akero

Statistical Analysis Plan

Akero Therapeutics, Inc

AK-US-001-0102

A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND EFFICACY OF EFRUXIFERMIN IN NON-CIRRHOTIC SUBJECTS WITH NONALCOHOLIC STEATOHEPATITIS (NASH)

[redacted]

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Reviewers

The following reviews of the SAP were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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Glossary of Abbreviations

Abbreviation	Term
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
Apo	Apolipoprotein
AST	aspartate aminotransferase (SGOT)
ATC	anatomical therapeutic chemical
BLQ	below limit of quantification
BMD	Bone Mineral Density
BMI	body mass index
CAP	controlled attenuation parameter
CI	confidence interval
CLDQ	Chronic Liver Disease Questionnaire
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus-19 infection
CP	Child-Pugh
CRN	Clinical Research Network
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DXA	Dual Energy X-ray Absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDISH	evaluation of drug-induced serious hepatotoxicity
EFS	event-free survival
EFX	efruxifermin
ELF	Enhanced Liver Fibrosis Panel
EOS	End of Study
ET	Early Termination
FAS	full analysis set
US FDA	United States Food and Drug Administration
FGF21	fibroblast growth factor 21
GGT	gamma glutamyl transferase
H	high
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HE	hepatic encephalopathy
HLGT	high-level group term
HLT	high-level term
HOMA	homeostasis model assessment of insulin resistance, (HOMA-IR) and beta cell function (HOMA-B)
INR	International Normalized Ratio
IQR	interquartile range
kPa	kilopascal

Abbreviation	Term
L	low
LBAS	liver biopsy analysis set
LDL-C	low-density lipoprotein cholesterol
LDL-P	low-density lipoprotein particle
LLN	lower limit of normal
LLOQ	low limit of quantification
LLT	low-level term
Lp	Lipoprotein
LS	least square
LSM	liver stiffness measurement
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MFAS	Modified Full Analysis Set
MMRM	mixed-model repeated-measures
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging – proton density fat fraction
NAb	neutralizing antibody
NAFLD	non-alcoholic fatty liver disease
NAS	non-alcoholic fatty liver disease activity score
NASH	nonalcoholic steatohepatitis
NCI	National Cancer Institute
NMR	nuclear magnetic resonance
PK	pharmacokinetics
PPS	per-protocol set
Pro-C3	N-terminal Type III Collagen Propeptide
PT	preferred term
QTcF	Fridericia corrected QT interval
QW	every week
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
T2D	type 2 diabetes
TB	Total bilirubin
TEAE	treatment emergent adverse event
TESAE	treatment-emergent serious AE
TFLs	tables, figures and listings
ULN	upper limit of normal
WHO	World Health Organization

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	18 Apr 2022	Amendment 4
eCRF	17 Aug 2021	PROD 3.0

This SAP describes listings, summaries, and analyses of data collected from Screening through the Week 24 visit or Early Termination, the 30-Day Follow-up visit, and also during long-term follow-up through Week 96 of subjects enrolled in this Phase 2b study.

2. Protocol Details

2.1

2.1.3 [redacted]

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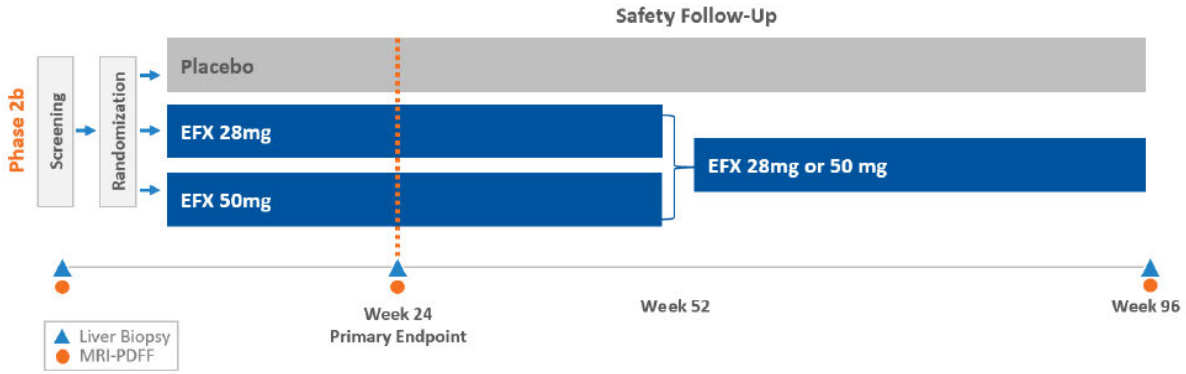
2.2 Overall Study Design

[redacted]

[redacted]

[redacted]



[redacted]

2.3 [redacted]

[redacted]

3. Efficacy and Safety Variables

3.1 Primary Efficacy Endpoint

The primary endpoint is:

- Proportion of subjects who achieve improvement in liver fibrosis, defined as ≥ one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis) at Week 24.

3.2 Secondary Efficacy Endpoints

The secondary endpoints are:

- Proportion of subjects who achieve resolution of steatohepatitis (defined as a NAS of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) and no worsening of liver fibrosis as determined by the NASH CRN criteria at Week 24 and Week 96.
- Proportion of subjects who achieve improvement in liver fibrosis by ≥ one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis) at Week 96.
- Proportion of subjects who achieve improvement in liver fibrosis by ≥ one stage (NASH CRN fibrosis score) at Week 24 and Week 96.
- Change from baseline in hepatic fat fraction measured by MRI-PDFF at Week 24 and Week 96.
- Change from baseline of lipoproteins – Lp (a), total cholesterol, triglycerides, Non-HDL-C, HDL-C, LDL-C, and LDL-P and in markers of lipid metabolism (ApoB and ApoC-III).
- Change from baseline of markers of glycemic control – HbA1c, C-peptide, Adiponectin and HOMA-IR.
- Change from baseline in non-invasive markers of fibrosis – ELF, Pro-C3, C3M, NIS-4 and liver stiffness assessed by transient elastography (FibroScan®).
- Change from baseline of body weight.

3.3 Exploratory Efficacy Endpoints

The exploratory endpoints are:

- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
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3.4 Estimands

In line with ICH E9 (R1) addendum, five attributes (treatment, population, endpoint, intercurrent events, and population-level summary) have been specified to translate the primary efficacy objective into treatment effect that is to be estimated (estimand).

The treatment conditions of interest are EFX 28 mg administered weekly, and EFX 50 mg administered weekly, and are compared with matching placebo administered weekly in addition to standard of care.

The population of subjects targeted is adults with NASH with liver fibrosis as defined by the inclusion/exclusion criteria.

The treatment effect is assessed by the primary histological endpoint of improvement in liver fibrosis and no worsening of steatohepatitis at Week 24.

Intercurrent events are handled through a composite strategy (see Table 1).

The population-level summary of the treatment effect will be quantified by comparing observed responder proportions supported by the risk ratio of each investigational product compared to placebo (EFX 28 mg versus placebo or EFX 50 mg versus placebo) calculated from the odds ratio obtained through Cochran-Mantel-Haenszel (CMH) test detailed in the Section 7.6.1.

Table 1 Approach for Intercurrent Events for the Primary Endpoint at Week 24

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The estimands attributes for all secondary and exploratory histological endpoints are defined in the same manner as for the primary endpoint described above.

3.5 Safety Variables

The safety measurement is the safety and tolerability of EFX in NASH subjects with stage 2 or 3 fibrosis.

Safety analyses include: summaries of extent of exposure, adverse events (AEs), clinical laboratory evaluations, endogenous FGF21, Bone Mineral Density (BMD), vital sign assessments, electrocardiogram (ECG), body weight, anti-drug antibody

(ADA) and neutralizing antibody (NAb) assessments, and concomitant medication usage.

- Adverse events (AEs) and serious adverse events (SAEs): From the time of obtaining informed consent until 30 days after the last administration of study drug, all SAEs and non-serious AEs related to protocol-mandated procedures will be recorded on the SAE/AE eCRF. All other untoward medical occurrences observed during screening, including exacerbation or changes in medical history, will be captured on the medical history eCRF.

  The Investigator will assign the following AE attributes:

  - AE diagnosis or syndrome(s) (if not known, signs or symptoms)
  - Dates of onset and resolution (if resolved)
  - Seriousness
  - Severity
  - Relatedness to study drug or study-related procedures
  - Action taken with study treatment
- Adverse events of special interest (AESIs): The following conditions. assessed by clinical and laboratory evidence, will be monitored as AESIs during this study:
  - Injection Site Reactions
  - Diarrhea
  - Hypoglycemia
  - Neurological and Psychiatric Events
  - Adjudicated DILI Events

  Suspected DILI events will be assessed and adjudicated by the Data Monitoring Committee (DMC).

  During the course of the study, additional AESIs may be identified by the Sponsor. The Investigator will assess and record in detail any additional information for AESIs on the AE eCRF.
- Overdose: Any overdose, with or without associated AEs, will be recorded as non-compliance on the eCRF.

4. Pharmacokinetic/Pharmacodynamic variables

Pharmacokinetic samples to assess plasma EFX concentrations will be collected at specified time points as defined in the Schedule of Assessments.

No pharmacodynamic endpoint is identified in protocol.

5. Analysis populations

The study analysis sets are detailed below.

5.1 All Randomized Subjects

All subjects randomized will be included in the All Randomized Subjects set.

5.2 Liver Biopsy Analysis Set

The primary analysis set for histological analyses will be the Liver Biopsy Analysis Set (LBAS) which will be a subset of the Full Analysis Set (FAS). It will include all FAS subjects who have baseline and on-study liver biopsy results corresponding to the appropriate time point.

Note: Week 24 and Week 96 LBAS populations may be distinct analysis populations.

5.3 Full Analysis Set

The analysis set for non-histological efficacy analyses will be the FAS which will include all subjects who were randomized into the study.

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 the treatment group to which they were randomized.

5.4 Modified Full Analysis Set

The analysis set for additional supplementary efficacy analyses will be the MFAS which will include all subjects who were randomized into the study 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 the treatment group to which they were randomized.

5.5 Safety Set

The analysis set for safety analyses will be the Safety Set which includes all subjects who received at least one dose of study drug.

All subjects who receive at least one dose of study drug will be included in the Safety Set. All safety endpoints will be summarized using the Safety Set and will be based on the actual treatment received if this differs from the randomized treatment. Some endpoints may be analyzed in additional populations or subgroups.

5.6 Pharmacokinetics Set

The Pharmacokinetics (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.

5.7 Biomarkers Analysis Set

The Biomarkers Analysis Set will include data from subjects in the Safety Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific biomarkers or parameters of interest.

5.8 MRI-PDFF Analysis Set

The MRI-PDFF Analysis Set will be a subset of the FAS. It will include all FAS subjects who have baseline and on-study measurements assessed by MRI-PDFF.

5.9 Per Protocol Set

The Per Protocol Set (PPS) will be a subset of the LBAS and will include subjects who finish at least 16 weeks of dosing, are evaluated for NASH CRN fibrosis stage and NAS at Week 24 (or early termination after 22 weeks on treatment) and do not have important protocol deviations.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data, or that may significantly affect a subject's rights, safety, or well-being. Section 5.9.1 details the deviations that will be considered as basis to exclude subjects from PPS.

5.9.1 Important Protocol Deviations Leading to Exclusion from the PPS Analysis

The occurrence of any deviation listed in Table 2 might have an important influence on the primary efficacy endpoint and will be reviewed to determine subjects

excluded from the PPS. Protocol waivers will not be taken into consideration (e.g. if a subject used a prohibited medication during the study, the subject would be excluded from the PPS).

Table 2 Data Review to Identify Important Protocol Deviations

Type	Important Protocol Deviation Leading to Exclusion from the PPS	Method of Identification
Inclusion/Exclusion Criteria	Subject with violations of eligibility criteria.	Programmable check of eligibility eCRF as per Protocol Deviation Management Plan
Inclusion Criteria 8-9	Subject was not on stable dose of medications prior to screening	Medical monitoring review of prior medications eCRF
Prohibited medication	Subject who used prohibited concomitant medications (Table 3 of clinical study protocol) with significant potential to affect the results/interpretation of the on-treatment liver biopsy.	Medical monitoring as per Protocol Deviation Management Plan (see notes below)
Week 24 liver biopsy not conducted or outside of window	Subject's Week 24 liver biopsy was not conducted or was outside of the acceptable study window (i.e., within 22 to 28 weeks of Day 1).	Programmable check of time window of Week 24 liver biopsy
Minimum exposure to study treatment	A subject who did not receive at least 16 doses of the randomized treatment at the time of Week 24 liver biopsy.	Programmable check of eCRF Study drug administration record and Week 24 liver biopsy date.
Accidental or Emergency Unblinding	A subject with a record of accidental or emergency unblinding in the interactive web response system.	Medical monitoring review of blinded interactive web response system
Errors in Treatment Allocation	A subject who received more than two doses different from the randomized treatment.	Biometrics review of unblinded interactive web response system

Type	Important Protocol Deviation Leading to Exclusion from the PPS	Method of Identification

Notes:
Prohibited Medication. The project physician will review concomitant medications to identify subject who used prohibited concomitant medications (Table 3 of clinical study protocol) or did not maintain stable dose levels of conditionally allowed concomitant medications (Table 4 of clinical study protocol) during the study. Any subject excluded from the PPS for prohibited medication will be identified prior to database lock and unblinding.

Errors in Treatment Allocation. A subject who received more than two doses different from the randomized treatment will be excluded from the PPS. The assessment must be made by the biometrics project team after the study is unblinded, unless arrangements are made for an independent programmer/statistician to do this beforehand.

As defined in the table, a number of the important protocol deviations leading to exclusion from the PPS will be determined programmatically from the data. Those criteria which require clinical or medical monitoring interpretation will be reviewed and classified prior to database lock.

Each important protocol deviation leading to exclusion from the PPS occurring during the study will be reviewed and approved by Akero Therapeutics prior to database lock and unblinding. Should additional important protocol deviations leading to exclusion from the PPS, not anticipated at the time of preparing this SAP, be identified during the study (and prior to unblinding) they will be documented in a Per Protocol Set Identification Summary and included in all relevant protocol deviation reviews and approvals.

5.10 Special Subpopulations

Efficacy, safety, and baseline characteristics will be pooled across randomization stratification groups and summarized by treatment group. Analysis populations are specified in Table 3.

Table 3 Summary of Outcome Variables and Analysis Sets

Outcome Variable	***Analysis Set(s)***
Disposition and Baseline	
Screening	All Consented Subjects
Disposition, Analysis Populations, Protocol Deviations, Demographics and Baseline Characteristics, Medical History	All Randomized Subjects
Efficacy and Clinical Endpoints	

Outcome Variable	***Analysis Set(s)***
Primary: improvement in liver fibrosis (≥ one stage) and no worsening of steatohepatitis at Week 24	LBAS PPS FAS
Secondary: resolution of steatohepatitis and no worsening of liver fibrosis at Week 24 and Week 96, improvement in liver fibrosis (≥ one stage) and no worsening of steatohepatitis at Week 96, improvement in liver fibrosis (≥ one stage) at Week 24 and Week 96 [1]	Endpoints at Week 24: LBAS PPS FAS Endpoints at Week 96: LBAS (Week 24 and Week 96) FAS MFAS
Secondary: change from baseline in hepatic fat fraction by MRI-PDFF at Week 24 and Week 96	MRI-PDFF Analysis Set
Secondary: lipoproteins (Lp (a), total cholesterol, triglycerides, Non-HDL-C, HDL-C, LDL-C and LDL-P) and markers of lipid metabolism (ApoB and ApoC-III) change from baseline	FAS
Secondary: markers of glycemic control (HbA1c, C-peptide, Adiponectin and HOMA-IR) change from baseline	Biomarkers Analysis Set
Secondary: noninvasive markers of fibrosis (ELF, Pro-C3, C3M, NIS-4) change from baseline	Biomarkers Analysis Set LBAS
Secondary: liver stiffness by transient elastography change from baseline	FAS LBAS
Secondary: body weight change from baseline	FAS
Exploratory: resolution of steatohepatitis AND improvement in liver fibrosis (≥ one stage) at Week 24 and Week 96, improvement in liver fibrosis (≥ two stages) and no worsening of steatohepatitis at Week 24 and Week 96, two stage improvement in liver fibrosis at Week 24 and Week 96	Endpoints at Week 24: LBAS PPS Endpoints at Week 96: LBAS (Week 24 and Week 96) MFAS

Outcome Variable	***Analysis Set(s)***
Exploratory: fibrosis stage and NAFLD Activity Score (NAS) on liver histology at Week 24 and Week 96	LBAS PPS
Exploratory: event-free survival (EFS)	FAS
Exploratory: adjudicated cardiovascular endpoints at Week 48, Week 96 and end of study	FAS
Exploratory: bone biomarkers change from baseline	Biomarkers Analysis Set
Exploratory: cardiovascular and metabolic risk factors (e.g., incidence of Type 2 Diabetes, body mass index (BMI), and blood pressure)	Safety Set
Exploratory: non-invasive measures of fibrosis associated with histological regression and/or progression of fibrosis and clinical complications of cirrhosis	LBAS
Exploratory: markers of liver injury and function	FAS LBAS
Exploratory: MRI-PDFF based quantitation of hepatic fat	MRI-PDFF Analysis Set
Exploratory: Plasma concentrations of EFX	PK Analysis Set
Exploratory: waist-to-hip ratio change from baseline	FAS PPS
Exploratory: health-related quality of life (CLDQ-NASH) change from baseline	FAS PPS
Safety Endpoints	
Concomitant medications	Safety Set
Extent of exposure	Safety set
Adverse events (AEs)	Safety set
Laboratory evaluations, electrocardiogram (ECG) and vital sign assessments	Safety set
Bone Mineral Density	Safety Set

Outcome Variable	***Analysis Set(s)***
Endogenous FGF21	Safety Set
Anti-drug antibody (ADA) and neutralizing antibody (NAb)	Safety set
[1] Apply rules for intercurrent events as for primary efficacy endpoint.	

6. Data Handling

6.1 Time points and Visit Windows

Day 1 is defined as the day of first dose of study drug. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

Scheduled visits will be assigned to analysis visits as recorded on the eCRF. Unscheduled and early termination visits completed within 21 days following the last dose of study drug will be assigned to analysis visits according to the following visit windows.

Chemistry, hematology, lipids, coagulation and markers of liver injury and function:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 1	8	5	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	323
Week 48	337	324	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

Markers of glycemic control, bone biomarkers and lipid metabolism biomarkers:

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	197
Week 32	225	198	253
Week 40	281	254	309
Week 48	337	310	421
Week 72	505	422	589
Week 96	673	590	EOS

Serum fibrosis biomarkers:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 12	85	44	127
Week 24	169	128	253
Week 48	337	254	421
Week 72	505	422	589
Week 96	673	590	EOS

Body weight:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 1	8	5	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	323
Week 48	337	324	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

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 88	617	590	645
Week 96	673	646	EOS

FibroScan examination:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 24	169	86	253
Week 48	337	254	505
Week 96	673	506	EOS

CP score assessment:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 12	85	44	127
Week 24	169	128	253
Week 48	337	254	505
Week 96	673	506	EOS

MRI-PDFF based quantitation of hepatic fat:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 24	169	86	421
Week 96	673	422	EOS

DXA scan measurement:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 48	337	170	505
Week 96	673	506	EOS

Waist-to-hip ratio:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 12	85	44	127
Week 24	169	128	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	323
Week 48	337	324	351

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
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

Health-related quality of life (CLDQ-NASH):

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 12	85	44	127
Week 24	169	128	183
Week 28	197	184	225
Week 36	253	226	281
Week 44	309	282	323
Week 48	337	324	351
Week 52	365	352	519
Week 96	673	520	EOS

Liver histology:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 24	169	113	421
Week 96	673	422	EOS

ADA and NAb:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 8	57	30	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

Within an analysis visit window, the measurement from the scheduled visit will be used if available. If multiple scheduled visits occur within a single visit window, then the visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later visit will be used in the analysis.

If no scheduled visit occurs, the measurement from the unscheduled 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.

6.2 Handling of Dropouts, Missing Data, and Outliers

Subjects in the FAS with missing liver biopsy data will be considered as non-responder in the analyses of histological endpoints on the FAS. With these exceptions, values for missing data will not be imputed unless specified. The same handling of missing liver biopsy data will also be applied for the MFAS, which is a subset of the FAS.

Where appropriate, safety data for subjects who 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. Values for missing safety laboratory data will not be imputed; however, a missing baseline result will be replaced with a screening result, if available. 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.

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

Below limit of quantification (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).

No rules for outlier detection are planned.

7. Statistical Methods

7.1 General Principles

All data processing, summarization and analyses will be performed using Fortrea's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The following principles will be applied to all tables, figures, and listings (TFLs) unless otherwise stated:

Principle	Value
Significant tests	Two-sided and use a 5% significance level for main effects and 10% significance level for interaction terms.
Treatment group labels and order presented	Placebo EFX 28 mg EFX 50 mg All EFX (as applicable) Total (as applicable)
Tables	Data in summary tables presented by assessment or parameter, treatment group, and visit (where applicable).
Listings	All individual subject data will be listed as measured and presented by treatment group, subject, and visit (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of non-missing values (n), arithmetic mean, arithmetic standard deviation (SD), median and range (minimum and maximum). Descriptive statistics for certain continuous data will include geometric mean and geometric coefficient of variation. 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).
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)].
Denominator for percentages	Number of subjects in the analysis set, unless stated otherwise in table shell.
Include "Missing" as category	Demographics and Other Baseline Characteristics only.

Principle	Value
Display for 0 percentages	Blank
Display collected value	Minimum and maximum
Display 1 decimal place	Q1 (25th Percentile), Q3 (25th Percentile), Mean, Mean Difference, Median, Standard Deviation, and Confidence Interval for all parameters except DXA parameters.
Display 3 decimal places	Q1 (25th Percentile), Q3 (25th Percentile), Mean, Mean Difference, Median, Standard Deviation, and Confidence Interval for DXA parameters; p-value.
Limit of precision for displays	1 decimal place, unless otherwise specified.
Date Format	DDMMMYYYY

7.1.1 Definition of Baseline

For all variables except lipids, liver enzymes variables, and blood pressure, 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 available measurement (including unscheduled visit) prior to the first dose of study drug may be used as the baseline value unless it is stated otherwise. The scheduled baseline visit for FibroScan, liver biopsy, MRI-PDFF, and DXA scan is Screening.

Baseline lipid variables including Total Cholesterol, HDL-C, LDL-C, Triglycerides, non-HDL-C, VLDL-C, VLDL-T, HDL-P, IDL-P, LDL-P, VLDLT-P, HDL particle size, LDL particle size, VLDL particle size, Lp (a), and lipoprotein insulin resistance will be the average of Screening and Baseline visit (Day 1) values. If one is missing, the available one will be used.

Baseline liver enzymes variables including ALT, AST and ALP will be the average of Pre-Baseline and Baseline visit (Day 1) values. If one is missing, the available one will be used. If both are missing, the available Screening value 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.

7.2 Subject Disposition and Data Sets Analyzed

Subject disposition, randomization, study visits, and analysis sets will be listed. Additionally, the subject visits impacted by COVID-19 will be listed.

Counts and percentages of subjects who were screened (i.e. signed informed consent), discontinued early during screening (screen failures), and randomized will be summarized in total based on all screened subjects. Reasons for screen failures will also be summarized. In addition, the number of screening failures which were noted to have a COVID-19 as a contributory factor will 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 the treatment
- Subjects who withdrew from the treatment
- 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 for the discontinuation/withdrawal will be summarized. In addition, early discontinuation from the treatment contributed by COVID-19 and early discontinuation from the study contributed by COVID-19 will be summarized.

A summary of subject enrollment by stratification factor will also be provided by treatment group and in total for All Randomized Subjects.

Counts and percentages of subjects in each analysis population will be summarized by treatment and in total based on All Randomized Subjects.

7.3 Protocol Deviations

All protocol deviations and COVID-19 related protocol deviations will be listed.

All important protocol deviations leading to exclusion from the PPS (see Section 5.9.1) will be listed and summarized by treatment group for All Randomized Subjects.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline measurements will be listed and summarized by treatment group and in all EFX subjects and total for All Randomized Subjects.

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Age categories (<65 years, ≥65 years, ≥75 years)

- Sex
- Race
- Ethnicity
- Height (cm) at Screening
- 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)
- Waist circumference (cm) at Baseline
- Hip circumference (cm) at Baseline
- Waist-to-hip ratio at Baseline
- T2D status at Screening
- Fibrosis stage at Screening
- Statin use at baseline
- Vitamin E/ Thiazolidinedione use at baseline
- NAS and NAS components at Screening
- Median Liver Stiffness Measurement (LSM) in kiloPascals (kPa) as Evaluated by FibroScan at Screening
- Median Controlled Attenuation Parameter (CAP) at Screening
- ALT (U/L) and AST (U/L) at Baseline
- ALT and AST categories at Baseline (≤ULN, >ULN)
- Systolic blood pressure at baseline, Diastolic blood pressure at baseline, and Systolic blood pressure category at baseline (<130mmHg, >=130mmHg)
- Fasting values of Triglyceride (mg/dL), Total Cholesterol (mg/dL), LDL-C (mg/dL), HDL-C (mg/dL), and non-HDL-C (mg/dL) at Baseline
- Endogenous FGF21 at Baseline
- Serum fibrosis biomarkers: ELF score, Pro-C3 (µg/mL), C3M, Pro-C3/C3M, NIS-4 at Baseline
- Pro-C3 categories at Baseline (<14 µg/mL, ≥14 µg/mL)
- Liver Injury Biomarkers: MELD score and CP score at Baseline
- Bone Biomarkers: P1NP and CTX-1 at Baseline

- Insulin Sensitivity and Glycemic Control Biomarkers: Hemoglobin A1c (%), Fasting values of Insulin, Blood Glucose, Adiponectin, and HOMA-IR at Baseline

Other baseline measurements, such as safety laboratory, ADA, vital signs, and ECG, will be summarized by treatment group with the post-baseline measurements.

7.4.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 (or a later version if updated during the study). All medical history will be listed, and the number and percentage of subjects with any medical history will be summarized for All Randomized Subjects by treatment group and in total by system organ class (SOC) and preferred term (PT).

7.4.2 Previous and Concomitant Medications

Medications received prior to or concomitantly with study drug will be coded by Fortrea using the WHODrug Dictionary Version Sep 2020 Global Dictionary Version B3 (or a later version if updated during the study) preferred terms and Anatomical Therapeutic Chemical (ATC) Classification codes.

For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications of the randomized treatment period 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) and started prior to the 30-Day follow-up visit of the randomized treatment period.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

The use of any prior medication or concomitant medication will be listed for All Randomized Subjects. Counts and percentages of subjects taking concomitant medications by therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term will be summarized by treatment and in total based on the Safety Set.

7.5 Measurements of study drug Compliance

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

7.6 Efficacy

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.

Note that for analyses using an MMRM model, the model will first use an unstructured covariance matrix. In the event that there are convergence issues, an autoregressive heterogeneous (ARH(1)) covariance structure will be used, followed by autoregressive structure (AR(1)) if convergence issues still exist.

In addition, for analyses using the CMH test, it is noted that the CMH test statistic is not defined in the event there are no responses in one treatment arm and that there may be issues with numerical stability of the estimated odds ratio (and related statistics, e.g. p-values) in the event of few responses within a treatment arm. Therefore, the nominal p-value and corresponding population level summaries will be generated using Fisher's Exact Test on the 2x2 contingency table of an individual active treatment arm (EFX 28mg or EFX 50mg) and Placebo, and the response variable (histology response or non-response) for a given endpoint in the event that there are no responses in a treatment arm for a given population. The analysis with all EFX subjects in a given analysis population will also be generated in this case. Further, in the event of insufficient responses (e.g. less than approximately 3 responses in a given arm) to assess numerical stability of the CMH odds ratio estimate, the Fisher's Exact Test odds ratio estimate and p-value may also be summarized in order to assess the impact of limited responses on the stability of the CMH test.

7.6.1 Primary Efficacy Analysis

The primary efficacy analysis will be conducted when all the planned subjects complete the 24-Week visit. A CMH test will be used to compare the differences in proportions of subjects who achieve a ≥ 1-stage improvement in fibrosis compared to baseline without worsening of steatohepatitis between the EFX arms and the placebo arm, adjusting for stratification factors. The analysis will be performed using the LBAS. The point estimates and 95% confidence intervals (CIs) for the differences in proportions will be calculated. The 95% CI will be constructed using the Miettinen and Nurminen method. In addition, the odds ratio and risk ratio point estimate and 95% CI will be summarized for each EFX arm compared to placebo. 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. P-values will be presented.

The same analysis will be repeated on the PPS and FAS. For any subjects in the FAS with a missing efficacy value, the efficacy variable will be considered as non-responder.

7.6.2 Secondary Efficacy Analysis

7.6.2.1 Proportion of subjects who achieve resolution of steatohepatitis and no worsening of liver fibrosis at Week 24 and Week 96

A CMH test will be used to compare the differences in proportions of subjects who achieve resolution of steatohepatitis and no worsening of liver fibrosis at Week 24 and Week 96 between the EFX arms and the placebo arm, adjusting for stratification factors. The analysis will be performed using the LBAS. The point estimates and 95% CIs for the differences in proportions, and p-values will be calculated. The 95% CI will be constructed using the Miettinen and Nurminen method. In addition, the odds ratio and risk ratio point estimate and 95% CI will be summarized for each EFX arm compared to placebo.

The same analysis will be repeated on the PPS and FAS for Week 24 and repeated on the FAS, Week 24 LBAS, and MFAS for Week 96. For any subjects with a missing efficacy value, the efficacy variable will be considered as non-responder.

A descriptive summary will present the shift from Week 24 response to Week 96 response for the Week 24 LBAS, subjects with a Week 24 biopsy but missing Week 96 biopsy will be summarized in the missing category in this summary. In addition, a descriptive summary will present the number of subjects with steatohepatitis resolution at Week 24 (with no improvement in fibrosis) and the number of subjects with fibrosis improvement (>= 1 stage) with no worsening of steatohepatitis at Week 96.

7.6.2.2 Proportion of subjects who achieve improvement in liver fibrosis (≥ one stage) and no worsening of steatohepatitis at Week 96

A CMH test will be used to compare the differences in proportions of subjects who achieve improvement in liver fibrosis (≥ one stage) and no worsening of steatohepatitis at Week 96 between the EFX arms and the placebo arm, adjusting for stratification factors. The analysis will be performed using the LBAS. The point estimates and 95% CIs for the differences in proportions, and p-values will be calculated. The 95% CI will be constructed using the Miettinen and Nurminen method. In addition, the odds ratio and risk ratio point estimate and 95% CI will be summarized for each EFX arm compared to placebo.

The same analysis will be repeated on the FAS, Week 24 LBAS, and MFAS at Week 96. For any subjects with a missing efficacy value, the efficacy variable will be considered as non-responder.

A descriptive summary will present the shift from Week 24 response to Week 96 response for the Week 24 LBAS, subjects with a Week 24 biopsy but missing Week 96 biopsy will be summarized in the missing category in this summary. In addition, a descriptive summary will present the number of subjects with one stage fibrosis improvement at Week 24 with no worsening of steatohepatitis that shift to >= 2 stage improvement in fibrosis at Week 96.

7.6.2.3 Proportion of subjects who achieve improvement in liver fibrosis (≥ one stage) at Week 24 and Week 96

A CMH test will be used to compare the differences in proportions of subjects who achieve improvement in liver fibrosis (≥ one stage) at Week 24 and Week 96 between the EFX arms and the placebo arm, adjusting for stratification factors. The analysis will be performed using the LBAS. The point estimates and 95% CIs for the differences in proportions, and p-values will be calculated. The 95% CI will be constructed using the Miettinen and Nurminen method. In addition, the odds ratio and risk ratio point estimate and 95% CI will be summarized for each EFX arm compared to placebo.

The same analysis will be repeated on the PPS and FAS for Week 24 and repeated on the FAS, MFAS, and Week 24 LBAS for Week 96. For any subjects in the FAS with a missing efficacy value, the efficacy variable will be considered as non-responder.

A descriptive summary will present the shift from Week 24 response to Week 96 response for the Week 24 LBAS, subjects with a Week 24 biopsy but missing Week 96 biopsy will be summarized in the missing category in this summary.

7.6.2.4 Change from baseline in hepatic fat fraction measured by MRI-PDFF at Week 24 and Week 96

An analysis of covariance (ANCOVA) model with baseline covariate will be used to evaluate the changes and percent changes from baseline in hepatic fat fraction between the EFX arms and the placebo arm at Week 24, controlling for stratification factors. A mixed-model repeated-measures (MMRM) with baseline covariate will be used to evaluate the changes and percent changes from baseline in hepatic fat fraction between the EFX arms and the placebo arm at Week 24 , Week 48, and Week 96, controlling for stratification factors. Least square (LS) means, 95% CIs, and p-values will be presented. The analysis will be performed using the MRI-PDFF Analysis Set.

7.6.2.5 Change from baseline of lipoproteins and markers of lipid metabolism

An MMRM model with baseline covariate will be used to evaluate the changes and percent changes from baseline in lipoproteins (Lp (a), total cholesterol, triglycerides, Non-HDL-C, HDL-C, LDL-C, and LDL-P) and markers of lipid metabolism (ApoB and ApoC-III) between the EFX arms and the placebo arm at scheduled visits, controlling for stratification factors. Least square (LS) means, 95% CIs, and p-values will be presented. The analysis will be performed using the FAS.

Non-HDL cholesterol will be calculated as Total Cholesterol - HDL-C.

Summaries and boxplots will be presented for actual values and changes from baseline in Lp (a), total cholesterol, triglycerides, Non-HDL-C, HDL-C, LDL-C, LDL-P, and ApoB and ApoC-III at the collection time points defined in the Schedule of Assessments by treatment group.

7.6.2.6 Change from baseline of glycemic control biomarkers

An MMRM model with baseline covariate will be used to evaluate the changes and percent changes from baseline in HbA1c, C-peptide, Adiponectin, and HOMA-IR between the EFX arms and the placebo arm at scheduled visits, controlling for stratification factors. LS means, 95% CIs, and p-values will be presented. The analysis will be performed using the Biomarkers Analysis Set.

Summaries and boxplots will be presented for actual values and changes from baseline in HbA1c, C-peptide, Adiponectin, and HOMA-IR at the collection time points defined in the Schedule of Assessments by treatment group.

7.6.2.7 Change from baseline of serum fibrosis biomarkers

An MMRM model with baseline covariate will be used to evaluate the changes and percent changes from baseline in ELF, Pro-C3, C3M, and NIS-4 between the EFX arms and the placebo arm at scheduled visits, controlling for stratification factors. LS means, 95% CIs, and p-values will be presented. The analysis will be performed using the Biomarkers Analysis Set and LBAS.

Summaries and boxplots will be presented for actual values and changes from baseline in ELF, Pro-C3, C3M, and NIS-4 at the collection time points defined in the Schedule of Assessments by treatment group.

7.6.2.8 Change from baseline in liver stiffness and controlled attenuation parameter (CAP) as evaluated by FibroScan

An ANCOVA model with baseline covariate will be used to evaluate the changes and percent changes from baseline in liver stiffness (kPa) and CAP (dB/m) between the EFX arms and the placebo arm at Week 24, controlling for stratification factors. An

MMRM model with baseline covariate will be used to evaluate the changes and percent changes from baseline in liver stiffness and CAP between the EFX arms and the placebo arm at Weeks 24, 48, and 96, controlling for stratification factors. LS means, 95% CIs, and p-values will be presented. The analysis will be performed using the FAS and LBAS.

Summaries and boxplots will be presented for actual values and changes from baseline in liver stiffness at the collection time points defined in the Schedule of Assessments by treatment group.

In addition, the proportion of patients with interquartile range (IQR)/Median ratio <30% for liver stiffness and IQR <40dB/m for CAP, will be summarized by visit.

7.6.2.9 Change from baseline of body weight

An MMRM model with baseline covariate will be used to evaluate the changes and percent changes from baseline in body weight between the EFX arms and the placebo arm at scheduled visits, controlling for stratification factors. LS means, 95% CIs, and p-values will be presented. The analysis will be performed using the FAS.

Summaries and boxplots will be presented for actual values and changes from baseline in body weight at the collection time points defined in the Schedule of Assessments by treatment group.

7.6.3 Exploratory Analysis

The same efficacy analyses used for the secondary efficacy variables will be used for the exploratory efficacy variables.

7.6.3.1 Proportion of subjects who achieve resolution of steatohepatitis AND improvement in liver fibrosis (≥ one stage) at Week 24 and Week 96

A CMH test will be used to compare the differences in proportions of subjects who achieve resolution of steatohepatitis AND improvement in liver fibrosis (≥ one stage) at Week 24 and Week 96 between the EFX arms and the placebo arm, adjusting for stratification factors. The analysis will be performed using the LBAS. The point estimates and 95% CIs for the differences in proportions, and p-values will be calculated. The 95% CI will be constructed using the Miettinen and Nurminen method. In addition, the odds ratio and risk ratio point estimate and 95% CI will be summarized for each EFX arm compared to placebo.

The same analysis will be repeated on the PPS for Week 24. The analysis will be repeated using the MFAS, Week 24 LBAS, and Week 96 LBAS at Week 96.

A descriptive summary will present the shift from Week 24 response to Week 96 response for the Week 24 LBAS, subjects with a Week 24 biopsy but missing Week 96 biopsy will be summarized in the missing category in this summary.

7.6.3.2 Liver histology as measured by the fibrosis stage and NAFLD Activity Score

The analysis of fibrosis stage and NAS will be performed using the LBAS and PPS. Fibrosis stage at baseline and post-baseline time points, change from baseline, and shift from baseline frequencies will be summarized by treatment group. In the calculation of change and shift from baseline, fibrosis stage 1A, 1B, and 1C will be considered as stage 1.

In addition, a descriptive summary will present the change from baseline in fibrosis at Week 24 and the change from baseline in fibrosis at week 96, irrespective of change in steatohepatitis.

NAS and components at baseline and post-baseline time points and the change from baseline frequencies together with mean (SD) and median will be summarized by treatment. Shift from baseline frequencies will be presented for the individual components of NAS as well.

7.6.3.3 Proportion of subjects who achieve improvement in liver fibrosis (≥ two stages) and no worsening of steatohepatitis at Week 24 and Week 96

A CMH test will be used to compare the differences in proportions of subjects who achieve improvement in liver fibrosis (≥ two stages) and no worsening of steatohepatitis at Week 24 and Week 96 between the EFX arms and the placebo arm, adjusting for stratification factors. The analysis will be performed using the LBAS. The point estimates and 95% CIs for the differences in proportions, and p-values will be calculated. The 95% CI will be constructed using the Miettinen and Nurminen method. In addition, the same test will be performed to compare the difference in proportions of subjects who achieve two stage improvement in liver fibrosis at Week 24 and Week 96 between the EFX arms and the placebo arm. In addition, the odds ratio and risk ratio point estimate and 95% CI will be summarized for each EFX arm compared to placebo.

The same analysis will be repeated on the PPS for Week 24. The analysis will be repeated using the MFAS, Week 24 LBAS, and Week 96 LBAS at Week 96.

A descriptive summary will present the shift from Week 24 response to Week 96 response for the Week 24 LBAS, subjects with a Week 24 biopsy but missing Week 96 biopsy will be summarized in the missing category in this summary.

7.6.3.4 Clinical outcomes of event-free survival

EFS will be assessed by time to the first clinical event including progression to cirrhosis as determined by central pathology, adjudicated liver decompensation events, liver transplantation and all-cause mortality using the FAS. For subjects without any clinical event at the analysis cutoff date, EFS will be censored on the date of last assessment. The number and percentage of subjects with clinical event and subjects censored at the time of analysis will be presented. The 50th percentile of Kaplan-Meier estimates will be used to estimate the median duration of EFS (months). A two-sided 95% CI will be provided for this estimate. The 25th and 75th percentiles, and the range (minimum, maximum) will be presented as well. The range will be determined including censored observations.

In the event that the median EFS is not reached, the pointwise confidence interval for the survival probability at clinically relevant timepoints may be presented.

7.6.3.5 Proportion of subjects with adjudicated cardiovascular endpoints

The analysis of proportion of subjects with adjudicated cardiovascular endpoints, including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, hospitalization for cardiac failure, and urgent or emergency visits for heart failure at Week 48, Week 96, and end of study will be performed using the FAS. A CMH test will be used to compare the differences in proportions of subjects with adjudicated cardiovascular endpoints between the EFX arms and the placebo arm, adjusting for stratification factors. The point estimates and 95% CIs for the differences in proportions, and p-values will be calculated. The 95% CI will be constructed using the Miettinen and Nurminen method. In addition, the odds ratio and risk ratio point estimate and 95% CI will be summarized for each EFX arm compared to placebo.

7.6.3.6 Changes from baseline in bone biomarkers

The analysis of changes from baseline in bone biomarkers will be performed using the Biomarkers Analysis Set. An MMRM model with baseline covariate will be used to evaluate the changes and percent changes from baseline in P1NP and CTX-1 between the EFX arms and the placebo arm at scheduled visits, controlling for stratification factors. LS means, 95% CIs, and p-values will be presented.

Summaries and boxplots will be presented for actual values and changes from baseline in P1NP and CTX-1 at the collection time points defined in the Schedule of Assessments by treatment group.

7.6.3.7 Changes in cardiovascular and metabolic risk factors

The analysis of changes in cardiovascular and metabolic risk factors will be performed using the Safety Set. Descriptive summaries and boxplots of BMI and blood pressure will be presented by treatment group and visit.

An MMRM model with baseline covariate will be used to evaluate the changes from baseline in blood pressure between the EFX arms and the placebo arm at scheduled visits, controlling for stratification factors. Least square (LS) means, 95% CIs, and p-values will be presented. The analysis will be performed using the Safety Set.

A CMH test will be used to compare the differences in proportions of subjects with new onset of T2D between the EFX arms and the placebo arm, adjusting for stratification factors. The new onset of T2D is defined as a single HbA1C value of 6.5% or higher when baseline HbA1c <6.5%. The analysis will be performed using the Safety Set.

7.6.3.8 Non-invasive measures of fibrosis can predict histological regression and/or progression of fibrosis and clinical complications of cirrhosis

Correlation models will be fitted to explore the correlation coefficient between non-invasive measures of fibrosis and histological fibrosis (CRN fibrosis stage of liver biopsy) and clinical complications of cirrhosis (MELD score and CP score). Non-invasive measures of fibrosis include serum biomarkers (ELF and Pro-C3) and imaging (liver stiffness by FibroScan). In addition, correlation between the imaging marker for hepatic fat (MRI-PDFF) and histological fibrosis and NASH resolution will also be explored. The analysis will be performed using the LBAS.

7.6.3.9 Change from baseline in markers of liver injury and function

The analysis of markers of liver injury and function, including ALT, AST, ALP, GGT, bilirubin, INR, albumin, uric acid, platelets, MELD score, and CP score will be performed using the FAS and LBAS. Summaries of actual values and changes from baseline will be presented by treatment group and visit.

CP score will be calculated as below, ranging from 5-15:

	1 point	**2 point**	**3 point**
Bilirubin (Total)	<2 mg/dL (<34.2 µmol/L)	2-3 mg/dL (34.2-51.3 µmol/L)	>3 mg/dL (>51.3 µmol/L)
Albumin	>3.5 g/dL (>35 g/L)	2.8-3.5 g/dL (28-35 g/L)	<2.8 g/dL (<28 g/L)
INR	<1.7	1.7-2.2	>2.2

Ascites	No ascites	Mild to moderate (diuretic responsive/controlled)	Severe (diuretic refractory/poorly controlled)
Encephalopathy	No Encephalopathy	Grade 1-2	Grade 3-4
Class A = 5-6 points Class B = 7-9 points Class C = 10-15 points			

An MMRM model with baseline covariate will be used to evaluate the changes and percent changes from baseline in markers of liver injury and function between the EFX arms and the placebo arm at scheduled visits, controlling for stratification factors. LS means, 95% CIs, and p-values will be presented.

Summaries and boxplots will be presented for actual values and changes from baseline in ALT, AST, ALP, GGT, bilirubin, INR, albumin, uric acid, MELD score, and CP score at the collection time points defined in the Schedule of Assessments by treatment group.

7.6.3.10 MRI-PDFF based quantitation of hepatic fat

The analysis of MRI-PDFF based quantitation of hepatic fat will be performed using the MRI-PDFF Analysis Set. Summaries of actual values and absolute and percent changes from baseline will be presented by treatment group and visit. A CMH test will be used to compare the differences in proportions of subjects with relative reduction ≥30% and ≥50% in hepatic fat and with liver fat content ≤5% at Week 24 and Week 96 between the EFX arms and the placebo arm, adjusting for stratification factors. The point estimates and 95% CIs for the differences in proportions, and p-values will be calculated. The 95% CI will be constructed using the Miettinen and Nurminen method.

7.6.3.11 Change from baseline in waist-to-hip ratio

The analysis of change from baseline in waist-to-hip ratio will be performed using the FAS and PPS. Summaries of actual values and changes from baseline will be presented by treatment group and visit. An MMRM model with baseline covariate will be used to evaluate the changes from baseline in waist-to-hip ratio between the EFX arms and the placebo arm at scheduled visits, controlling for stratification factors. LS means, 95% CIs, and p-values will be presented.

7.6.3.12 Changes from baseline in health-related quality of life (CLDQ-NASH)

The analysis of changes from baseline in CLDQ-NASH will be performed using the FAS and PPS. Summaries of CLDQ-NASH total score and domain scores will be presented by treatment group and visit. An MMRM model with baseline covariate

will be used to evaluate the changes from baseline in total score between the EFX arms and the placebo arm at scheduled visits, controlling for stratification factors. LS means, 95% CIs, and p-values will be presented.

7.6.4 Sensitivity Analysis

Analyses of the primary efficacy endpoint (improvement in liver fibrosis and no worsening of steatohepatitis at Week 24) in the PPS and FAS will be performed as a sensitivity analysis. Analyses of secondary endpoints of resolution of steatohepatitis and no worsening of liver fibrosis at Week 24 and improvement in liver fibrosis at Week 24 will also be presented for the PPS and FAS.

In addition, tipping point analysis will be performed to evaluate various deviations from the assumption of non-response for the primary efficacy endpoint in the FAS. For subjects with missing liver biopsy data at Week 24, responder status will be imputed in an increasing manner by subject level for each treatment group. Specifically, for each subject, a responder/non-responder status will be imputed with the scenario where all subjects being non-responders up to the scenario where all subjects are responders. This will include all possible scenarios of responder status for all missing data, including scenarios where subjects on EFX groups have worse outcomes than subjects on placebo (see table below). For each scenario, an analysis similar to the primary analysis will be performed.

"Response" in Missing in Placebo Group	"Response" in Missing in EFX Group						
	0	1	2	…	m-2	m-1	m [1]
0	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx
1	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx
2	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx
…	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx
n-2	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx
n-1	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx
n [2]	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx	p=0.xxx

[1] m = total number of subjects with missing data at Week 24 in EFX group
[2] n = total number of subjects with missing data at Week 24 in Placebo group

7.6.5 Subgroup Analysis

Subgroup analysis will be performed for the efficacy endpoints (see Table 4). The group variables are as follows:

- Baseline T2D (yes or no)
- Baseline fibrosis score (F2 or F3)
- Statin use at baseline (yes or no)
- Endogenous FGF21 at baseline (>median or ≤median)
- Pro-C3 at baseline (<14 µg/mL or ≥14 µg/mL)
- Baseline hypertension status (yes or no)
- BMI categories at Baseline (>median or ≤median)

Additional subgroups will be presented for the primary efficacy endpoint as follows:

- Age categories (<65 years, ≥65 years, ≥75 years)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- NAS at Screening (≤5, >5)
- Baseline liver fat (<10%, ≥10% to <20%, ≥20%)

Table 4 Summary of Subgroup Analysis

Endpoint	***Subgroup***
Primary: improvement in liver fibrosis (one stage) and no worsening of steatohepatitis at Week 24	LBAS subgroups: age category, ethnicity, NAS at Screening, baseline liver fat, baseline T2D, baseline fibrosis score, statin use at baseline, endogenous FGF21 at baseline, and baseline BMI category
Secondary: resolution of steatohepatitis and no worsening of liver fibrosis at Week 24 and 96	LBAS subgroups: baseline T2D, baseline fibrosis score, and statin use at baseline
Secondary: improvement in liver fibrosis (≥ one stage) at Week 24 and 96	LBAS subgroups: baseline T2D, baseline fibrosis score, and statin use at baseline
Secondary: change from baseline in hepatic fat fraction by MRI-PDFF at Week 24 and 96	MRI-PDFF Analysis Set subgroups: baseline T2D, baseline fibrosis score, statin use at baseline, and baseline liver fat
Secondary: improvement in liver fibrosis (one stage) and no worsening of steatohepatitis at Week 96	LBAS subgroups: age category, ethnicity, NAS at Screening, baseline liver fat, baseline T2D, baseline fibrosis score, statin use at baseline, endogenous FGF21 at baseline, and baseline BMI category
Secondary: lipoproteins (Lp (a), total cholesterol, triglycerides, Non-HDL-C, HDL-C, LDL-C and LDL-P) and markers of	FAS subgroups: statin use at baseline, baseline T2D, and baseline fibrosis score

Endpoint	***Subgroup***
lipid metabolism (ApoB and ApoC-III) change from baseline	
Secondary: markers of glycemic control (HbA1c, C-peptide, Adiponectin and HOMA-IR) change from baseline	Biomarkers Analysis Set subgroups: baseline T2D and statin use at baseline
Secondary: serum fibrosis biomarkers (ELF, Pro-C3, C3M, NIS-4) change from baseline	Biomarkers Analysis Set subgroups: baseline T2D, baseline fibrosis score, and statin use at baseline for ELF, Pro-C3, C3M, and NIS-4; Pro-C3 at baseline for Pro-C3
Secondary: liver stiffness change from baseline	LBAS subgroups: baseline T2D, baseline fibrosis score, and statin use at baseline
Secondary: body weight change from baseline	FAS subgroups: baseline BMI category, baseline T2D, baseline fibrosis score
Exploratory: improvement in liver fibrosis (one stage) and resolution of steatohepatitis at Week 96	LBAS subgroups: age category, ethnicity, NAS at Screening, baseline liver fat, baseline T2D, baseline fibrosis score, statin use at baseline, endogenous FGF21 at baseline, and baseline BMI category
Exploratory: fibrosis stage and NAFLD Activity Score (NAS) on liver histology at Week 24	LBAS subgroups: baseline T2D and baseline fibrosis score
Exploratory: improvement in liver fibrosis (≥ two stages) and no worsening of steatohepatitis at Week 24 and two stage improvement in liver fibrosis at Week 24	LBAS subgroups: baseline T2D, baseline fibrosis score, and statin use at baseline
Exploratory: cardiovascular and metabolic risk factors (blood pressure)	Safety Set subgroup: baseline hypertension status
Exploratory: MRI-PDFF based quantitation of hepatic fat	MRI-PDFF Analysis Set subgroups: baseline T2D, baseline liver fat
Exploratory: health-related quality of life (CLDQ-NASH) change from baseline	FAS subgroups: baseline T2D

7.7 Safety

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 and total (as applicable). Data for the follow-up period will be included in data listings.

7.7.1 Extent of Exposure

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 Set with descriptive statistics and with counts and percentages of subjects with exposure in the following categories:

- >0 to ≤4 weeks
- >4 to ≤8 weeks
- >8 to ≤12 weeks
- >12 to ≤16 weeks
- >16 to ≤20 weeks
- >20 to ≤24 weeks
- >24 to ≤52 weeks
- >52 weeks to ≤72 weeks
- >72 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 number of injections: 1-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90, and >90.

7.7.2 Adverse Events

Clinical and laboratory AEs will be coded using the MedDRA Version 23.1 (or a later version if updated during the study). SOC, High-Level Group Term (HLGT), High-Level Term (HLT), PT, and Lower-Level Term (LLT) will be attached to the clinical database. AE severity will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0). The relationship between an AE and study drug will be assessed (Related/ Not related) and also the relationship to study procedures.

AEs will be classified as either pre-treatment AEs or TEAEs as follows:

- pre-treatment AEs are events that start prior to the date of first dose of study drug.
- TEAEs are events with start date on or after the date of first dose of study drug and up to 30 days after date of last dose of study drug.

Any AEs leading to premature discontinuation of study drug will be summarized separately.

An overview table will summarize the number and percentage of subjects with at least one of the following AEs, where subjects with more than one event in a particular category are counted only once in that category:

- Any TEAEs;
- Any TEAEs by maximum severity grade (a subject will be counted in only one category);
- Study drug-related TEAEs (overall and by maximum severity);
- Study procedure related TEAEs (overall and by maximum severity);
- Any TEAEs of special interest (overall, injection site reaction, diarrhea, hypoglycemia, neurological or psychiatric event, or DILI)
- Any TEAEs of decompensated liver disease events including ascites, hepatic encephalopathy (HE), or variceal bleeding;
- Any SAEs;
- Any treatment-emergent SAEs (TESAEs);
- Any TEAEs leading to premature discontinuation of study drug;
- Any TEAEs leading to premature discontinuation of study from the end of study eCRF;
- Any TEAE leading to death.

Summaries (number and percentage of subjects) will be presented by SOC and PT for each of the categories in the overview (with the exception of Any TEAEs leading to premature discontinuation of study). Common TEAEs (PTs with an incidence ≥15% in any treatment group) will be presented by SOC and PT as well. Summaries will also be presented by SOC, PT and maximum severity grade for TEAEs, study drug-related TEAEs, and study procedure related TEAEs. In these summaries, subjects with more than one AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT. For summaries by maximum severity grade, subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT.

All AEs collected during the course of the study will be presented in data listings with fields for treatment-emergent event (Yes / No), Start and end dates, Outcome (Fatal / Not resolved or Not recovered / Recovered or resolved / Recovered or resolved with sequelae [describe sequelae] / Unknown), Relationship to study treatment (Related / Not related), Relationship to study procedures (Related [specify procedure] / Not related), Toxicity Grade (CTCAE v 5.0), Action taken with the study drug (Dose not changed/ Drug interrupted/ Drug withdrawn/ Not

applicable), Any other action (Yes [specify]/ No), Event of clinical interest (DILI/ Injection site reaction/ Diarrhea/ Hypoglycemia/ Neurological or Psychiatric event).

In addition, corresponding listings of SAEs and additional SAE details, AESIs and separate listing details of DILI and injection site reactions, decompensated liver disease events, TEAEs leading to discontinuation of study drug, and AEs leading to death will be produced.

7.7.3 Laboratory Evaluations

Safety laboratory tests of chemistry, hematology/coagulation, and endogenous FGF21 (Table 5) received from central laboratory will be summarized (n, mean, SD, median, minimum, and maximum) by treatment group and study visit along with the corresponding change from baseline values. Data for all laboratory tests, including urine/miscellaneous, unscheduled local laboratory tests recorded to the eCRF, and any additional analytes will be listed.

Table 5 Clinical Laboratory Assessments

Chemistry		Hematology/ Coagulation	Urine/ Miscellaneous
Sodium Potassium Chloride Bicarbonate Calcium Magnesium Phosphorus Glucose[b] BUN Creatinine Total protein Albumin Uric acid LDH	Total bilirubin (TBL) direct bilirubin Alkaline phosphatase (ALP) ALT (SGPT) AST (SGOT) GGT CK hsCRP Amylase Lipase[c] 3 Hydroxybutyrate	**Hematology** RBC count Hemoglobin (Hgb) Hematocrit (Hct) Platelet count WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, and basophils ANC **Coagulation** PT aPTT INR PAI-1 Fibrinogen	**Urine** Drug screening: amphetamines, cocaine and opiates (i.e., heroin, morphine) **Miscellaneous** Screening Serology Tests HBsAg HBcAb HBV DNA Hep A IgM Anti-HCV antibody HCV RNA HIV Endogenous FGF21[b] Pregnancy test[a]

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; GGT = gamma-glutamyl transferase; HbA1c = Glycated Hemoglobin A1c; HBcAb = total hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-Reactive Protein; INR = International Normalized Ratio; LDH = lactate dehydrogenase; PAI-1 = Plasminogen Activator Inhibitor-1; PT = prothrombin time; RBC = red blood cell; RNA = ribonucleic acid; TBL= total bilirubin; WBC = white blood cell
a For female subjects of childbearing potential only. Serum pregnancy test at screening and urine pregnancy test at other time points.
b Samples to be collected in the morning following an overnight fast of at least 8 hours.
c Reflex lipase testing is performed in subjects with total amylase > 1.5 ULN.

All laboratory data will be reported in Conventional units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings. For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Baseline for each laboratory analyte is the pre-dose measurement on Baseline visit (Day 1) with exceptions as defined in Section 7.1.1. For post-baseline, within an analysis visit window, the analyte measurement from the scheduled visit will be used if available. If multiple scheduled visits occur within a single visit window, then the visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later visit will be used in the analysis.

If no scheduled visit occurs, the measurement from the unscheduled 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.

Laboratory values will be assigned toxicity grades, when available, using criteria based on the NCI-CTCAE, version 5.0 (Table 6). These criteria are derived using only the numeric laboratory measurement, baseline measurement and normal range limits. Where defined, low and high shifts will be summarized separately. The incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any scheduled or unscheduled post-baseline assessment up to and including the date of last dose of study drugs plus 30 days, will be summarized by treatment group and visit. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment-emergent. The percentage incidence of graded treatment-emergent abnormalities will be calculated out of the number of subjects with non-missing value at the specified time point.

Table 6 Laboratory Toxicity Grade Criteria of Selected Clinical Laboratory Assessments

Serum Chemistry	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
ALT	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	>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
AST	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
TBILI	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
ALP	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	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

Serum Chemistry	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine (Cr)	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
CPK	CPK increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5 - 10 x ULN	>10 x ULN
Potassium (K)	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Amylase	Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and NCS	>2.0 - 5.0 x ULN and CS; >5.0 x ULN and NCS	>5.0 x ULN and CS
Glucose	Hypoglycemia	<LLN – 55 mg/dL; <LLN – 3.0 mmol/L	<55 - 40 mg/dL; <3.0 – 2.2 mmol/L	<40 - 30 mg/dL; <2.2 – 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
GGT	GGT increased	>ULN – 2.5 x ULN if baseline was normal; >2 – 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	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	Anemia	<LLN – 10.0 g/dL; <LLN – 6.2 mmol/L; <LLN - 100 g/L	<10.0-8.0 g/dL; <6.2 – 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	
Hemoglobin	Hemoglobin increased	>ULN & increase in >0 - 2 g/dL	>ULN & increase in >2 - 4 g/dL	>ULN & increase in >4 g/dL	
CD4 lymphocytes	CD4 lymphocytes decreased	<LLN – 500/mm³; <LLN – 0.5 x 10e9/L	<500 - 200/mm³; <0.5 - 0.2 x 10e9/L	<200 - 50/mm³; <0.2 - 0.05 x 10e9/L	<50/mm³; <0.05 x 10e9/L
Neutrophils	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 (WBC) Count	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	Platelet count decreased	<LLN – 75000/mm³; <LLN -75.0 x 10e9 /L	<75000 - 50000/mm³; <75.0 - 50.0 x 10e9 /L	<50000 - 25000/mm³; <50.0 - 25.0 x 10e9 /L	<25000/mm³; <25.0 x 10e9/L

Coagulation	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
INR	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 other parameters, not listed in Table 6 separate laboratory shift tables will present directional shifts from baseline to above the laboratory standard upper limit

of normal (ULN) or below the lower limit of normal (LLN) using the maximum increase and/or decrease observed throughout the course of treatment and including the 30-day follow-up visit. Scheduled and unscheduled assessments will be included in this analysis.

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

7.7.4 Vital Signs

The following vital signs will be collected from subjects in seated or semi-recumbent position.

- systolic and diastolic blood pressure (mmHg);
- heart rate (bpm);
- respiration rate (breaths/min);
- oral/ intra-aural body temperature (°C).

Descriptive summaries by treatment and visit will be presented for the mean of triplicate measures (rounded to the nearest integer) at Baseline, Week 12 Week 24, Week 48, and Week 96, and for single measurements collected at all other visits. The summary at each visit will pool assessments in seated or semi-recumbent positions. Vital signs data and changes from baseline will be summarized by visit using standard descriptive statistics for the Safety population. Baseline for each vital sign is the pre-dose measurement on Baseline visit (Day 1) with exceptions as defined in Section 7.1.1. For post-baseline, only data from scheduled visits will be included in the summary tables.

7.7.5 Electrocardiograms

The following quantitative ECG measurements will be recorded on the eCRF:

- heart rate (bpm)
- QRS (msec);
- RR (msec);
- PR (msec);
- QT (msec);
- Fridericia corrected QT (QTcF) interval (msec).

An overall Investigator assessment of ECG will be provided (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant").

The ECG measurements and changes from baseline in ECG will be listed and summarized by treatment group and visit using standard descriptive statistics for the Safety Set.

The Investigator assessment will be listed and the number and percentage of subjects within each assessment category will be tabulated by treatment group and visit for the Safety Set.

Baseline for each ECG measurement is the pre-dose measurement on Baseline visit (Day 1) with exceptions as defined in Section 7.1.1. For post-baseline, only data from scheduled visits will be included in the by visit summary tables.

The number and percentage of subjects with absolute QTcF interval values in the pre-specified categories (>450, >480, and >500 msec), and QTcF interval change (>30 and >60 msec) will be summarized. The summary of maximum post-baseline QTcF will include scheduled and unscheduled visits.

7.7.6 Other safety assessments

7.7.6.1 Physical examination

Clinically relevant physical exam findings prior to the first dose of study drug will be recorded on the medical history eCRF and clinically significant findings after the first dose of study drug will be recorded as AEs.

7.7.6.2 DXA scan measurements

DXA scan measurements will include bone mineral density of the lumbar spine and femoral neck. An MMRM model with baseline covariate will be used to evaluate the changes from baseline in DXA scan measurements between the EFX arms and the placebo arm at Week 48 and Week 96, controlling for stratification factors. Least square (LS) means, 95% CIs, and p-values will be presented. The analysis will be performed using the Safety Set.

Summaries and boxplots will be presented for actual values and changes from baseline in DXA scan measurements at the collection time points defined in the Schedule of Assessments by treatment group.

7.7.6.3 Anti-drug antibody and neutralizing antibody

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 negative result at or before dosing and positive result post dose. Titers will also be summarized descriptively for positive ADAs.

7.8 Pharmacokinetic Analysis

Plasma EFX concentrations will be listed and summarized at the time points listed in the Schedule of Assessments for the PK Set. Summary statistics for plasma EFX include geometric mean and geometric CV.

7.9 Interim Analysis

Throughout the study, all TEAEs, clinical assessments, clinical laboratory parameters, and the criteria for DILI will be closely monitored with subjects entering close observation, as required.

An external DMC that consists of two hepatologists, one cardiologist, one endocrinologist, and a statistician will review the progress of the study. The DMC will convene after 45 subjects (approximately 15 per treatment group) have completed the Week 12 assessments. The DMC will receive all reports of SAEs and convene as needed to monitor for safety and additional meetings will be scheduled as required.

Week 24 analysis will be conducted when all the planned subjects have completed the 24-week visit. The analysis will be performed by the unblinded DMC supporting team at Fortrea and the analysis results will be reviewed by the unblinded team at Akero Therapeutics. Treatment assignment should remain blinded until after the database lock. Akero unblinded team will be prevented from being involved in day-to-day administration of study conduct after they are unblinded.

All Subjects will remain in the same treatment group for the duration of the study.

8. Changes in Planned Analysis

Not applicable.

Note that while Protocol Amendment 4 indicated that all EFX-treated subjects would switch to a single dose of EFX, after further consultation with regulatory bodies, all subjects were maintained on the as randomized EFX dose until Week 96.

9. Data Issues

This section is not required at this time, but will be populated if applicable in a future approved version of this document.

10. References

1 European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf

11. Appendices

11.1 Appendix 1: Document History

Document Version, Status, Date	Summary/Reason for Changes
Version 1, Final, 27 Jul 2021	Not applicable; the first version
Version 2, Final, 19 Aug 2022	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]

Version 3, Final,

07 Feb 2024

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