder

5. Population level summary: the treatment effect will be quantified by comparing observed responder proportions supported by the risk ratio of EFX compared to placebo (EFX 28 mg versus placebo or EFX 50 mg versus placebo) calculated from the odds ratio obtained through a CMH test.

3.4.1.2 Primary Analysis

Between-group comparisons (EFX doses vs placebo) of proportions of subjects who achieve a ≥ 1 stage improvement in fibrosis without worsening of steatohepatitis at Week 36 will be performed using the CMH test stratified by baseline T2D status (Yes vs No) from EDC and diagnosis of cryptogenic cirrhosis presumed secondary to NASH (Yes vs No) from EDC.

The primary efficacy endpoint will be tested at Type I error rate of 0.05, two-sided without adjustment for multiplicity for the comparisons between EFX arms and the placebo arm. For each treatment group to placebo, the odds ratio, risk ratio and the corresponding 95% confidence intervals (CI) will be provided. The point estimates and 95% CI for the treatment group differences in proportions will be calculated using the method developed by Miettinen and Nurminen (1985). The general association p-value will also be provided.

Counts and percentage of responders in each treatment group will be provided.

The SAS sample code can be found below:

****

```
      TREATMENT: 0 (Placebo), 1 (EFX 28 mg), 2 (EFX 50 mg),
      T2D : yes or no
      DiagSecondarytoNASH: yes or no
      Responder: yes or no
    ************************************************************************;
    proc freq data=Dataset;
    tables T2D*DiagSecondarytoNASH*TREATMENT*RESPONDER / cmh
riskdiff(common);

    run;
```

3.4.1.3 Sensitivity Analysis

The following sensitivity analyses will be performed for the primary endpoint and key histology endpoints:

- The primary analysis will be repeated on the 36-Week PP analysis set. No imputation will be performed.
- The primary endpoint analysis will be repeated in the 36-Week LBAS with stratification factors from IRT.
- The primary endpoint analysis will be repeated in the FAS where subjects with missing biopsies will be considered non-responders.
- The primary endpoint analysis will be repeated in the FAS with multiple imputation (MI) using logistic regression under the assumption of missing not at random (MNAR).

Multiple Imputation Method:

The multiple imputation procedure will be conducted by two parts: PROC MI and PROC MIANALYZE

- Multiple imputation (using SAS® PROC MI). Missing data will be imputed 100 times to generate 100 complete data sets via a placebo-based pattern mixture model under missing not at random (MNAR) assumption. The seed will be 98765. The imputed values will be obtained using a logistic model with baseline T2D status (yes or no) from EDC, baseline diagnosis of cryptogenic cirrhosis presumed secondary to NASH (yes or no) from EDC, and Age category at Baseline (<65 or ≥65).

The SAS sample code can be found below:

```
    ************************************************************************
      TREATMENT: 0 (Placebo), 1 (EFX 28 mg), 2 (EFX 50 mg),
      T2D: yes or no
      DiagSecondarytoNASH: yes or no
      AGE_Group: <65 or ≥65
      Responder: yes or no
    ************************************************************************;
    proc mi seed=98765 nimpute=100;
    class TREATMENT RESPONDER T2D DiagSecondarytoNASH AGE_Group;
    monotone logistic(RESPONDER=TREATMENT T2D DiagSecondarytoNASH AGE_Group);
    mnar model(RESPONDER/modelobs=(TREATMENT=0));
    var TREATMENT RESPONDER T2D DiagSecondarytoNASH AGE_Group;
run;
```

If the imputation model does not converge, the model may be reduced to include stratification factors only.

- Analysis of imputed datasets. Each of the 100 completed data sets will be analyzed using the CMH test described above.
- Combination estimated across imputed datasets (using SAS PROC MINANLYZE). The results from the 100 completed data sets obtained in the analysis step are combined for the inference. The pooled estimate of the response rate along with two-sided 95% CI for each treatment arm will be obtained using the method developed by Rubin (1987).

For the endpoint of fibrosis improvement >= 1 stage at Week 96 with no worsening of NAS at Week 96 only, an additional multiple imputation analysis will be performed with the model constructed from the same covariates as the placebo-based pattern mixture model described above, but using all complete cases (i.e. specifying option modelobs = CCMV in code above) to perform the imputation.

3.4.1.4 Subgroup Analysis

Subgroup analyses will be performed for the primary efficacy endpoint. The primary analysis will be repeated for the following group variables,

- Age (<65 years, ≥65 years, ≥75 years)
- Sex
- Ethnicity (Hispanic vs not)
- Type 2 diabetes status at Baseline (Yes, No)
- NAS category (≤3, >3)
- Cryptogenic cirrhosis presumed secondary to NASH vs Definitive NASH at Baseline
- Duration of cirrhosis diagnosis ≥1 year vs < 1 year relative to first dose
- Statin use at Baseline (Yes, No)
- BMI at Baseline (<median vs ≥median)
- ELF at Baseline (<11.3, ≥11.3)
- Liver stiffness > 20 vs ≤20 by FibroScan
- GLP-1 RA based therapies at baseline (Yes, No)

GLP-1 RA based therapies use at baseline will include subjects that had a concomitant medication in the preferred terms Semaglutide, Dulaglutide, Liraglutide, Exenatide, or Tirzepatide starting prior to first dose and medication end date is on or after first dose.

3.4.2 Secondary Efficacy Endpoints

The estimand attributes for all secondary histological endpoints are defined in the same manner as for the primary endpoint in Section 3.4.1.1. Stratification factors will be based on EDC.

The following secondary efficacy endpoints are listed to evaluate the effect of EFX on achieving NASH resolution and fibrosis regression:

- Proportion of subjects who achieve NASH resolution defined as ballooning = 0 and inflammation = 0 or 1, determined by the NASH CRN criteria at Week 36 and Week 96

- Proportion of subjects who achieve ≥ 1 stage improvement in fibrosis and no worsening of steatohepatitis at Week 96
- Proportion of subjects who achieve ≥ 1 stage improvement in fibrosis at Week 36 and Week 96
- Proportion of subjects who achieve NASH resolution (defined as a NAS of 0-1 for inflammation and 0 for ballooning) and ≥ 1 stage improvement in fibrosis (based on NASH CRN fibrosis score) at Week 36 and Week 96

The between-group comparisons (EFX doses vs placebo) of proportions will be analyzed using the CMH test stratified by baseline T2D status (Yes vs No) and diagnosis of cryptogenic cirrhosis presumed secondary to NASH (Yes vs No). The analysis will be performed using the 36-Week LBAS and 96-Week. For each treatment group to placebo, the odds ratio, risk ratio, and the corresponding 95% CI will be provided. The point estimates and 95% CI for the treatment group differences in proportions will be calculated. The general association 2-sided p-value will also be provided.

Counts and percentage of responders in each treatment group will be provided.

In addition, descriptive shift tables by treatment group showing the subject counts for shift in response from Week 36 to Week 96 will be generated as follows (for the Week 36 LBAS):

- Subjects achieving ≥ 1 stage improvement in fibrosis and no worsening of steatohepatitis at Week 36 vs subjects achieving ≥ 1 stage improvement in fibrosis and no worsening of steatohepatitis at Week 96.
- Subjects achieving NASH resolution at Week 36 vs subjects achieving ≥ 1 stage improvement in fibrosis and no worsening of steatohepatitis at Week 96 (subjects with definitive NASH at baseline only)
- Subjects achieving NASH resolution at Week 36 vs subjects achieving NASH resolution at Week 96 (subjects with definitive NASH at baseline only)
- Subjects who achieve NASH resolution and ≥ 1 stage improvement in fibrosis at Week 36 vs subjects who achieve NASH resolution and ≥ 1 stage improvement in fibrosis at Week 96 (subjects with definitive NASH at baseline only)

In addition, the shift tables using the same row and column variables will summarize:

The proportion of subjects with a maintained response at Week 96 from Week 36, defined as the proportion of subjects with response at Week 36 that also responded at Week 96 divided by the total number of responders at Week 36 that had a Week 96 biopsy.

The proportion of subjects with a new response at Week 96 from Week 36, defined as the proportion of subjects with no response at Week 36 that responded at Week 96 divided by the total number of non-responders at Week 36 that had a Week 96 biopsy.

The endpoint analyses at Week 36 and Week 96 will be repeated in:

- The FAS where subjects with missing biopsies will be imputed using placebo-based multiple imputation method.
- The FAS where subjects with missing biopsies will be considered non-responders.

- The 36-Week and 96-week PP analysis set.

For all analyses of NASH resolution, any subjects meeting baseline scores of 0 on ballooning and 0 or 1 on inflammation, will be excluded.

The following secondary efficacy endpoints are listed to evaluate treatment effect via analyzing the changes from baseline.

- Absolute and percentage change from baseline in Pro-C3 (Gen2 ELISA), corrected Pro-C3, and liver stiffness by FibroScan®.
- Absolute change from baseline in ELF score, components of ELF, and FAST score.

$$\text{FAST} = \frac{e^{-1.65 + 1.07*\ln(LSM) + 2.66*10^{-8}*CAP^3 - 63.3*AST^{-1}}}{1 + e^{-1.65 + 1.07*\ln(LSM) + 2.66*10^{-8}*CAP^3 - 63.3*AST^{-1}}}$$

- Absolute and percentage change from baseline in TG, total cholesterol, HDL-C, non-HDL-C, and LDL-C
- Absolute and percentage change from baseline in HbA1c, C-Peptide, adiponectin, insulin, and HOMA-IR
    - Subgroup analyses by Baseline T2D status
- Absolute and percentage change from baseline in body weight

For the other continuous secondary efficacy endpoints with more than one post baseline measurements, the change from baseline will be analyzed using mixed-model repeated-measures (MMRM), including fixed effects for treatment group, visit, the treatment group by visit interaction, stratification factors, and the baseline value as a covariate. An unstructured covariance matrix will be used (TYPE = UN). All analyses will be performed using the FAS. No imputation will be performed.

The SAS sample code can be found below:

```
**********************************************************************
  USUBJID: Unique subject identifier
  TREATMENT: 0 (Placebo), 1 (EFX 28 mg), 2 (EFX 50 mg)
  T2D : yes or no
  DiagSecondarytoNASH: yes or no
  BASE: Baseline Value for Specified parameter
  VISIT: All Scheduled Visits
  CHG: Change from baseline to each scheduled visit for specified
parameter
**********************************************************************;
proc mixed;
  class USUBJID T2D DiagSecondarytoNASH TREATMENT VISIT;
  model CHG = T2D DiagSecondarytoNASH TREATMENT BASE VISIT
TREATMENT*VISIT;
  Repeated VISIT / TYPE=UN sub=USUBJID;
  lsmeans VISIT*TREATMENT / cl pdiff slice=VISIT;
run;
```

Least-squares (LS) means for change from baseline will be provided for each treatment group and the difference between each EFX group and placebo will be estimated with the 2-sided

p-value and 95% CIs. Normality of the data distribution will be tested for the model residuals by the Shapiro-Wilk normality test.

Descriptive statistics on the values and changes from baseline will be presented for the continuous secondary efficacy parameters at each scheduled visit defined in the Schedule of Assessments (Appendix A and Appendix B in protocol) by treatment group.

For ELF and liver stiffness by FibroScan®, scatter plots for each time point and boxplots of changes from Baseline by visit will be provided for each treatment group. In addition, spaghetti plots of individual subject versus time points will be created for each treatment group. Plot of LS Mean and standard error of change from baseline in corrected Pro-C3 over time will be provided for each treatment group.

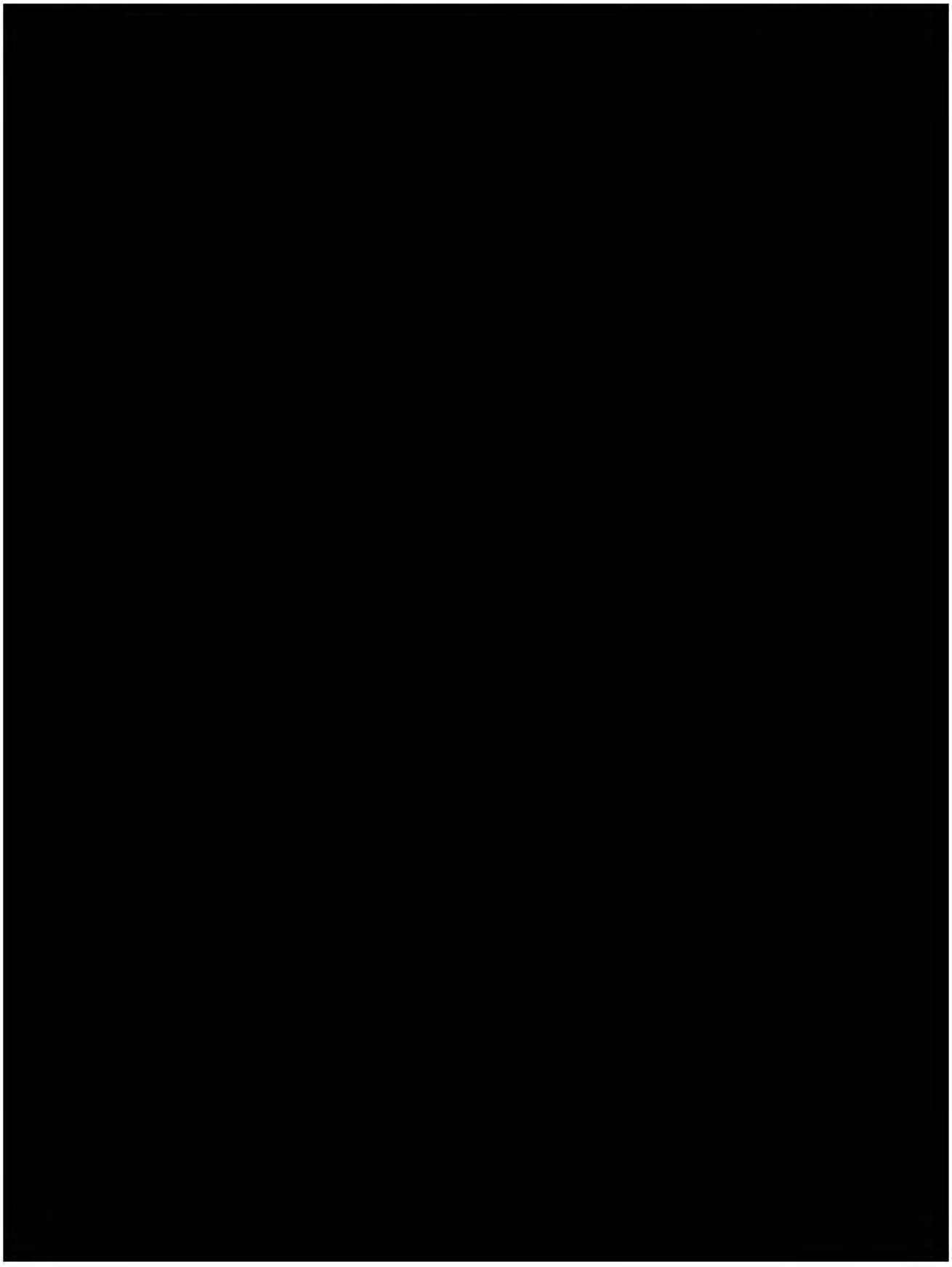
A sensitivity analysis will be performed at the end of study analysis for the liver stiffness by FibroScan® parameter excluding assessments that did not meet quality criteria (e.g. assessments failing quality metrics such as those with IQR/Median >30%). Subjects with baseline assessment not meeting the quality criteria will be excluded from the sensitivity analysis.



[redacted]

[redacted]

[redacted]



3.5 Safety Assessment

The safety of EFX will be assessed during the study through the reporting of AEs, clinical laboratory tests, ECG, ultrasounds, vital sign assessments, ADA and NAb assessments.

All safety data collected on or after the date that study drug is first dispensed up to the date of last dose of study drugs plus 30 days will be summarized by treatment group. Data for the follow-up period will be included in data listings.

Safety data will be summarized by actual treatment received (and in total for selected analyses) based on the Safety Analysis Set unless otherwise specified.

3.5.1 Adverse Events

All AEs will be coded to system organ class and preferred term using MedDRA version 24.0

Treatment-emergent adverse events (TEAEs) are defined as one or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drugs.

Injection site reactions, diarrhea, hypoglycemia, neurological and psychiatric events and drug-induced liver injuries (DILI) will be monitored as AEs of special interest (AESIs) during this study.

An overview of AEs will be provided including counts and percentages of subjects with the following:

- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs (overall and by maximum severity)
- Any study procedure related TEAEs (overall and by maximum severity)
- Any TEAEs of special interest (overall, injection site reactions, diarrhea, hypoglycemia, neurological and psychiatric events, DILI)
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to premature discontinuation of study drug prior to Week 36
- Any TEAEs leading to premature discontinuation of study drug after Week 36
- Any TEAEs leading to premature discontinuation of study drug
- Any TEAEs leading to premature discontinuation of study
- Any drug-related TEAE leading to discontinuation of study drug
- Any SAEs leading to death

Counts and percentages of subjects will also be presented by system organ class and preferred term for each of the categories in the overview and a summary TEAE table with preferred term with incidence rate >= 15% in any treatment group, as well as the same table for TEAEs related to study drug. AESI will be summarized by system organ class and preferred term in each

category. Listings will be provided of all AEs, including AESIs, SAEs, TESAE, TEAEs leading to discontinuation of study drug, drug-related TEAEs leading to discontinuation of study drug, and leading to discontinuation of study drug prior to Week 36, and SAEs leading to death.

3.5.2 Adjudication Committees

External adjudication committees will be established to adjudicate cardiovascular events and cases that meet protocol-defined criteria for liver-related events for the study.

Counts and percentages of subjects who experienced potential hepatic events and cardiovascular events will be presented by treatment group.

Subjects with confirmed adjudicated events will be listed.

3.5.3 Clinical Laboratory Tests

Chemistry, hematology, coagulation and others samples will be collected at the time points listed in the Schedule of Assessments(Appendix A and Appendix B in protocol).

All continuous central laboratory parameters will be summarized descriptively by value at baseline and each planned post-baseline visit, together with the corresponding changes from baseline. All categorical laboratory parameters will be tabulated at baseline and each planned post-baseline visit.

For the selected parameters, graded treatment-emergent laboratory abnormalities will be presented for laboratory data using the grading scheme in the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Laboratory	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Blood bilirubin increased	Total Bilirubin >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	Total Bilirubin >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	Total Bilirubin >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	Total Bilirubin >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline;	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN

Laboratory	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
			>1.5 - 3.0 x ULN		
	CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
	Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L	Potassium >6.0 - 7.0 mmol/L	Potassium >7.0 mmol/L
	Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
	Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L;
	GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Hematology	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 – 80 g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L	
	Hemoglobin increased	Hemoglobin > ULN & Increase in >0 - 2 g/dL	Hemoglobin > ULN & Increase in >2 - 4 g/dL	Hemoglobin > ULN & Increase in >4 g/dL	
	lymphocytes count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 x 0.2 - 10e9 /L	<200/mm3; <0.2 x 10e9 /L
	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
Coagulation	INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation	>2.5; >2.5 x baseline if on anticoagulation	

For the other parameters, the incidence of abnormalities (as defined by normal ranges) prior to the first dose of study drug and after the first dose of study drug will be summarized with counts and percentages of subjects.

The incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drugs plus 30 days, will be summarized with counts and percentages of subjects by treatment group. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment-emergent. If no pre-treatment laboratory value is available, the baseline value will be assumed to be normal (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities.

Evaluation of drug-induced serious hepatotoxicity (eDISH) plot will be provided to display peak serum ALT and TB levels for each subject. The peak serum AST versus TB levels for each subject will also be provided.

3.5.4 Abdominal Ultrasound

Abdominal ultrasounds will be performed and read locally at Screening, Week 24, Week 48, Week 72 and Week 96 to monitor liver and gallbladder health.

Counts and percentages of subjects who have abnormal gallbladder and liver findings or not will be presented by treatment group for each visit.

Abdominal ultrasounds data including any abnormal gallbladder and liver findings, and potential hepatocellular carcinoma, will be listed for all subjects.

3.5.5 Vital Signs

Height will be measured without shoes at Screening. Temperature will be collected at the Screening and Day 1 visits only. Other vital signs (body weight, BMI, systolic and diastolic blood pressure, heart rate, and respiration rate) will be measured as outlined in the Scheduled of Assessment (Appendix A and Appendix B in protocol). Triplicate vital sign measurement including systolic blood pressure, diastolic blood pressure, and heart rate will be performed at Baseline (Day 1), Weeks 12, Week 36, Week 48 and Week 96.

Values and changes from baseline to each visit and timepoint for vital signs will be summarized descriptively. Triplicate measurements will be averaged prior to summary.

For optional PK substudy, triplicate vital sign data will be averaged and summarized for each visit.

3.5.6 12-Lead Electrocardiograms

12-lead ECG will be measured at Screening, Baseline (Day 1), Week 36, Week 48, Week 72 and Week 96.

Values and changes from baseline of ECG parameters (heart rate, PR interval, QRS Interval, QT interval, QTcF interval and RR interval) and overall interpretation will be summarized by visit. The number and percentage of subjects with absolute QTcF interval values in the pre-specified categories (>450, >480, and >500 msec), and QTc interval change (>30 and >60 msec) will be summarized.

3.5.7 Immunogenicity Analysis

The incidence of pre-existing, treatment-emergent positive ADA, positive ADA at any time point, negative ADA at all time points, and NAb, if any, will be summarized by treatment and period. Pre-existing ADA is defined as positive ADA result at or before dosing. Treatment emergent positive ADA is defined as a negative result at or before dosing and positive result post dose. Titers will also be summarized descriptively for positive ADAs.

Efficacy and safety variables may be analyzed based on the positive ADA and negative ADA subjects. Additionally, the impact of immunogenicity on PK and pharmacodynamics will be analyzed.

All ADA and NAb data will be listed.

3.6 PK Assessment

PK sampling will be obtained pre-dose at the time points listed in the Schedule of Assessments (Appendix A and Appendix B in protocol). Approximately 18 subjects who provide their additional specific consent will participate in the optional PK substudy. Serial blood sample will be collected relative to the first dose of study drug on Day 1 (Table 9 in protocol). In addition, sparse PK samples will be collected 48 to 96 hours post-dose following any 2 visits between Week 6 and Week 12, inclusive.

Plasma EFX concentrations will be listed and summarized by treatment group, visit, and time point for the PK Analysis Set.

3.7 Optional Genetic Substudy

For subjects who provide their additional specific consent for the optional genomic substudy, a blood sample will be collected on Day 1.

Optional genetic substudy data will be listed.

3.8 Optional Peripheral Blood Mononuclear Cell Substudy

Approximately 75 subjects who provide their additional specific consent will participate in the optional peripheral blood mononuclear cell (PBMC) substudy. Blood samples will be collected on Day 1, Week 4, Week 20, Week 36, Week 52, Week 96, Early Termination, and 30-day Follow-up Visit.

Optional PBMC substudy data will be summarized descriptively and listed.

4 DATA MONITORING COMMITTEE (DMC)

An external DMC that consists of at least one hepatologist, one endocrinologist, one cardiologist and one statistician will review the progress of the study. The DMC will convene after approximately 50% subjects have received at least 1 dose of study drug and have either completed the Week 12 assessments or prematurely discontinued. The DMC will receive all reports of SAEs, potential DILI events for evaluation and convene as needed to monitor for safety. The DMC will provide recommendations to Akero whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

While the DMC will be asked to advise Akero regarding future conduct of the study, including possible early study termination based on the stopping rules from the protocol, Akero retains final decision-making authority on all aspects of the study.

5 INTERIM ANALYSIS

No formal interim analysis is planned. However, a Week 36 primary endpoint analysis is planned after all randomized subjects have completed their Week 36 visit (or prematurely discontinued from the study prior to Week 36).

At the database lock for the Primary Analysis, an unblinded statistical team will analyze the data. All the details will be provided in a separate unblinding plan.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

No additional changes is applicable.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

[1] Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4: 213–226

[2] Newsome PN, Sasso M, Deeks JJ, Paredes A, Boursier J, Chan WK, Yilmaz Y, Czernichow S, Zheng MH, Wong VW, Allison M, Tsochatzis E, Anstee QM, Sheridan DA, Eddowes PJ, Guha IN, Cobbold JF, Paradis V, Bedossa P, Miette V, Fournier-Poizat C, Sandrin L, Harrison SA. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol. 2020 Apr;5(4):362-373