Statistical Analysis Plan

Protocol BIO89-100-002

A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Properties of BIO89-100 Administered Subcutaneously in Subjects with Nonalcoholic Steatohepatitis (NASH) or with Nonalcoholic Fatty Liver Disease (NAFLD) and at High Risk of NASH

Phase 1b

SAP Version: 1.0 (Final)
Date: 21AUGUST2020

Prepared by:

On Behalf of ProSciento Inc.

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This statistical analysis plan has been reviewed and approved by:

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[redacted]

Abbreviations

ADA	anti-drug antibodies
AEs	adverse events
ALT	alanine transaminase
AST	aspartate transaminase
ATC	anatomic therapeutic chemistry
$AUC_{0\text{-}tau}$	area under the curve since last dose
BMI	body mass index
CBC	complete blood count
CK-18	cytokeratin-18
CAP	controlled attenuation parameter
C_{max}	maximum concentration
COVID-19	Coronavirus disease 2019
C-SSRS	columbia-suicide severity rating scale
CTCAE	common terminology criteria for adverse events
CTX	carboxy-terminal collagen crosslinks
CV%	coefficient of variation
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDISH	evaluation of drug induced serious hepatotoxicity
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
EOS	end of study
ET	early termination
FFA	free fatty acids
FGF21	fibroblast growth factor 21
FU	follow-up
HA	Hyaluronic acid
HbA1c	hemoglobin a1c
HDL-c	high density lipoprotein
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model of assessment of insulin resistance
hsCRP	high-sensitivity c-reactive protein
IGF-1	insulin-like growth factor-1
IP	investigational product
LDL-c	low density lipoprotein
LS	least squares
MAD	multiple ascending dose
MAR	missing at random
MedDra	medical dictionary for regulatory activities
MMRM	mixed model repeated measures
MNAR	missing not at random

MRI-PDFF	magnetic resonance imaging – proton density fat fraction
n	sample size
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
non-HDL	non-high density lipoprotein
OGTT	oral glucose tolerance test
P1NP	n-terminal propeptide of type 1 collagen
PD	pharmacodynamics
PEG	polyethylene glycol
PIIINP	Amino-terminal propeptide of type III procollagen
PMM	pattern-mixture model
Pro-C3	n-terminal propeptide of type iii collagen
PT	preferred term
Q2W	every two weeks
QTcF	corrected qt interval by Fridericia
QW	weekly
SAEs	serious adverse events
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SE	standard error
SMC	safety monitoring committee
SOC	system organ class
$t_{1/2}$	half-life
TB	total bilirubin
TEAE	treatment-emergent adverse event
TIMP-1	tissue inhibitor of metalloproteinase 1
t_{max}	time to maximum concentration
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VCTE	vibration-controlled transient elastography
WHO	world health organization
WOCBP	women of child-bearing potential

1. Introduction

This statistical analysis plan (SAP) describes the statistical methods and procedures to be implemented in clinical study BIO89-100-002. This statistical analysis plan is based on study protocol BIO89-100-002 Version 3.0 dated 25 March 2020. If the data suggest and warrant it, deviations from this plan will be considered. However, any deviations from the SAP must be substantiated by sound statistical rationale and documented in the final clinical study report.

2. Study Objectives

2.1. Primary Objectives

The primary objectives of the study are:

- To evaluate the safety and tolerability of ascending multiple subcutaneous (SC) injections of BIO89-100 in subjects with nonalcoholic steatohepatitis (NASH) or who have nonalcoholic fatty liver disease (NAFLD) and at a high risk of NASH.
- To characterize BIO89-100 pharmacokinetics

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the immunogenicity of BIO89-100 as measured by presence of anti-drug antibodies (ADA)
- To characterize biomarkers, pharmacodynamics (PD) profile and biological activity of BIO89-100 administered at ascending doses and with both weekly (QW) and every two weeks (Q2W) dosing intervals
- To evaluate the time, dose, and exposure relationship of BIO89-100 on biological activity, as assessed by biomarkers and PD

2.3. Exploratory Objectives

The exploratory objective of the study is:

- [redacted]

3. Study Overview

3.1. Study Design

Study BIO89-100-002 is a randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study to evaluate the safety, tolerability, PK and PD profiles and immunogenicity of BIO89-100 administered SC in approximately 83 subjects with NASH, or with NAFLD who are at a high risk of NASH. This multi-site study will consist of 6 cohorts, and will evaluate 2 dosing schedules, weekly (QW; cohorts 1 to 4) and every 2 weeks (Q2W; Cohorts 5 and 6).

Table 1: Dose Escalation Cohorts

Cohort	Randomized Group/Dose Level	Frequency and Route of Administration	Number of Subjects	
			BIO89-100	Placebo
1	BIO89-100 3 mg QW	Weekly (QW), SC to abdomen (1 injection) Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85 Total doses (initial 4 weeks + 8 week extension): 5 + 8	6	2
2	BIO89-100 9 mg QW	QW, SC to abdomen (1 injection) Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85 Total doses (initial 4 weeks + 8 week extension): 5 + 8	12	3
3	BIO89-100 18 mg QW	QW, SC to abdomen (1 injection) Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85 Total doses (initial 4 weeks + 8 week extension): 5 + 8	14	4
4	BIO89-100 27 mg QW	QW, SC to abdomen (1 injection) Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85 Total doses (initial 4 weeks + 8 week extension): 5 + 8	9	3
5	BIO89-100 18 mg Q2W	Every 2 weeks (Q2W), SC to abdomen (1 injection) Days 1, 15, 29, 43, 57, 71 and 85. Total doses (initial 4 weeks + 8 week extension): 3 + 4	14	4
6	BIO89-100 36 mg Q2W	Q2W, SC to abdomen (2 injections) Days 1, 15, 29, 43, 57, 71 and 85. Total doses (initial 4 weeks + 8 week extension): 3 + 4	9	3

The study will include a Screening period, a Treatment period, and a Follow-up period. The treatment duration will be 12 weeks, consisting of a 4-week study for initial safety assessment (primary endpoint) with an 8-week extension phase for efficacy and safety assessments. The study includes an individual safety checkpoint after 4 weeks of treatment (through Day 30), to

ensure that only individuals with an acceptable safety profile will proceed to the 8-week extension phase.

There will be 2 dose escalation decisions. After Cohort 1 completes the Day 36 visit, the Safety Monitoring Committee (SMC) will decide whether subjects can be randomized into Cohorts 2 and 5 (both to start concurrently). After at least eight subjects from both Cohort 2 and Cohort 5, including at least 1 subject on placebo in each cohort, complete the Day 36 visit, the SMC will decide whether subjects can be randomized into Cohorts, 3,4 and 6 (all to start concurrently).

3.2. Study Activities

Please refer to the appendix for the schedule of activities and pharmacokinetic sample collection schedules:

- Table 1 Schedule of Activities for Cohorts 1-4
- Table 2 PK Sample Collection for Cohorts 1-4 – QW Dosing Interval
- Table 3 Schedule of Activities for Cohorts 5 and 6
- Table 4 PK Sample Collection for Cohorts 5 and 6 – Q2W Dosing Interval

3.3. Randomization Schedule and Blinding Procedures

Eligible subjects will be randomized in the order they are enrolled into the study. For Cohort 1, eight eligible subjects will be randomized in a 3:1 ratio to active (BIO89-100): control (placebo). For Cohort 2, fifteen subjects will be randomized in a 4:1 ratio to active: control. For cohorts 4 and 6, twelve eligible subjects will be randomized in each cohort in a 3:1 ratio to active: control. For Cohorts 3 and 5, eighteen subjects will be randomized in each cohort in a ratio of 7:2 active: control, stratified by biopsy confirmed NASH with fibrosis status F1, F2 or F3 (Yes, No), with each stratum of nine subjects in each cohort.

3.4. Stratification Factors

Cohorts 3 and 5, will be stratified by biopsy confirmed NASH with fibrosis status F1, F2 or F3 (Yes, No).

3.5. Sample Size and Power

No formal sample size calculation was performed for the primary endpoint(s) as the total of approximately 83 subjects, consisting of 6:2 (Cohort 1), 12:3 (Cohort 2), 9:3 (Cohorts 4 and 6) or 14:4 (Cohorts 3 and 5) receiving active: placebo, respectively is considered adequate to inform on the endpoints for this Phase 1b study.

A power assessment based on magnetic resonance imaging – proton density fat fraction (MRI-PDFF) endpoint (percent change from baseline to End of Treatment in liver fat content, an important biomarker) shows that 9, 12 and 14 subjects in a dose cohort compared to the pooled 19 placebo subjects will provide [redacted] power, respectively, to detect a difference in mean percentage change from baseline between treatment groups of [redacted], assuming

a standard deviation of [redacted] in each group. Calculation was based on two-sample one-sided t-test with alpha at 0.05 (e.g., two-sided alpha at 0.10).

Subjects who withdraw from the study before the Day 50 assessments may be replaced at the discretion of the Sponsor.

3.6. Interim Analysis

No efficacy interim analysis is planned. Sponsor may perform administrative interim analyses to support objectives such as study planning and regulatory interactions.

3.7. Safety Monitoring Committee

A Safety Monitoring Committee (SMC), comprised of a Principal Investigator participating in the study, the Clinical Research Organization (CRO) Medical Monitor and the Sponsor Medical Monitor, will review blinded safety data for dose escalation decisions. The operations of the SMC will be defined in the SMC Charter.

4. Study Endpoints

4.1. Primary Endpoints

This study has primary safety and primary pharmacokinetic endpoints.

4.1.1. Safety Endpoints

The primary safety endpoints are:

- Subject incidence of treatment emergent adverse events (TEAEs)
- Subject incidence of TEAEs by severity
- Subject incidence of serious TEAEs
- Number of subjects who discontinued due to TEAEs
- Number of subjects who discontinued due to related TEAEs

4.1.2. Pharmacokinetic Endpoints

The primary pharmacokinetic endpoints are:

- Maximum concentration (C_{max}) on Day 1
- C_{max} on Day 29
- Area under the curve since last dose ($AUC_{0\text{-}tau}$) on Day 1
- $AUC_{0\text{-}tau}$ on Day 29
- Time to maximum concentration (t_{max}) on Day 1
- t_{max} on Day 29
- Half-life ($t_{1/2}$) on Day 1
- $t_{1/2}$ on Day 29

4.2. Secondary Endpoints

The secondary immunogenicity endpoints are:

- Incidence and characteristics of ADA after dosing (e.g., titer and/or binding specificity, to the fibroblast growth factor 21 (FGF21) and polyethylene glycol (PEG) part of BIO89-100 and neutralizing immunogenicity).
- Impact/correlation of the presence of ADAs on serum BIO89-100 concentrations and clinical safety.

The secondary pharmacodynamics endpoints are:

Anthropomorphic measurements:

- Change from baseline and percent change from baseline in body weight over time.
- Change from baseline and percent change from baseline in body mass index (BMI) over time.

Laboratory parameters:

- Change from baseline and percent change from baseline in triglycerides over time
- Change from baseline and percent change from baseline in non-high density lipoprotein (non-HDL) cholesterol over time
- Change from baseline and percent change from baseline in high density lipoprotein (HDL-c) over time
- Change from baseline and percent change from baseline in low density lipoprotein (LDL-c) over time
- Change from baseline and percent change from baseline in hemoglobin A1c (HbA1c) over time
- Change from baseline and percent change from baseline in homeostatic model of assessment of insulin resistance (HOMA-IR) over time

Liver function tests:

- Change from baseline and percent change from baseline in alanine transaminase (ALT) over time
- Change from baseline and percent change from baseline in aspartate transaminase (AST) over time
- Change from baseline and percent change from baseline in adiponectin over time
- Change from baseline and percent change from baseline in N-terminal propeptide of type III collagen (Pro-C3) over time
- Change from baseline and percent change from baseline in free fatty acids (FFA) over time
- Change from baseline and percent change from baseline in adipo-IR (fasting free fatty acids × fasting insulin) over time

Imaging measures:

- Change from baseline and percent change from baseline in MRI-PDFF over time

- Percentage reduction from baseline in MRI-PDFF ≥ 30% at Day 50 and Day 92
- MRI-PDFF < 5% at Day 50 and Day 92

4.3. Other Safety Endpoints

The other safety endpoints are:

- Change from baseline in vital signs
- Incidence and shifts of clinically significant vital signs
- Incidence of clinically significant physical examination findings
- Incidence and shifts of clinically significant electrocardiograms (ECG)
- Incidence and shifts of clinically significant laboratory abnormalities
- Change from baseline in safety laboratory evaluations including complete blood count (CBC), blood biochemistry, cortisol and urinalysis over time

4.4. Exploratory Endpoints

[redacted]

[redacted]

5. Definitions

5.1. Definition of Study Day

The day subjects receive their first dose of investigational product will be considered Study Day 1. Study day will be defined by the number of days from Study Day 1. If index date is prior to Study Day 1, study day will be defined as the index date minus the Study Day 1 date. If index date is on or after Study Day 1 date, the study day will be defined as index date minus the Study Day 1 date plus 1 day. If a subject is randomized but never dosed, study day will be calculated using the randomization date and randomization date will be set to Study Day 1.

For subjects with study interruptions due to COVID-19, post-interruption study day will be calculated as: (Index date) – (the date of Study Day 1) + 1 – (the interruption duration as defined in the study interruption CRF). Visits post-interruption due to COVID-19 will use this corrected study day for visit windowing.

5.2. Handling of Missing or Partial Dates

Date imputation will only be used for determining treatment-emergent status for adverse events or identifying concomitant medications. Actual data values as they appear in the database will be shown in the subject level listings.

5.2.1. Adverse Event Date Imputations

In cases of incomplete dates for adverse events, the missing components will be assumed as the most conservative values as possible. The imputation rules described below will attempt to conservatively capture AEs with missing onset dates as treatment-emergent, unless information

of AE stop date/time was prior to first dose date, which would automatically disqualify the treatment-emergent status. The original values with no imputation applied will be presented in the data listings.

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

5.2.2. Medication/Procedure Date Imputations

Imputation of partial start and end dates for medications/procedures is done for the purpose of classifying concomitant, pre-treatment, and baseline medications/procedures. The original values with no imputation applied will be presented in the data listings.

For medications/procedures with completely missing start dates, no imputation will be performed.

For medications/procedures with partial start dates:

- If "day" is the only missing field, impute the "day" as the first of the month.
- If "day" and "month" are the missing fields, impute the "day" and "month" to January 1.
- If only day is missing, and month and year are the same as first dose date then consider as concomitant. For a medication/procedure that is not checked as ongoing and the start date is completely missing:
    - and from the end date (either complete, partial or completely missing) it can be deduced to be prior to the first dose date of randomized investigational product, then consider as pre-treatment.
    - Otherwise, consider as concomitant.

For medications/procedures with completely missing end dates and ongoing is not checked:

- End date will not be imputed, furthermore:

- If start date is on or after Study Day 1, then consider as concomitant medication/procedure
- If start date is prior to Study Day 1, or start date is also completely missing, then consider as pre-treatment medication/procedure
- If start date is on Study Day 1, then consider as baseline medication/procedure

For medications/procedures with partial end dates:

- If "day" is the only missing field, and if month and year are the same as the start date and ongoing is not checked, then impute "day" as the start date "day"; otherwise impute as the last day of the month.
- If "day" and "month" are the missing fields, if year is the same as the start date and ongoing is not checked, then impute "day" and month as the start date day and start date month; otherwise impute as December 31.

For medications/procedures that have both completely missing start dates and end dates, no imputation will be made; these medications/procedures will be assumed to be concomitant.

5.3. Definition of Study Baseline

For study measurements (safety labs, PD, biomarkers and exploratory labs) except ALT or AST, lipids, and vital signs, each subject's baseline value for that measurement will be defined as the latest pre-dose value. This will be determined by chronologically sorting all scheduled and unscheduled values prior to first dose date and time and taking the latest value unless noted otherwise. Subjects who are randomized but are not dosed will use their latest measurement as baseline up to Study Day 1.

Baseline will be presented with each post-baseline change in the summary tables to allow easier review.

5.3.1. Study Baseline of ALT and AST

For ALT and AST, the baseline value will be defined as the average of all values performed during screening and Study Day 1 based on the following table. The baseline for ALT and AST are calculated and captured in the eCRF.

ALT or AST Screening Assessments			Day 1 ALT or AST assessment	**Baseline value**
Assessment 1	Assessment 2	Assessment 3 (if applicable)		
Normal	Normal	Not applicable	Any	Average of Assessment 1, Assessment 2 and Day 1 (3 tests)
Normal	Abnormal and ≤40% increase from Assessment 1	Not applicable	Any	Average of Assessment 1, Assessment 2 and Day 1 (3 tests)
Normal	Abnormal and >40% increase from Assessment 1	Normal or ≤40% increase from Assessment 1	Any	Average of Assessment 1, Assessment 2, Assessment 3 and Day 1 (4 tests)
Normal	Abnormal and >40% increase from Assessment 1	Abnormal and >40% increase from Assessment 1	**Not applicable, subject excluded.**	**Not applicable, subject excluded.**
Abnormal	≤40% increase from Assessment 1	Not applicable	Any	Average of Assessment 1, Assessment 2 and Day 1 (3 tests)
Abnormal	>40% increase from Assessment 1	≤40% increase from Assessment 1	Any	Average of Assessment 1, Assessment 2, Assessment 3 and Day 1 (4 tests)
Abnormal	>40% increase from Assessment 1	>40% increase from Assessment 1	**Not applicable, subject excluded.**	**Not applicable, subject excluded.**

5.3.2. Study Baseline for Lipids

For lipids, the baseline will be determined as the average of all pre-dose measurements within 30 days prior to Study Day 1, e.g. measurements taken at -29 ≤ Study Day ≤ 1 (Pre-dose).

5.3.3. Study Baseline for Vital Signs

For vital signs of blood pressure and pulse, measurements will be taken in duplicate starting from randomization. Baseline for these measures should be the last average (of the duplicate measurements) on or prior to Study Day 1 and prior to first dose if subject is dosed.

5.4. Definition of Duration of Exposure

The intended duration of exposure for QW dosing will be defined as the date of the last dose of investigational product minus Study Day 1 date plus 8 days. The intended duration of exposure for Q2W dosing will be defined as the date of the last dose of investigational product minus Study Day 1 date plus 15 days.

5.5. Definition of Age

Age will be defined as the duration in days of date of signed informed consent or index date minus the birthdate divided by 365.25. Index date refers to specific visits if age is needed at specific visits (for example age at specific visits will be used when deriving FIB-4 score or eGFR).

5.6. Dose Compliance

Dose compliance percentage will be the actual number of received doses divided by the expected number of doses to be received up to EOT. Partial doses will contribute to the actual number of received doses.

5.7. Definition of Pre-treatment Medication and Pre-treatment Procedures

Pre-treatment medications are defined as any medication that start and stop being taken prior to Study Day 1.

Pre-treatment procedures are defined as any procedure that were started and completed prior to Study Day 1.

5.8. Definition of Baseline Medication

Medications that have Study Day 1 within the duration of exposure will be considered baseline medications.

5.9. Definition of Concomitant Medication and Concomitant Procedures

Concomitant medications are defined as any medication that is taken any day on or after Study Day 1. This includes medications that were started prior first dose and that were continued to be taken after Study Day 1.

Concomitant procedures are defined as any procedures that are performed any day on or after Study Day 1. This includes procedures that were started prior first dose and that continued into Study Day 1.

5.10. Definition of Randomized Treatment Group

The definition of randomized treatment group, also known as the planned treatment group, will be the treatment group that a subject was randomized to. Placebo from each cohort will be pooled. The randomized treatment groups for summary purpose are: BIO89-100 3 mg QW, BIO89-100 9 mg QW, BIO89-100 18 mg QW, BIO89-100 27 mg QW, BIO89-100 18 mg Q2W, BIO89-100 36 mg Q2W, and Placebo.

5.11. Definition of Actual Treatment Group

The definition of actual treatment group will be the assigned treatment group based on what the subject actually received. If a subject receives at least one dose of BIO89-100, then that subject will be considered a subject of the active treatment group of the cohort that they were randomized to. If a subject receives only placebo doses, then their actual treatment group will be

placebo group. Placebo from each cohort will be pooled. The actual treatment groups for summary purpose are: BIO89-100 3 mg QW, BIO89-100 9 mg QW, BIO89-100 18 mg QW, BIO89-100 27 mg QW, BIO89-100 18 mg Q2W, BIO89-100 36 mg Q2W and Placebo.

5.12. Definition of Treatment Emergent Adverse Event

Treatment-emergent adverse events will be defined as those occurring at or after the time of the first administration of investigational product, eg, first dose date and time, through study termination, or existing prior to the time of and worsening after the time of the first administration of investigational product. Adverse events with onset prior to the first administration of investigational product that end before Study Day 1 or do not worsen after Study Day 1 will be classified as pre-treatment.

5.17. Adipo-IR

Adipo-IR will be calculated by multiplying fasting insulin (uU/mL) with the fasting free fatty acids (mmol/L) concentrations.

5.18. Estimated Glomerular Filtration Rate (CKD-EPI)

The eGFR using the CKD-EPI equation will be derived for post-baseline visits. Baseline eGFR will not be derived and will come from the source data.

For Males:

$$\begin{aligned}\text{eGFR}[\text{mL/min/1.73m}^2] &= 141 \\ &* \min\left(\frac{\text{Serum Creatinine}[\text{mg/dL}]}{0.9}, 1\right)^{-.411} \\ &* \max\left(\frac{Serum\ Creatinine[\text{mg/dL}]}{0.9}, 1\right)^{-1.209} * 0.993^{Age[years]} \\ &* 1.159[if\ black]\end{aligned}$$

For Females:

$$\begin{aligned}\text{eGFR}[\text{mL/min/1.73m}^2] &= 141 \\ &* \min\left(\frac{\text{Serum Creatinine}[\text{mg/dL}]}{0.7}, 1\right)^{-.329} \\ &* \max\left(\frac{Serum\ Creatinine[\text{mg/dL}]}{0.7}, 1\right)^{-1.209} * 0.993^{Age[years]} * 1.018 \\ &* 1.159[if\ black]\end{aligned}$$

5.19. Definition of Study Interruption

Study interruption will be defined as any interruption lasting ≥2 weeks and allowed up to 4 weeks (+4 days). that is due to any causes related COVID-19 pandemic and will require extra handling when deriving analysis visits.

5.20. Definition of Actual Time

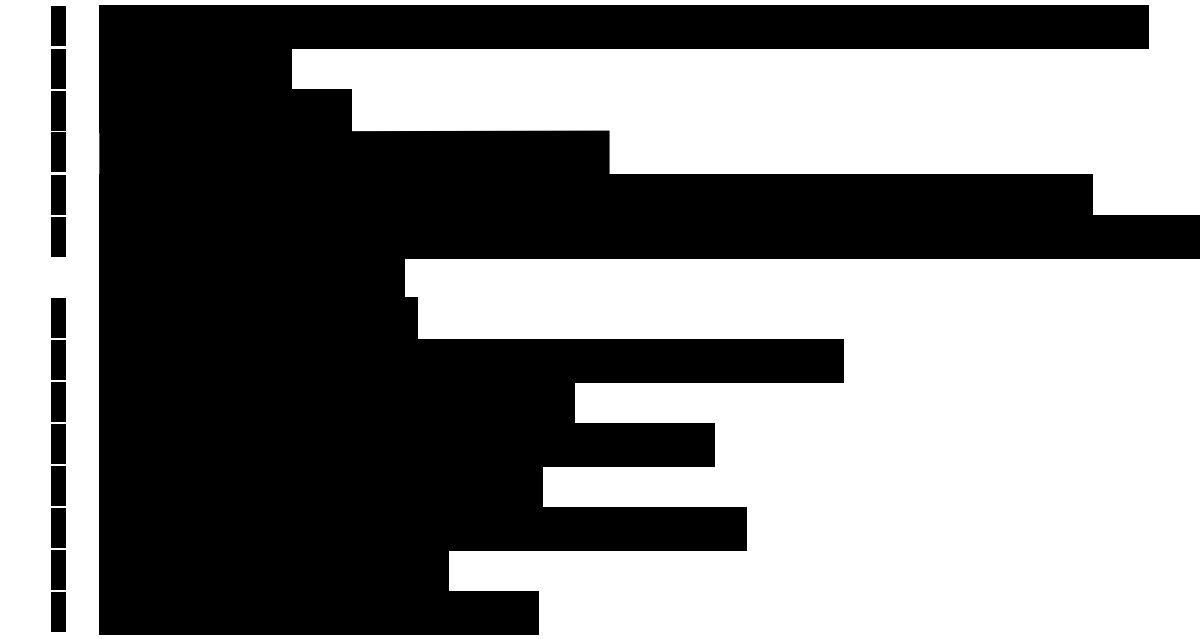
For PK analysis, actual time will be defined as:

Actual Time=Actual Sample Collection Time - Actual Last Dosing Time (before the corresponding sample collection)

6. Potential Covariates

The stratification factor of biopsy confirmed NASH with fibrosis status (F1, F2, F3) Yes or No will be considered as a potential covariate to be adjusted for in the statistical models.

[redacted]



Subgroup analyses will be descriptive in nature.

8. Analysis Populations

The number of subjects in each analysis population by treatment group will be summarized.

8.1. Screened Analysis Set

The Screened Analysis set will consist of all subjects who signed informed consent and undergone screening.

8.2. Randomized Analysis Set

The Randomized Analysis set will consist of all Screened Analysis set subjects who are assigned a randomization number in the study. For analysis purposes, subjects will be analyzed according to the randomized treatment group. Subjects who are replaced will still be counted as randomized subjects.

8.3. Safety Analysis Set

The Safety Analysis set will consist of all randomized subjects who receive at least 1 dose of investigational product. In this population, subjects will be summarized based upon the actual treatment group.

8.4. Pharmacokinetics Analysis Set

The Pharmacokinetics Analysis set will consist of all subjects in the Safety Analysis set who received at least one dose of investigational product and have at least one on study PK measurement. The analysis population for any population PK modeling may be defined separately in a population PK data analysis plan.

8.5. Pharmacodynamics Analysis Set

The Pharmacodynamics Analysis set will consist of all subjects in the Safety Analysis set who have measurable post-baseline PD data. For analysis purposes, subjects will be analyzed according to randomized treatment group. The analysis set will be used for all PD data other than MRI and Fibroscan measures. This set will be used for correlation analysis.

8.6. Pharmacodynamics Analysis Set - MRI

The Pharmacodynamics Analysis set – MRI will consist of all subjects in the Safety Analysis set who have measurable post-baseline MRI assessment. For analysis purposes, subjects will be analyzed according to randomized treatment group. This set will be used for MRI related endpoints.

8.7. Pharmacodynamics Analysis Set - Fibroscan

The Pharmacodynamics Analysis set – Fibroscan will consist of all subjects in the Safety Analysis set who have measurable post-baseline Fibroscan. For analysis purposes, subjects will be analyzed according to randomized treatment group. This set will be used for Fibroscan related endpoints.

9. Statistical Methods of Data Analyses

9.1. General Considerations

In general, placebo subjects from each cohort will be pooled for summary.

9.1.1. Statistical Notation and Presentation

All data collected from all subjects in the electronic data capture will be presented in the subject level listings. All continuous data will be listed with the same precision as presented in the database. Data listings will be sorted by cohort, treatment group, subject ID and time point. Missing values will be represented by an empty cell and no imputation will be made. If imputation is used for analysis, excluding treatment-emergent and concomitant medication determinations, the imputed values will be listed with a derivation type column in the listing indicating that origin of the imputed value.

Continuous data will be summarized in tables using number of subjects or sample size (n), mean, median, standard deviation (SD), minimum and maximum. For logarithm-transformed data, the geometric mean, standard error (SE) of the geometric mean and geometric coefficient of variation (CV%) will also be provided.

Categorical data will be summarized in two ways, by subject and by time point. Subject data will be summarized using the count of distinct subjects that fall in the category and the percentage of the total number of subjects. Population counts, either the number of subjects or the number of assessments at the time point, will be used as the denominator in the calculation of percentages unless specified otherwise.

The original units (conventional) and SI units will be presented in listings. In general, conventional units will be used for tables and figures, unless otherwise specified. Insulin will use the conventional unit of uU/mL; estimated glomerular filtration rate will be presented using SI units.

Minimum and maximum values will use the precisions of the original value. Means, least squares (LS) means, and medians will be rounded to one decimal place greater than the precision of the original value up to a max of two decimal places. The limits of confidence intervals, standard deviations and standard errors will be rounded to two decimal places greater than the precision of the original value. Derived PK and PD data will be presented with three significant figures. Percentages will be rounded to the nearest tenth. Two-sided p-values will be presented with four decimal places and values less than 0.0001 will be presented as <.0001.

9.1.2. Statistical Modeling Methods

A mixed model repeated measures (MMRM) analysis will be used to analyze the change from baseline and/or percent change from baseline in the pharmacodynamic endpoints. The model will include baseline as a covariate, treatment group, visit, and the interaction between treatment group and visit as factors. The covariance will be unstructured; if the model fails to converge, other structures such as compound symmetry will be considered. The LS means and the LS mean difference will be presented by visit with their corresponding standard error, p-values and two-sided 90% and 95% confidence intervals.

If strong evidence exists that the normality assumptions are violated for, but not limited to, triglycerides or MRI-PDFF, non-parametric methods will be considered such as the Wilcoxon Rank Sum test.

There will be no adjustments for multiplicity in this study.

9.1.3. Analysis Visits and Visit Windowing

In general, all scheduled visits will be used as analysis visit for descriptive analysis tables and listings.

If a scheduled visit is missing, an unscheduled visit may be mapped to take its place if and only if it is within the visit window of the missing scheduled visit. The following table describes the visit mapping of unscheduled post-baseline visits in the event that a scheduled visit is missing. If there are multiple unscheduled visits, the closest one to the projected date will be selected; if there are ties, the later measurement will be used.

Parameter	Analysis Visit/Time Point Window
Labs	Study Day ± 3 days from Target Day ET visits are mapped to the nearest missing analysis visit, using the same window, after unscheduled visits are considered.
MRI; Fibroscan	**Day 50:** 36<= Study Day <= 64 (± 14 Days); **Day 92:** Study Day >= 78; ET visits within Study Day < 65 will be mapped to Day 50; ET visits with Study Day >= 65 will be mapped to Day 92.
Vital Signs	Study Day ± 3 days from Target Day; ET visits are mapped to the nearest missing analysis visit, using the same window, after unscheduled visits are considered.
Anthropomorphic Measures	Study Day ± 3 days from Target Day (For body weight) Study Day ± 14 days from Target Day (For waist-hip ratio related parameters) ET visits are mapped to the nearest missing analysis visit, using the same window, after unscheduled visits are considered
ECG	Study Day ± 3 days from Target Day ; ET visits are mapped to the nearest missing analysis visit after unscheduled visits are considered using Study Day
PK	Depending on the time point, the window for each time point is specified in the PK sampling schedule. If multiple unscheduled records are available, the sample collected closest to the nominal time will be selected. If the distance is the same, the later one will be selected. (Actual time should be used for PK analysis)

Measurements from all protocol planned visits will be summarized in descriptive tables and figures. For pharmacodynamic endpoints that are analyzed using MMRM analysis, only measurements taken at weekly analysis visits (eg, Day 1, Day 8, 15, 22, 29, 36, etc) will be included in the analysis and corresponding data presentation. Analyses will utilize the measurements taken at the scheduled visits whenever they are available. If not available, the analysis will use the measurement mapped to that scheduled visit (whichever is the closest to the target date, and if there are two measurement before and after the target day with same duration, use the measurement taken at the later day) If there are duplicate results from the same sample are available, eg, with the identical sampling date and time, the average value will be used for data analysis and both raw data and average value will be listed. EOS/ET visits will be summarized in descriptive summary. ET visits will be eligible to be to mapped to missing protocol planned visits, but will not on its own be considered an analysis visit or time point.

9.1.4. Assessments Below and Above the Limit of Quantification

For summarization of PK concentration values and data analysis, assessments that are below the lower limit of quantification (LLOQ) will be set to zero prior to summarization. For PK concentration graphs, assessments that are below the lower limit of quantification will be set to half of LLOQ prior to graphing. For PK concentration assessments that are above the upper limit of quantification (ULOQ), the record will be set to missing prior to summarization or graphing. For other exploratory PK analysis such as population PK, assessment that are below the LLOQ may be defined differently.

For all other assessments that are below the lower limit of quantification will be imputed to half of the LLOQ for summarization; assessments that are above the upper limit of quantification will be imputed to the ULOQ for summarization.

For listings, records that are LLOQ or ULOQ will be listed as such together with the imputed value in separate columns.

9.2. Pharmacokinetic Analyses

Serum concentration and PK parameter data will analyzed using the Pharmacokinetics Analysis Set.

9.2.1. Analysis of Serum Concentrations of BIO89-100

The serum concentration of BIO89-100 over time will be listed and plotted by individual and also summarized by treatment group. Serum concentration data will also be presented using arithmetic statistics.

9.2.2. Analysis of PK Parameters

The following PK endpoints will be summarized by treatment group:

- C_{max} within a dosing interval (Day 1 and Day 29), the maximum serum concentration within each dosing interval.
- $AUC_{0\text{-}tau}$ within a dosing interval (Day 1 and Day 29), derived using linear-log trapezoidal rule; assuming linear curve when concentrations are increasing and exponential decay when concentrations are decreasing.
- t_{max}, the time at which C_{max} is observed in reference to the start of the dosing interval during dosing interval (Day 1 and Day 29).
- $t_{1/2}$, the time at which the concentration is half of the observed maximum concentration within the dosing interval during dosing interval (Day 1 and Day 29).

PK parameters will be calculated separately by designate of 89bio.

9.3. Study Subjects

Subject enrollment by site will be summarized. The number of subjects who were screened, randomized, early discontinued from investigational product, early discontinued from study, and completers will be summarized.

9.3.1. Subject Disposition

Subject disposition will be presented for the Randomized Analysis set. The number of subjects randomized, included in each analysis population, who completed study or had early terminated from the study and the reason, who completed IP regimen or discontinued IP regimen prematurely and the reason will be summarized by treatment group and overall. The number of subjects who were screened will be summarized based on Screened Analysis Set.

Subject disposition will also be summarized by subgroup of biopsy confirmed NASH.

In addition, a listing will be provided for subjects who had been impacted by COVID-19, eg, study interruptions and the duration of their study interruption, withdrew from investigational product, withdrew from study, or had protocol deviation.

9.3.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics data will be summarized descriptively using Randomized Analysis Set by treatment group and overall. Demographics and baseline characteristics include but not limited to, age (continuous and categories: <65, 65 to <75 and ≥75 years), sex, race and ethnicity, height, body weight, body mass index (continuous and categories: <25, 25 to <30, 30 to <35, and ≥35 kg/m^2), [redacted], central obesity (waist circumference of >102 cm for males, >88 cm for females, or body mass index (BMI) >30 kg/m^2); biopsy confirmed NASH (yes/no); [redacted] triglycerides (continuous and categories: <150, 150 to <200 and ≥200 mg/dL), non-HDL, HDL-c, LDL-c (continuous and categories: <130, ≥130 mg/dL), [redacted], ALT, increased ALT (ALT ≥ 40 U/L in males, ALT ≥ 30 U/L in females),AST, adiponectin, Pro-C3, Pro-C3 subgroup (<14.71, ≥14.71 ng/mL), [redacted], subjects meeting at least one or two out of the following five criteria: baseline ALT >1x ULN, VCTE ≥7.6 kPa, ELF≥7.7, Pro-C3≥14.71 ng/mL, FIB-4 score > 1.3. FFA, adipo-IR, hsCRP, MRI-PDFF, [redacted], endogenous FGF21, type 2 diabetes mellitus history (yes/no), HbA1c, HOMA-IR, fasting plasma glucose, [redacted] The criteria where the subjects qualified for the study, eg, 1) NASH with fibrosis (stages F1, F2 or F3) or 2) Central obesity with T2DM or 3) Central obesity WITH either increased ALT and/or Fibroscan VCTE score ≥7 KPa per protocol definitions will also be summarized.

Demographics and baseline characteristics summary will be repeated by subgroup of "biopsy confirmed NASH with fibrosis status (F1, F2, F3)" (yes/no).

9.3.3. Biopsy History

The number and percentage of subjects with biopsies within 24 months of screening will be summarized by fibrosis stage (F0, F1, F2, F3, F4), NAFLD activity score (continuous with range, categorical: score from 0 to 8), steatosis score (continuous with range, categorical), ballooning degeneration score (quartiles, categorical), lobular inflammation score (continuous with range, categorical). The percentages for this table will be based on the number of subjects with biopsies within 24 months.

9.3.4. Medical History

The number and percentage of subjects will be summarized by medical history code (System organ class and preferred term) and by treatment group and overall for the Randomized Analysis set. Medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA version 23.0 – Apr 2020).

9.3.5. Inclusion/Exclusion Criteria

Inclusion and exclusion criteria failures will not be summarized, but will be listed for the Screened Analysis set.

9.3.6. Investigational Product Administration

Investigational product administration data such as the number and percentage of subjects who were administered full doses of investigational product each time, the number and percentage of subjects who were administered at least one partial dose, total number of injections administered over the study, investigational product exposure and investigational product compliance over the entire study will be summarized for the Safety Analysis set.

All investigational product administration data including injection site, incomplete injections their volumes and reason for incompleteness, full or partial doses administered and total volume of injections will be listed by visit.

9.3.7. Concomitant Medication

The World Health Organization Drug Dictionary (B3 WHO Drug Global – Mar 2019) will be used to code the verbatim descriptions of prior and concomitant medications into the Anatomic Therapeutic Chemistry (ATC) classification system. Each verbatim name will be classified by anatomical main group, ATC level 1, therapeutic subgroup, ATC level 2, pharmacological subgroup, ATC level 3, and chemical subgroup, ATC level 4.

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

Pre-treatment medications will not be summarized, but will be in listings.

Baseline medications will also be summarized by ATC classification level 2 and 4.

9.3.8. Concomitant Procedures

All procedures, pre-treatment and concomitant, will be listed.

9.3.9. Protocol Deviations

Important protocol deviations will be summarized by treatment group for the Randomized Analysis set. All protocol deviations will be reviewed by study team to identify notable deviations prior to database lock. All protocol deviations will be listed.

9.4. Pharmacodynamic Analyses

Pharmacodynamic analysis will use Pharmacodynamic Analysis Set and will be analyzed based on randomized treatment group.

9.4.1. Analyses of Anthropomorphic Measurements

The observed values and the change from baseline and percent change from baseline for body weight, BMI, [redacted] will be presented by visit and treatment group.

MMRM analysis will be used to analyze the change from baseline and percent change from baseline in anthropomorphic measurements.

Line plots (± SE) of the change from baseline LS mean over time may be presented by treatment group.

9.4.2. Analyses of Laboratory Parameters

9.4.2.1. Lipids

The observed values and the change from baseline and percent change from baseline for triglycerides, non-HDL cholesterol, HDL-c, LDL-c, [redacted] will be presented by visit and treatment group. Only records where fasting is confirmed will be used for summary and analysis.

The following categories will be included in the descriptive summary by visit:

- Triglycerides <150, 150-<200, ≥200 mg/dL
- LDL-c <130 and ≥ 130 mg/dL

MMRM analysis will be used to analyze the change from baseline and percent change from baseline in lipids.

Non-parametric analysis of the change from baseline and percent change from baseline by visit for triglycerides will be compared by treatment group and the p-value from the Wilcoxon Rank Sum test will be presented. The Hodges-Lehmann estimate of location shift will be used to estimate the median and the exact 90% confidence limits.

Line plots (± SE) of the change from baseline LS mean over time may be presented by treatment group.

In addition, waterfall plots for the individual percent change from baseline to Day 50, change from baseline to Day 50, percent change from baseline to Day 92, change from baseline to Day 92 will be generated.

9.4.2.2. Metabolic Biomarkers

The observed values and the change from baseline and percent change from baseline for [redacted], Adiponectin, HbA1c, HOMA-IR, FFA, Adipo-IR (fasting FFA * fasting insulin), [redacted], fasting glucose and fasting insulin (not from OGTT) will be presented by visit and treatment group.

HOMA-IR value is calculated by multiplying fasting Glucose (mg/dL) with fasting Insulin (uIU/ml) and then dividing by 405.

HOMA-IR value (SI units) is calculated by multiplying fasting Glucose (mmol/L) with fasting Insulin (uIU/ml) and then dividing by 22.5.

MMRM analysis will be used to analyze the change from baseline in metabolic biomarkers.

9.4.2.3. Liver Biomarkers

The observed values and the change from baseline for ALT, AST, [redacted] (derived from hyaluronic acid [HA], amino-terminal propeptide of type III procollagen [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1]), INR, Pro-C3, total bilirubin (TB), direct bilirubin, [redacted] will be presented by visit and treatment group.

A listing of only abnormal liver biomarker records will be provided.

MMRM analysis will be used to analyze the change from baseline in liver biomarkers.

Line plots (± SE) of the change from baseline LS mean over time may be presented by treatment group.

9.4.2.3.1. Sensitivity Analysis for Liver Biomarkers

Subject [redacted] had an adverse event that resulted in a spike of ALT and other liver biomarkers on Day 92 visit. The event was deemed unlikely related to investigational product. After receiving medical treatments, these liver biomarkers returned to normal level by End of Study visit (Day 113).

In order to estimate the treatment effect assuming the adverse event affecting the liver biomarkers did not occur (Hypothetical Strategy), the sensitivity analysis is planned prior to study unblinding, and the sensitivity analysis will set this subject's scheduled Day 92 record as missing, and then impute it with the last unscheduled central lab liver biomarkers measured after Day 92 visit but prior Day 113 visit. Sensitivity analysis using this different estimand will be applied to all descriptive, inferential and subgroup analyses summarizing liver biomarkers.

This sensitivity analysis will only be applied to pharmacodynamic analyses where the PD Analysis Set is used. All central lab records will be used for safety analysis purpose without impute Day 92 record.

9.4.2.4. Suspected Drug Induced Liver Injury

Suspected drug induced liver injury will be summarized in two ways.

For subjects with baseline ALT or AST are within normal range, then the proportion of subjects meeting the following criteria will be summarized by visit and over the entire study; for entire study summary all visits including unscheduled will be considered and the maximum value will be selected among all visits:

- ALT or AST >2x ULN
- ALT or AST >8x ULN
- ALT or AST >5x ULN for a duration of at least 2 weeks
- ALT or AST >3x ULN and (TB >2x ULN or Normalized Ratio (INR) >1.5)
- ALT or AST >3x ULN (the protocol includes with the criteria the following that will not be considered in the summary table: with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [> 5%])

For subjects with baseline ALT or AST >ULN, then the proportion of subjects meeting the following criteria will be summarized:

- ALT or AST >2x ULN or bilirubin >1.5x ULN
- Baseline ALT or AST <2x ULN
    - ALT or AST >5x baseline value
- Baseline ALT or AST ≥2x ULN but <5x ULN
    - ALT or AST >3x baseline value
- Baseline ALT or AST ≥5x ULN
    - ALT or AST >2x baseline value
- ALT or AST increase >2× baseline value AND the increase is accompanied by a concomitant total bilirubin increase to >2× ULN OR the INR concomitantly increases by >0.2.
- ALT or AST increase >2× baseline value (the protocol includes with the criteria the following that will not be considered in the summary table: in the presence of signs and symptom(s) such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%])

An evaluation of drug induced serious hepatotoxicity (eDISH) plot will be generated.

Any subjects that meet the criteria for suspected DILI will be summarized in a listing.

[redacted]

9.4.3. Analyses of MRI Measures

The observed values and the change from baseline and percent change from baseline in MRI-PDFF, [redacted] will be presented by visit and treatment group.

The following criteria will also be summarized at Day 50 and Day 92 based on observed data at that visit:

- Percentage reduction from baseline MRI-PDFF ≥30% and <30%
- MRI-PDFF ≥5% or < 5%

MMRM analysis will be used to analyze the change from baseline and percent change from baseline in MRI-PDFF, abdominal visceral fat, abdominal subcutaneous fat, liver volume.

In addition, a bar chart of LS mean (± SE) percent change from baseline to Day 50, change from baseline to Day 50, percent change from baseline to Day 92, change from baseline to Day 92 in MRI-PDFF by treatment group.

9.4.3.1. Responder Analysis

Responder analysis will be performed for MRI-PDFF. The proportion of subjects that reach a percentage reduction of ≥10, ≥20, ≥30, ≥40 and ≥50 in MRI-PDFF will be summarized based on observed data at that visit. The following will be analyzed with a Fisher's Exact Test.

- Proportion of subjects who have ≥30 percent reduction in MRI-PDFF from baseline to Day 92.

- Proportion of subjects who have ≥30 percent reduction in MRI-PDFF from baseline to Day 50.
- Proportion of subjects who have MRI-PDFF <5% at Day 92.
- Proportion of subjects who have MRI-PDFF <5% at Day 50.

9.4.3.2. Supportive Analysis

Supportive analysis of MRI-PDFF will be performed: with sensitivity analysis to assess impact of missing data using multiple imputation using a pattern-mixture model (PMM) approach using control-based pattern imputation, correlation analysis and non-parametric analysis.

9.4.3.2.1. Multiple Imputation Using Control Based Pattern-Mixture Model

Multiple imputation will be performed using the placebo group to impute the missing values for the BIO89-100 subjects. This imputation will account for the possibility that not all data are missing at random. This method of multiple imputation assumes that the missing data post study discontinuation for BIO89-100 subjects are missing not at random (MNAR). By using the placebo subject data to impute the missing data from the BIO89-100 group, the analysis will produce a conservative estimate of the treatment effect of BIO89-100, although not as conservative as the worst observed case analysis.

Prior to applying the control-based pattern mixture, the first step will be to impute the non-monotone missing data assuming the missing at random (MAR) assumption. Only missing data that are sandwiched by two non-missing records in time will be imputed using the MAR assumption. Visit window mapping should also decrease the amount of non-monotone missing imputations that need to be done. After the non-monotone missing data patterns are filled in then the control-based imputation is applied.

Missing Data Pattern	Baseline	D50	D92
Monotone	X	X	.b
Non-Monotone	X	.a	X

.a is a missing value that will be imputed assuming the MAR assumption because it is sandwiched by two non-missing records; the earlier records will be imputed first.
.b is a missing value that will be imputed assuming the NMAR assumption because it is monotone missing.

9.4.3.3. Correlation Analysis

Correlation analysis will be performed for MRI-PDFF and key liver biomarker data using the PD analysis set. The pairwise Pearson correlation will be calculated for each combination of MRI-PDFF, CAP score, VCTE score, ALT, AST, ELF Score, Pro-C3, triglycerides, LDL and HDL change from baseline within Day 50, within Day 92 and between Day 50 and Day 92 by treatment group (subjects on BIO89-100 only) and for pooled placebo.

9.4.3.4. Non-Parametric Analysis

Non-parametric analysis of the change from baseline and percent change from baseline to Day 50 and Day 92 for MRI-PDFF will be compared by treatment group and the p-value from the

Wilcoxon Rank Sum test will be presented. The Hodges-Lehmann estimate of location shift will be used to estimate the median and the exact 90% confidence limits.

[redacted]

9.5. Safety Analyses

Safety analysis will use the Safety Analysis Set and will be analyzed based on actual treatment group.

9.5.1. Adverse Events

All adverse events will be coded using the MedDRA (version 23.0 – Apr 2020).

The incidence and number of events of the following will be summarized by treatment and overall:

- Overall TEAE Summary*
- TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- Serious TEAEs by SOC and PT
- Serious Related TEAEs by SOC and PT
- Serious TEAEs Leading to Study Discontinuation by SOC and PT
- Serious TEAEs Leading to Investigational Product Discontinuation by SOC and PT
- Related TEAEs by SOC and PT
- TEAEs Leading to Study Discontinuation by SOC and PT
- Fatal TEAE (will be provided in a listing)
- TEAEs by SOC, PT and Maximum CTCAE Grade
- TEAEs by SOC, PT and CTCAE Grade
- TEAEs Leading to Investigational Product Discontinuation by SOC and PT
- TEAEs by PT in Descending Frequency
- TEAE by SOC and PT in subgroup of Biopsy confirmed NASH (Yes if F1, F2, F3, else No) Yes/No

When calculating incidence; subjects will only be counted once per SOC, PT, or grade.

When deriving relationship of AEs to study treatment, categories with the relationship of "definitely related", "probably related", "possibly related" will be considered "related". If an AE has missing relationship, it will be assumed to be related to the investigational product for analysis purposes. If an AE has missing CTCAE grade, the missing grade will be imputed as a severe grade 3 adverse event. Any TEAE related to VOCID19 will be provided in a listing.

TEAEs by System Organ Class (SOC) and Preferred Term (PT) by subgroup of biopsy confirmed NASH (Yes if F1, F2, F3, else No) will be summarized.

*In the Overall TEAE summary, the most severe CTCAE grade will be summarized for each subject.

9.5.2. Clinical Laboratory Evaluations

The observed values and the change from baseline for labs (biochemistry, hematology, urinalysis) will be summarized by visit and treatment group. Pharmacodynamic endpoints summarized via MMRM will not be presented in the safety lab change from baseline tables.

A listing of only abnormal labs (biochemistry, hematology, urinalysis) will be provided.

Shift tables will use the reference range result of low, normal, high to summarize lab (biochemistry and hematology) or normal and abnormal for select urinalysis shifts from baseline to each post-baseline visit. All labs with a reference range result will be included in shift tables. The percentage of the shifts will be derived using the number of subjects at the baseline range level as the denominator. Pharmacodynamic endpoints summarized via MMRM will be presented in the safety lab shift tables.

The observed value and the change from baseline in cortisol will be summarized descriptively in the urinalysis tables.

9.5.3. Physical Examination Findings

Physical examination findings will be listed.

9.5.4. Vital Signs

The observed values and the change from baseline for vital signs will be summarized by visit and treatment group. On visits where multiple ECGs are taken, only pre-dose will be summarized.

The number of subjects meeting the following criteria will be summarized considering all post-baseline visits including unscheduled:

- Absolute value of SBP < 90 mm Hg
- Absolute value of DBP < 50 mm Hg
- Pulse rate <50 bpm
- Pulse rate > 120 bpm
- Maximum increase from baseline in SBP ≥30 mm Hg
- Maximum increase from baseline in DBP ≥20 mm Hg

- Maximum decrease from baseline in SBP ≥30 mm Hg
- Maximum decrease from baseline in DBP ≥20 mm Hg

Shift tables will be used to summarize clinically significant shifts from baseline to each post baseline visit in the following criteria:

- SBP and DBP:

Blood Pressure Category	Systolic mm Hg		Diastolic mm Hg
Hypotension	<90	Or	<60
Normal	<120	And	<80
Elevated	120-129	And	<80
Hypertension Stage 1	130-139	Or	80-89
Hypertension Stage 2	≥140	Or	≥90
Crisis	>180	And/or	>120

- HR (bpm): <50; 50-89; 90-99, ⩾100

9.5.5. 12-Lead Electrocardiograms

The observed values and the change from baseline for 12-lead ECGs parameters will be summarized by visit and treatment group. Only visits where ECGs were taken pre-dose will be summarized.

For corrected QT interval by Fridericia (QTcF), the number and percentage of subjects that have a change from baseline in QTcF >30 to 60msec and >60msec over the entire study considering all visits including unscheduled will be summarized.

Overall interpretation (Normal, Abnormal Not Clinically Significant and Abnormal Clinically Significant) will also be summarized.

The eCRF and central reader data will be listed in addition to a variable identifying if there is agreement between the PI and central reader (Y/N).

A shift table will be used to present the shifts from baseline to each visit using the following criteria:

- QTcF <450msec
- QTcF 450-480msec
- QTcF 481-500msec
- QTcF >500msec
- Not Done/Missing

9.5.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation, intensity of ideation, suicidal behavior, and suicidal behavior lethality from C-SSRS will be listed.

9.5.7. Immunogenicity Analyses

Results of immunogenicity assessment will be summarized by displaying the number of subjects with positive and negative tests. Antibody titers will be listed. Available binding specificity will be listed.

10. Changes to Planned Analysis in the Protocol

There are no changes to the planned analysis in the protocol.

11. Statistical Software

All statistical analyses will be performed using SAS version 9.4 or higher.

12. References

Kahn SE, Lachin JM, Zinman B, et al. Effects of rosiglitazone, glyburide, and metformin on beta-cell function and insulin sensitivity in ADOPT. *Diabetes.* 2011;60(5):1552-1560. doi: 10.2337/db10-1392.

Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*. 1999; 22(9): 1462-1470.

National Heart, Lung and Blood Institute (2020). *Low Blood Pressure*. Retrieved May 19, 2020, from https://www.nhlbi.nih.gov/health-topics/low-blood-pressure.

13. Appendix

Table 2 Schedule of Activities for Cohorts 1-4

Cohorts 1-4 Assessments	Screening Period			Treatment Period															FU Period	
Study Visit	[redacted]																			
Study Day																				
Informed consent	X																			
Medical history/demographics	X																			
Percutaneous liver biopsy (optional)[b]	X																			
Prior medications	X																			
Inclusion and exclusion criteria	X		X																	
Complete physical exam[c]	X												X						X	X
Symptom-directed physical exam[d]			X	B	P				B	B	B		B					[redacted]	B		
Body weight[e]	X			B					B	B	B		B						B		
Waist and hip measurements	X			B									B							X	X
Fibroscan[f]	X																			X	
12-lead ECG (single)[g]	X			B	X				B	B	B		B	X					B	X	X
Urine drug screen and alcohol breath test	X		X[h]																		
Clinical laboratory tests[i]	X	X		B	X				B	B	B		B	X					B	X	X
Cortisol (24 hour urine collection)[j]	X																			X	
Urinalysis	X		X											X						X	X
HbA1c	X		X																	X	X
Serology[k]	X																				
TSH	X																				

Cohorts 1-4 Assessments	**Screening Period**			**Treatment Period**															**FU Period**	
Study Visit	[redacted]																			
Study Day																				
Pregnancy test in WOCBP only[l]	X(S)		X					B	B	B		B					B	B	X	X
Vital signs[m]	X		X	X	P	X	X	X	X	X	X	X	P	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)			X														D50		X	
Randomization			X																	
Investigational product administration[n]				X				X	X	X		X					X	X		
PK blood collection[o]				X	X	X	X	B	B	B		X	X	X	X	X	[redacted]	B	X	
PD and biomarker blood sampling:																				
IGF-1, total				B				B	B			B							X	
Adiponectin				B				B				B							X	X
CK-18, ELF panel and Pro-C3				B								B							X	[redacted]
Free fatty acid				B				B				B							X	X
Oral glucose tolerance test (OGTT)[p]			X																X	
Insulin (not part of OGTT)				B				B				B								X
HOMA-IR calculation				X															X	X
MRI-PDFF; visceral fat; and subcutaneous fat[q]	X																		X	
Plasma sample for potential future bone biomarkers analysis[r]			X																X	X
Pharmacogenomic (DNA) blood sampling			X																	

Cohorts 1-4 Assessments	Screening Period			Treatment Period															FU Period	
Study Visit	[redacted]																			
Study Day																				
Exploratory biomarker analysis[s]			X														B at D50		X	X
Immunogenicity[t]				B					B			B					B at D50		X[u]	X
Endogenous FGF21[v]				B																
Adverse event monitoring[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Domiciled[x]			X	X	X						X	X	X							

Abbreviations: B = predose; D = Day; CK = cytokeratin; DNA = deoxyribonucleic acid; ECG=electrocardiogram; ELF = enhanced liver fibrosis; EOS = end of study; ET= early termination; FGF21 = fibroblast growth factor 21; FU = Follow-Up; HbA1c=hemoglobin A1c; IGF-1 = insulin-like growth factor; MRI-PDFF = magnetic resonance imaging based proton density fat fraction; P = Pre-discharge; PK = pharmacokinetic; Pro-C3 = N-terminal propeptide of type III collagen; S = serum; TSH = thyroid stimulating hormone; WOCBP = women of child-bearing potential.

Table 2 footnotes

All outpatient visits will have a study window of ±1 day.

a. For any subject who withdraws before completion of the study, an Early Termination (ET) visit will be conducted, if possible; with the same assessments as the Day 92 visit.
b. Optional liver biopsy may be performed for subjects who do not have a medical contraindication to undergoing a liver biopsy, and did not have a liver biopsy in the 24 months prior to screening. For subjects who underwent a previous liver biopsy >24 months prior to screening, that would not have qualified for the study based on results of the initial biopsy, there should be a sound clinical basis to expect different findings in a repeat biopsy based on medical judgment. Any biopsy will need to be approved in advance by Sponsor and only after the subject has met all other inclusion and exclusion criteria,
c. Complete physical exam done at screening to include recording height, weight, and calculating BMI.
d. Symptom-directed physical exam will be done pre-dose and prior to discharge from the Phase 1 unit on domiciled dosing visits (1st and 5th dose), and pre-dose on ambulatory dosing visits. Additional physical examinations will be performed if clinically indicated.
e. On domiciled and ambulatory visits, body weight will be measured pre-dose.
f. Fibroscan should be performed during screening, prior to magnetic resonance imaging (MRI) for all subjects.
g. 12-lead safety ECGs will be recorded as single bedside measurements; on domiciled dosing visits (1st and 5th dose), ECG will be measured pre-dose and 24 hours post-dose. On ambulatory dosing visits, ECG will be measured pre-dose. Additional ECG may be conducted if clinically indicated.
h. On Day -1, urine drug screen can be done at a local laboratory, however, a sample should also be collected for central laboratory evaluation.

i. Clinical laboratory tests will include biochemistry, hematology, and coagulation, and FSH for determination of post-menopausal status ; on domiciled dosing visits (1st and 5th dose), clinical laboratory will be collected pre-dose and 24 hours post dose; on ambulatory visits, clinical laboratory will be collected pre-dose. For all subjects, alanine transaminase (ALT) and aspartate transaminase (AST) will be collected twice during the Screening period (at least 2 weeks apart), with the 2nd assessment to be collected at Day -7 to Day -3. A 3rd assessment, if required, will be collected via unscheduled visit (refer to Exclusion criterion 3).
j. Ambulatory 24-hour urine collection for cortisol to be done within 14 days from baseline, on Day 50 and Day 92/ET. It is recommended that subjects collect urine for the 24 hours prior to D-7 to-3 visit and bring the container with them to this visit. Alternatively, urine can be collected for the 24 hours prior to the randomization visit (D-1) and brought to the site on D-1 (the result is not required for eligibility confirmation). For Day 50 and D92/ET – subject will start collection 24 hours before coming into the clinic and bring the sample to the visit.
k. Serology tests will include Hepatitis B surface antigen, Hepatitis C Virus, and Human Immunodeficiency Virus (HIV) 1 and 2 antibodies
l. Serum urine pregnancy test will be conducted at screening; at all other timepoints urine pregnancy test will be done to guide clinical decisions to dose on dosing days. Prior to the 1st dosing, the baseline urine pregnancy test will be performed on D-1 to allow for randomization on that day. If urine test is positive, a confirmatory serum pregnancy test will be conducted.
m. Vital signs include supine blood pressure, pulse, body temperature, and respiratory rate; vital signs will be measured pre-dose (prior to scheduled blood draws and study intervention administration); 1, 12 and 24 hours post-dose and prior to discharge on domiciled dosing visits (1st and 5th doses); on dosing ambulatory visits, vital signs will be measured pre-dose (prior to scheduled blood draws and study intervention administration) and prior to discharge; on non-dosing visits, vital signs will be measured prior to scheduled blood draws. Starting from randomization, blood pressure and pulse will be measured in duplicate, the first measurement will be taken up to 15 minutes before the indicated time point. Additional vital signs measurement may be done if clinically indicated. Subjects must be in a supine or semi-erect/seated position and resting for at least 5 minutes prior to measurements.
n. Study intervention will be administered SC to the abdomen region by qualified study personnel.
o. PK blood samples will be collected as shown in Table 3. Additional blood samples for PK analysis may be collected if clinically indicated (e.g., in case of SAE). For PK sample collection instruction/procedures, refer to the relevant manual.
p. Blood samples for OGTT test will be collected under fasting conditions (10 hours) at the following timepoints: 0 minutes (just prior to ingesting glucose), 30 minutes, 60 minutes, 90 minutes 120 minutes and 180 minutes. On Day 92/ET the insulin will be captured from the OGTT.
q. At Screening, MRI-PDFF to be done within 35 days of baseline (Day 1). On Days 50 and 92, MRI-PDFF to be done within ± 2 days of the planned visit date. If out of the window, MRI-PDFF should still be performed as close to the target day as possible, but protocol deviation should be recorded.
r. Samples for carboxy-terminal collagen crosslinks (CTX) and N-terminal propeptide of type 1 collagen (P1NP) will be obtained at the designated timepoints for storage and potential future analysis. The D42 sample will be obtained pre-dose.
s. Samples for RNA as well as plasma and serum samples will be collected for potential future exploratory assessments, to increase understanding of BIO89-100 biological activity and to identify potential existing and/or emerging biomarkers.
t. [redacted]

[redacted]

u. Immunogenicity sample on Day 92/ET will only be collected for subjects who early terminate from the study.
v. Baseline samples of endogenous FGF21 will be analyzed; [redacted]
w. The sites may take non-personally identifying photographs of potential injection site reactions (optional)
x. Subjects in Cohorts 1 to 4 will be domiciled at the clinic from 1 day prior to dosing until 24 hours post the 1st dose and the 5th dose. Other study visits will be ambulatory. On Day 8, Day 15 and Day 22 (ambulatory dosing visits), subjects will remain at the site for observation for at least 2 hours post dosing.

Table 3 PK Sample Collection for Cohorts 1-4 – QW Dosing Interval

Study Day	Dosing Day	Ambulatory Visit	Hours relative to 1st dose (Day 1)
[redacted]	X		[redacted]
		X	
		X	
		X	
	X	X	
	X	X	
	X	X	
	X		
		X	
		X	
		X	
	X	X	
	X	X	
	X	X	
	X	X	
	X	X	
		X	

Table 4 Schedule of Activities for Cohorts 5 and 6

Cohorts 5-6 Assessments	Screening Period			Treatment Period																FU Period	
Study Visit	[redacted]																				
Study Day																					
Informed consent	X																				
Medical history/demographics	X																				
Percutaneous liver biopsy (optional)[b]	X																				
Prior medications	X																				
Inclusion and exclusion criteria	X		X																		
Complete physical exam[c]	X												X							X	X
Symptom-directed physical exam[d]			X	B	P			X	B	X		B					B		B		
Body weight[e]	X			B				X	B	X		B				[redacted]	B		B		
Waist and hip measurements	X			B								B						X		X	X
Fibroscan[f]	X																	X		X	
12-lead ECG (single)[g]	X			B	X			X	B			B	X						[redacted]	X	X
Urine drug screen and alcohol breath test	X		X[h]																		
Clinical laboratory tests[i]	X	X		B	X			X	B	X		B	X							X	X
Cortisol (24 hour urine collection)[j]	X																			X	
Urinalysis	X		X										X					X		X	X
HbA1c	X		X																	X	X
Serology[k]	X																				
TSH	X																				
Pregnancy test in WOCBP only[l]	X(S)		X						B			B					B		B	X	X

Cohorts 5-6 Assessments	Screening Period			Treatment Period																FU Period	
Study Visit	[redacted]																				
Study Day																					
Vital signs[m]	X		X	X	P	X	X	X	X	X	X	X	P	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)			X															X		X	
Randomization			X																		
Investigational product administration[n]				X						X			X						X		
PK blood collection[o]				X	X	X	X	X	X	B	X		X	X	X	X	X		X	[redacted]	X	
PD and biomarker blood sampling:																					
IGF-1, total				B					X	B			B								X	
Adiponectin				B					X				B						X		X	X
CK-18, ELF panel and Pro-C3				B									B						X		X	[redacted]
Free fatty acid				B					X				B						X		X	X
Oral glucose tolerance test (OGTT)[p]			X																		X	
Insulin (not part of OGTT)				B					X				B						X			X
HOMA-IR calculation				X															X		X	X
MRI-PDFF; visceral fat; and subcutaneous fat[q]	X																		X		X	
Plasma sample for potential future bone biomarkers analysis[r]			X																X		X	X
Pharmacogenomic (DNA) blood sampling			X																			
Exploratory biomarker analysis[s]			X																X		X	X

Cohorts 5-6 Assessments	Screening Period			Treatment Period																FU Period	
Study Visit	[redacted]																				
Study Day																					
Immunogenicity[t]				B					B			B						X		X[u]	X
Endogenous FGF21[v]				B																	
Adverse event monitoring[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Domiciled[x]			X	X	X						X	X	X								

Abbreviations: B = predose; D = Day; CK = cytokeratin; DNA = deoxyribonucleic acid; ECG=electrocardiogram; ELF = enhanced liver fibrosis; EOS = end of study; ET= early termination; FGF21 = fibroblast growth factor 21; FU = Follow-Up; HbA1c=hemoglobin A1c; IGF-1 = insulin-like growth factor; MRI-PDFF = magnetic resonance imaging based proton density fat fraction; P = Pre-discharge; PK = pharmacokinetic; Pro-C3 = N-terminal propeptide of type III collagen; S = serum; TSH = thyroid stimulating hormone; WOCBP = women of child-bearing potential.

Table 4 footnotes

All outpatient visits will have a study window of ±1 day

* Between Visits 17 to 19, on Days 64 and 78 subjects will be contacted by phone to inquire about AEs and concomitant medications

a. For any subject who withdraws before completion of the study, an Early Termination (ET) visit will be conducted, if possible; with the same assessments as the Day 92 visit.
b. Optional liver biopsy may be performed for subjects who do not have a medical contraindication to undergoing a liver biopsy, and did not have a liver biopsy in the 24 months prior to screening.|For subjects who underwent a previous liver biopsy >24 months prior to screening, that would not have qualified for the study based on results of the initial biopsy, there should be a sound clinical basis to expect different findings in a repeat biopsy based on medical judgment. Any biopsy will need to be approved in advance by Sponsor and only after the subject has met all other inclusion and exclusion criteria.
c. Complete physical exam done at screening to include recording height, weight, and calculating BMI.
d. Symptom-directed physical exam will be done pre-dose and prior to discharge from the Phase 1 unit on domiciled dosing visits (1st and 3rd dose), and pre-dose on ambulatory dosing visits. Additional physical examinations will also be performed if clinically indicated.
e. On domiciled and ambulatory visits, body weight will be measured pre-dose.
f. Fibroscan should be performed during screening, prior to magnetic resonance imaging (MRI) for all subjects.
g. 12-lead safety ECGs will be recorded as single bedside measurements. On domiciled dosing visits (1st and 3rd dose), ECG will be measured pre-dose and 24 hours post-dose; on ambulatory dosing visits, ECG will be measured pre-dose. Additional ECG may be conducted if clinically indicated.
h. On Day -1, urine drug screen can be done at a local laboratory, however, a sample should also be collected for central laboratory evaluation

i. Clinical laboratory tests will include biochemistry, hematology, and coagulation, and FSH for determination of post-menopausal status ; on domiciled dosing visits (1st and 3rd dose), clinical laboratory will be collected pre-dose and 24 hours post dose; on ambulatory visits, clinical laboratory will be collected pre-dose. For all subjects, alanine transaminase (ALT) and aspartate transaminase (AST) will be collected twice during the Screening period (at least 2 weeks apart), with the 2nd assessment to be collected at Day -7 to Day -3. A 3rd assessment, if required, will be collected via unscheduled visit (refer to Exclusion criterion 3).
j. Ambulatory 24 hour urine collection for cortisol to be done within 14 days from baseline, on Day 50 and Day 92/ET. It is recommended that subjects collect urine for the 24 hours prior to D-7 to-3 visit and bring the container with them to this visit. Alternatively, urine can be collected for the 24 hours prior to the randomization visit (D-1) and brought to the site on D-1 (the result is not required for eligibility confirmation). For Day 50 and D92/ET – subject will start collection 24 hours before coming into the clinic and bring the sample to the visit.
k. Serology tests will include Hepatitis B surface antigen, Hepatitis C Virus, and Human Immunodeficiency Virus (HIV) 1 and 2 antibodies
l. Serum urine pregnancy test will be conducted at screening; at all other timepoints urine pregnancy test will be done to guide clinical decisions to dose on dosing days. Prior to the 1st dosing, the baseline urine pregnancy test will be performed on D-1 to allow for randomization on that day. If urine test is positive, a confirmatory serum pregnancy test will be conducted.
m. Vital signs include supine blood pressure, pulse, body temperature, and respiratory rate; vital signs will be measured pre-dose (prior to scheduled blood draws and study intervention administration); 1, 12 and 24 hours post-dose and prior to discharge on domiciled dosing visits (1st and 3rd doses); on dosing ambulatory visits, vital signs will be measured pre-dose (prior to scheduled blood draws and study intervention administration) and prior to discharge; on non-dosing visits, vital signs will be measured prior to scheduled blood draws. Starting from randomization, blood pressure and pulse will be measured in duplicate, the first measurement will be taken up to 15 minutes before the indicated time point. Additional vital signs measurement may be done if clinically indicated. Subjects must be in a supine or semi-erect/seated position and resting for at least 5 minutes prior to measurements.
n. Study intervention will be administered SC to the abdomen region by qualified study personnel.
o. PK blood samples will be collected as shown in **Table 5**. Additional blood samples for PK analysis may be collected if clinically indicated (e.g., in case of SAE). For PK sample collection instruction/procedures, refer to the relevant manual.
p. Blood samples for OGTT test will be collected under fasting conditions (10 hours) at the following timepoints: 0 minutes (just prior to ingesting glucose), 30 minutes, 60 minutes, 90 minutes 120 minutes and 180 minutes. . On Day 92/ET the insulin will be captured from the OGTT.
q. At Screening, MRI-PDFF to be done within 35 days of baseline (Day 1). On Days 50 and 92, MRI-PDFF to be done within ± 2 days of the planned visit date. If out of the window, MRI-PDFF should still be performed as close to the target day as possible, but protocol deviation should be recorded.
r. Samples for carboxy-terminal collagen crosslinks (CTX) and N-terminal propeptide of type 1 collagen (P1NP) will be obtained at the designated timepoints for storage and potential future analysis. The D42 sample will be obtained pre-dose
s. Samples for RNA as well as plasma and serum samples will be collected for potential future exploratory assessments, to increase understanding of BIO89-100 biological activity and to identify potential existing and/or emerging biomarkers.
t. [redacted]

[redacted]

u. Immunogenicity sample on Day 92/ET will only be collected for subjects who early terminate from the study.
v. Baseline samples of endogenous FGF21 will be analyzed; [redacted]
w. The sites may take non-personally identifying photographs of potential injection site reactions (optional)
x. Subjects in Cohort 5 and 6 will be domiciled at the clinic from 1 day prior to dosing until 24 hours post the 1st dose and 24 hours post the 3rd dose; other study visits will be ambulatory. On the Day 15 ambulatory dosing visit, subjects will remain at the study site for observation for at least 2 hours post dosing.

Table 5 PK Sample Collection for Cohorts 5 and 6 – Q2W Dosing Interval

Study Day	Dosing Day	Ambulatory Visit	Hours relative to 1st dose (Day 1)
[redacted]	X		[redacted]
		X	
		X	
		X	
		X	
	X	X	
		X	
	X		
		X	
		X	
		X	
		X	
	X	X	
	X	X	
	X	X	
	X	X	
		X	

13.1. Sample SAS Code

Sample SAS Code for MMRM analysis:

```
proc mixed data=indata;
class trt visit;
model chg /*or pchg*/ = base trt visit trt*visit/ ddfm=kr s;
repeated visit/type=UN subject=usubjid;
lsmeans trt*visit/pdiff cl alpha=0.1;
run;
```

Sample SAS Code for MMRM analysis with Fibrosis Status Y/N as factor:

```
proc mixed data=indata;
class trt visit biopsy_confirmed_NASH_yn;
model chg /*or pchg*/ = base trt visit biopsy_confirmed_NASH_yn trt*visit/
ddfm=kr s;
repeated visit/type=UN subject=usubjid;
lsmeans trt*visit/pdiff cl alpha=0.1;
run;
```

Sample SAS Code for Wilcoxon Rank Sum Non-Parametric analysis:

```
proc npar1way data=indata wilcoxon alpha=0.1;
class trt;
var chg /*or pchg*/;
exact wilcoxon;
run;
```

Sample SAS Code for Hodges-Lehman Estimation:

```
proc npar1way data=indata hl alpha=0.1;
class trt;
var chg /*or pchg*/;
exact hl;
run;
```

Sample SAS Code for Multiple Imputation Using Control Based Pattern-Mixture Model:

```
proc mi data = non_mono out=monotone niimpute=100 seed=123;
var trt01pn day50 day92;
mcmc chain = multiple impute=monotone;
run;
```

Note: Data needs to be in wide format for the multiple imputation procedure Also, dummy variables are need for categorical factors with more than two levels such as TREATMENT.

```
proc mi data=monotone out=imputed1 nimpute=1 seed = 124;
by _imputation_;
class trt01pn;
var trt01pn day50 day92;
monotone reg(/details);
mnar model (day50 day92/modelobs=( trt01pn =’0’));
run;
```

```
proc mixed data=imputed;
by _imputation_;
class subject trt visit;
model pchg = base trt visit trt *visit/ddfm=kr;
repeated visit / sub=subject type=un;
lsmeans trt *visit/pdiff cl;
ods output lsmeans=lsmeans diffs=diffs;
run;
proc sort data=lsmeans;
by trt visit _imputation;
run;
proc mianalyze parms=lsmeans;
modeleffects trt * visit;
ods output parameterestimates=lsm;
by trt visit;
run;
proc sort data=diffs;
by visit _imputation;
run;
proc mianalyze parms=diffs;
modeleffects trt * visit;
ods output parameterestimates=dif;
by visit;
run;
```

Statistical Analysis Plan

Protocol BIO89-100-002 (Part 2, Single Cohort)

A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Properties of BIO89-100 Administered Subcutaneously in Subjects with Nonalcoholic Steatohepatitis (NASH) or with Nonalcoholic Fatty Liver Disease (NAFLD) and at High Risk of NASH

Phase 1b/2a

SAP Version: 1.0 (Final)
Date: 16 DEC 2021

Prepared by: [redacted]
Pharmapace
On Behalf of ProSciento Inc.

Statistical Analysis Plan

Protocol BIO89-100-002 (Part 2, Single Cohort)

A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Properties of BIO89-100 Administered Subcutaneously in Subjects with Nonalcoholic Steatohepatitis (NASH) or with Nonalcoholic Fatty Liver Disease (NAFLD) and at High Risk of NASH

Phase 1b/2a

SAP Version: 1.0 (Final)
Date: 16 DEC 2021

This statistical analysis plan has been reviewed and approved by:

[redacted] Date: 2[redacted]-Dec-2021
89bio LTD

[redacted] Date: 2[redacted]-Dec-2021
89bio LTD

[redacted] Date: 2[redacted]-Dec-2021
89bio LTD

Table of Contents

Abbreviations

ADA	anti-drug antibodies
AEs	adverse events
AI	artificial intelligence
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
ATC	anatomic therapeutic chemistry
BMI	body mass index
CBC	complete blood count
CAP	controlled attenuation parameter
CI	confidence interval
COVID-19	Coronavirus disease 2019
CRO	clinical research organization
C-SSRS	columbia-suicide severity rating scale
CTCAE	common terminology criteria for adverse events
CTX	carboxy-terminal collagen crosslinks
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDISH	evaluation of drug induced serious hepatotoxicity
eGFR	estimated glomerular filtration rate
EOS	end of study
ET	early termination
FGF21	fibroblast growth factor 21
FIB-4	fibrosis-4 score
FU	follow-up
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1c
HDL-c	high density lipoprotein
HIV	human immunodeficiency virus
ICC	intraclass correlation coefficient
INR	international normalized ratio for prothrombin test
IP	investigational product
LDL-c	low density lipoprotein
LLOQ	lower limit of quantification
LS Mean	least-squares mean
MedDRA	medical dictionary for regulatory activities
MMRM	mixed-model repeated measures
MRI-PDFF	magnetic resonance imaging – proton density fat fraction
n	sample size

NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD activity score
NASH	nonalcoholic steatohepatitis
NASH CRN	NASH Clinical Research Network
non-HDL	non-high density lipoprotein
P1NP	n-terminal propeptide of type 1 collagen
PD	pharmacodynamics
PEG	polyethylene glycol
PK	pharmacokinetics
Pro-C3	n-terminal propeptide of type iii collagen
PT	preferred term
QTcF	corrected QT interval by Fridericia
QW	weekly
SAEs	serious adverse events
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SE	standard error
SMC	safety monitoring committee
SOC	system organ class
T2D	type 2 diabetes mellitus
TB	total bilirubin
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal
ULOQ	upper limit of quantification
VCTE	vibration-controlled transient elastography
WHO	world health organization
WOCBP	women of child-bearing potential

1. Introduction

This statistical analysis plan (SAP) describes the statistical methods and procedures to be implemented in Part 2 of clinical study BIO89-100-002. This statistical analysis plan is based on study protocol BIO89-100-002 Version 5.0 dated 11 March 2021. If the data suggest then deviations from this plan will be considered. However, any deviations from the SAP must be substantiated by sound statistical rationale and documented in the final clinical study report.

2. Study Objectives

2.1. Primary Objectives

The primary objectives of Part 2 of the study are:

- To evaluate the safety and tolerability of subcutaneous (SC) injections of 27 mg BIO89-100, administered weekly for 20 weeks, in subjects with biopsy-proven NASH (NAFLD activity score (NAS) ≥4, fibrosis stage F1 with high risk, F2 or F3).
- To characterize effect of BIO89-100 on liver histology

2.2. Secondary Objectives

The secondary objectives of Part 2 of the study are:

- To characterize biomarkers, pharmacodynamics (PD) profile and biological activity of BIO89-100
- To characterize effect of BIO89-100 on liver histology
- To characterize BIO89-100 pharmacokinetics (PK)

3. Study Overview

3.1. Study Design

Part 2 of study BIO89-100-002 is an open-label cohort (Cohort 7) in which BIO89-100 will be administered SC weekly at a single dose level (27 mg QW) to approximately 20 subjects with biopsy-proven NASH (NAS ≥4, fibrosis stage F1 with high risk, F2 or F3), to evaluate effect on histological endpoints.

Cohort	Dose Level[a]	Frequency and Route of Administration	Number of Subjects	
			BIO89-100	Placebo
7	27 mg	QW, SC to abdomen (2 injections) Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, 106, 113, 120, 127, and 134. Total doses: 20	20	NA

[a] The actual doses will be ±5% the mg dose due to technical considerations related to drug withdrawal from the vials into the syringes for injection. This difference is considered negligible for subject exposure.

The study will include a Screening period, a Treatment period, and a Follow-up period. After signing informed consent, subjects will undergo screening assessments to determine eligibility over a period of up to 60 days.

For each subject in Part 2 (Cohort 7), the total duration of study participation will be up to 229 days (31.5 weeks), excluding the potential study interruption due to the Coronavirus disease 2019 (COVID-19) pandemic:

- Screening period: ≤60 days (8.5 weeks)
- Treatment period: 141 days (20 doses in 19 weeks)
- Follow-up period 28 days (4 weeks)

3.2. Study Activities

Please refer to the appendix for the schedule of activities and PK sample collection schedules:

- Appendix 12.1 Schedule of Activities for Part 2 (Cohort 7)
- Appendix 12.2 PK Sample Collection for Part 2 (Cohort 7)

3.3. Randomization Schedule and Blinding Procedures

Part 2 will be open-label with all subjects receiving the same dose (i.e., 27 mg SC QW) of BIO89-100.

3.4. Stratification Factors

There are no stratification factors for Part 2.

3.5. Sample Size and Power

For Part 2, no formal power calculations were used to determine the sample size in Cohort 7 and the number of subjects was chosen based on clinical experience with similar proof-of-concept histology studies and feasibility. This sample size accounts for an anticipated [redacted] of subjects who will not undergo the post-baseline liver biopsy (e.g., [redacted] to have paired liver biopsies). With a sample size of [redacted], the 95% confidence interval of the histological response rate would have a half-width no greater than [redacted] assuming the histological response [redacted] The actual half-width will depend on the observed histological response rate.

3.6. Interim Analysis

No efficacy interim analysis is planned. Sponsor may perform administrative interim analyses to support objectives such as study planning and regulatory interactions.

3.7. Safety Monitoring Committee

Part 2 will not have a Safety Monitoring Committee (SMC) as described for Part 1 since there will be no dose escalation decisions to adjudicate. Part 2 safety data will be reviewed on an ongoing basis by the Sponsor and/or clinical research organization (CRO) Medical Monitors.

4. Study Endpoints

4.1. Primary Endpoints

Part 2 of this study has primary safety and primary efficacy endpoints, which are detailed in Sections 4.1.1 and 4.1.2, respectively.

4.1.1. Primary Safety Endpoints

The primary safety endpoints are:

- Subject incidence of treatment-emergent adverse events (TEAEs)
- Subject incidence of serious TEAEs

4.1.2. Primary Efficacy Endpoint

The primary efficacy endpoint is:

- At least a 2-point improvement in NAS with at least a 1-point improvement in ballooning or lobular inflammation, and no worsening of fibrosis

4.2. Secondary Endpoints

The secondary PD endpoints are:

Anthropometric measurements:

- Change from baseline and percent change from baseline in body weight over time

Laboratory parameters:

- Change from baseline and percent change from baseline in triglycerides over time
  - Change from baseline and percent change from baseline in triglycerides over time in subjects with baseline triglycerides ≥150 mg/dL
- Change from baseline and percent change from baseline in non-high density lipoprotein (non-HDL) cholesterol over time
- Change from baseline and percent change from baseline in high density lipoprotein (HDL-c) over time
  - Change from baseline and percent change from baseline in HDL-c over time in subjects with baseline HDL-c <40 mg/dL for males and <50 mg/dL for females
- Change from baseline and percent change from baseline in low density lipoprotein (LDL-c) over time
  - Change from baseline and percent change from baseline in LDL-c over time in subjects with baseline LDL-c ≥100 mg/dL
- Change from baseline and percent change from baseline in hemoglobin A1c (HbA1c) over time

Liver function tests:

- Change from baseline and percent change from baseline in alanine transaminase (ALT) over time
- Change from baseline and percent change from baseline in aspartate transaminase (AST) over time
- Change from baseline and percent change from baseline in n-terminal propeptide of type III collagen (Pro-C3) over time

Imaging measures:

- Change from baseline and percent change from baseline in magnetic resonance imaging – proton density fat fraction (MRI-PDFF)

Histology measures:

- Improvement of fibrosis ≥1 stage without worsening of NASH
- NASH resolution without worsening of fibrosis

PK measures:

- Trough concentration of BIO89-100

4.3. Other Safety Endpoints

The other safety endpoints are:

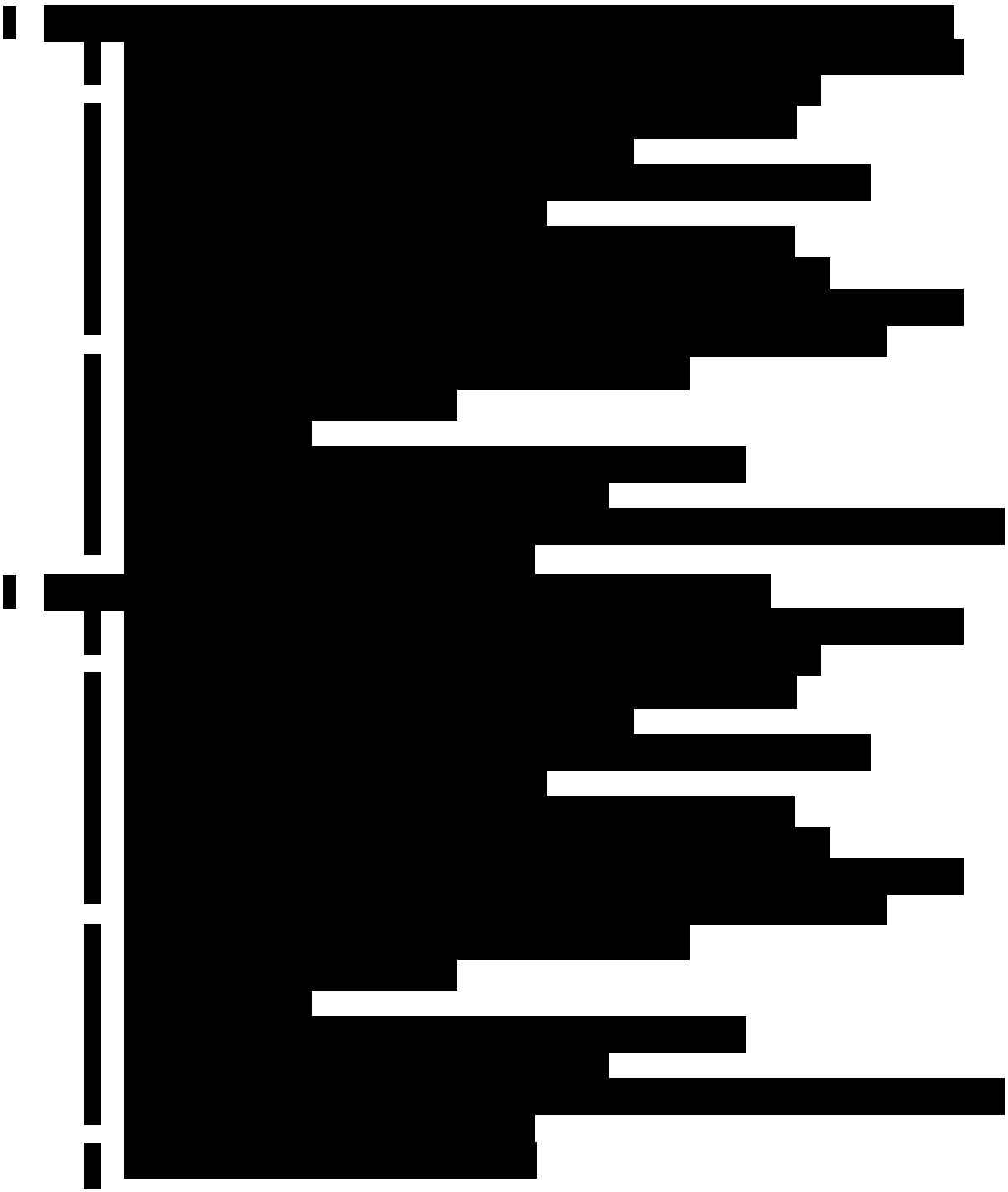
- Subject incidence of TEAEs by severity
- Number of subjects who discontinued due to TEAEs
- Number of subjects who discontinued due to related TEAEs
- Change from baseline in vital signs
- Incidence and shifts of clinically significant vital signs
- Incidence of clinically significant physical examination findings
- Incidence and shifts of clinically significant electrocardiograms (ECG)
- Incidence and shifts of clinically significant laboratory abnormalities
- Change from baseline in safety laboratory evaluations including complete blood count (CBC), blood biochemistry, urinalysis and bone biomarkers (CTX and P1NP)

Immunogenicity measures:

- Incidence and characteristics of anti-drug antibodies (ADA) after dosing (e.g., titer and/or binding specificity, to the fibroblast growth factor 21 (FGF21) and polyethylene glycol (PEG) part of BIO89-100 and neutralizing immunogenicity)
- Impact/correlation of the presence of ADAs on serum BIO89-100 concentrations and clinical safety

4.4. Exploratory Endpoints

[redacted]



5. Definitions

5.1. Definition of Study Day

The day subjects receive their first dose of investigational product (IP) will be considered Study Day 1. Study day will be defined by the number of days from Study Day 1. If index date is prior to Study Day 1, study day will be defined as the index date minus the Study Day 1 date. If index date is on or after Study Day 1 date, the study day will be defined as index date minus the Study Day 1 date plus 1 day. If a subject did not receive IP, the study day will be set as missing.

For subjects with study interruptions due to COVID-19, post-interruption study day will be calculated as: (Index date) – (the date of Study Day 1) + 1 – (the interruption duration as defined in the study interruption CRF). Visits post-interruption due to COVID-19 will use this corrected study day for visit windowing.

5.2. Handling of Missing or Partial Dates

Date imputation will only be used for determining treatment-emergent status for adverse events or identifying concomitant medications. Actual data values as they appear in the database will be shown in the subject level listings.

5.2.1. Adverse Event Date Imputations

In cases of incomplete dates for adverse events, the missing components will be assumed as the most conservative values as possible. The imputation rules described below will attempt to conservatively capture AEs with missing onset dates as treatment-emergent, unless information of AE stop date/time was prior to first dose date, which would automatically disqualify the treatment-emergent status. The original values with no imputation applied will be presented in the data listings.

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

5.2.2. Medication/Procedure Date Imputations

Imputation of partial start and end dates for medications/procedures is done for the purpose of classifying concomitant, pre-treatment, and baseline medications/procedures. The original values with no imputation applied will be presented in the data listings.

For medications/procedures with completely missing start dates, no imputation will be performed.

For medications/procedures with partial start dates:

- If "day" is the only missing field, impute the "day" as the first of the month.
- If "day" and "month" are the missing fields, impute the "day" and "month" to January 1.
- If only day is missing, and month and year are the same as first dose date then consider as concomitant. For a medication/procedure that is not checked as ongoing and the start date is completely missing:
    - and from the end date (either complete, partial or completely missing) it can be deduced to be prior to the first dose date of IP, then consider as pre-treatment.
    - Otherwise, consider as concomitant.

For medications/procedures with completely missing end dates and ongoing is not checked:

- End date will not be imputed, furthermore:
    - If start date is on or after Study Day 1, then consider as concomitant medication/procedure
    - If start date is prior to Study Day 1, or start date is also completely missing, then consider as pre-treatment medication/procedure
    - If start date is on Study Day 1, then consider as baseline medication/procedure

For medications/procedures with partial end dates:

- If "day" is the only missing field, and if month and year are the same as the start date and ongoing is not checked, then impute "day" as the start date "day"; otherwise impute as the last day of the month.
- If "day" and "month" are the missing fields, if year is the same as the start date and ongoing is not checked, then impute "day" and month as the start date day and start date month; otherwise impute as December 31.

For medications/procedures that have both completely missing start dates and end dates, no imputation will be made; these medications/procedures will be assumed to be concomitant.

5.3. Definition of Study Baseline

For study measurements (safety labs, PD, biomarkers and exploratory labs) except ALT or AST, lipids, and vital signs, each subject's baseline value for that measurement will be defined as the latest pre-dose value. This will be determined by chronologically sorting all scheduled and

unscheduled values prior to first dose date and time and taking the latest value unless noted otherwise.

Baseline will be presented with each post-baseline change in the summary tables to allow easier review.

5.3.1. Study Baseline of ALT and AST

For ALT and AST, the baseline value will be defined as the average of all values performed during screening and Study Day 1 based on the following table. The baseline for ALT and AST are calculated and captured in the electronic Case Report Form (eCRF).

ALT or AST Screening Assessments			Day 1 ALT or AST assessment	**Baseline value**
Assessment 1	Assessment 2	Assessment 3 (if applicable)		
Normal	Normal	Not applicable	Any	Average of Assessment 1, Assessment 2 and Day 1 (3 tests)
Normal	Abnormal and ≤40% increase from Assessment 1	Not applicable	Any	Average of Assessment 1, Assessment 2 and Day 1 (3 tests)
Normal	Abnormal and >40% increase from Assessment 1	Normal or ≤40% increase from Assessment 1	Any	Average of Assessment 1, Assessment 2, Assessment 3 and Day 1 (4 tests)
Normal	Abnormal and >40% increase from Assessment 1	Abnormal and >40% increase from Assessment 1	**Not applicable, subject excluded.**	**Not applicable, subject excluded.**
Abnormal	≤40% increase from Assessment 1	Not applicable	Any	Average of Assessment 1, Assessment 2 and Day 1 (3 tests)
Abnormal	>40% increase from Assessment 1	≤40% increase from Assessment 1	Any	Average of Assessment 1, Assessment 2, Assessment 3 and Day 1 (4 tests)
Abnormal	>40% increase from Assessment 1	>40% increase from Assessment 1	**Not applicable, subject excluded.**	**Not applicable, subject excluded.**

5.3.2. Study Baseline for Lipids

For lipids, the baseline will be determined as the average of all pre-dose measurements within 30 days prior to Study Day 1, e.g., measurements taken at -29 ≤ Study Day ≤ 1 (Pre-dose).

5.3.3. Study Baseline for Vital Signs

For vital signs of blood pressure and pulse, measurements will be taken in duplicate starting from enrollment. Baseline for these measures should be the average of all individual assessments during screening up to Study Day 1 and prior to first dose if subject is dosed.

5.4. Definition of Duration of Exposure

The intended duration of exposure for QW dosing will be defined as the date of the last dose of IP minus Study Day 1 date plus 8 days.

5.5. Definition of Age

Age will be defined as the duration in days of date of signed informed consent or index date minus the birthdate divided by 365.25. Index date refers to specific visits if age is needed at specific visits (for example, age at specific visits will be used when deriving FIB-4 score or eGFR).

5.6. Dose Compliance

Dose compliance percentage will be the actual number of received doses divided by the expected number of doses to be received up to the end of study (EOS). Partial doses will contribute to the actual number of received doses.

5.7. Definition of Pre-treatment Medication and Pre-treatment Procedures

Pre-treatment medications are defined as any medication that start and stop being taken prior to Study Day 1.

Pre-treatment procedures are defined as any procedure that were started and completed prior to Study Day 1.

5.8. Definition of Baseline Medication

Medications that have Study Day 1 within the duration of exposure will be considered baseline medications.

5.9. Definition of Concomitant Medication and Concomitant Procedures

Concomitant medications are defined as any medication that is taken any day on or after Study Day 1. This includes medications that were started prior first dose and that were continued to be taken after Study Day 1.

Concomitant procedures are defined as any procedures that are performed any day on or after Study Day 1. This includes procedures that were started prior to first dose and that continued into Study Day 1.

5.10. Definition of the Open-Label Treatment Group

The definition of the open-label treatment group is BIO89-100 27 mg QW.

5.11. Definition of Treatment-Emergent Adverse Event

Treatment-emergent adverse events will be defined as those occurring at or after the time of the first administration of IP, e.g., first dose date and time, through study termination (EOS+28 days of reporting window), or existing prior to the time of and worsening after the time of the first administration of IP. Adverse events with onset prior to the first administration of IP that end before Study Day 1 or do not worsen after Study Day 1 will be classified as pre-treatment.

[redacted]

5.13. Estimated Glomerular Filtration Rate (CKD-EPI)

The eGFR will be derived using the CKD-EPI equation.

For Males:

$$\begin{aligned}\text{eGFR}[\text{mL/min/1.73m}^2] &= 141 \\ &* \min\left(\frac{\text{Serum Creatinine}[\text{mg/dL}]}{0.9}, 1\right)^{-.411} \\ &* \max\left(\frac{Serum\ Creatinine[\text{mg/dL}]}{0.9}, 1\right)^{-1.209} * 0.993^{Age[years]} \\ &* 1.159[if\ black]\end{aligned}$$

For Females:

$$\begin{aligned}\text{eGFR}[\text{mL/min/1.73m}^2] &= 141 \\ &* \min\left(\frac{\text{Serum Creatinine}[\text{mg/dL}]}{0.7}, 1\right)^{-.329} \\ &* \max\left(\frac{Serum\ Creatinine[\text{mg/dL}]}{0.7}, 1\right)^{-1.209} * 0.993^{Age[years]} * 1.018 \\ &* 1.159[if\ black]\end{aligned}$$

5.14. Definition of Study Interruption

Study interruption will be defined as any interruption lasting ≥2 weeks and allowed up to 4 weeks (+4 days) that is due to any causes related COVID-19 pandemic and will require extra handling when deriving analysis visits.

5.15. Definition of Histology Outcomes

Resolution of NASH includes the total absence of ballooning (score=0) and absent or mild inflammation (score 0 to 1).

Worsening of fibrosis is defined as progression of fibrosis ≥1 stage in NASH CRN fibrosis score.

Fibrosis improvement is defined as ≥1-stage decrease in NASH CRN fibrosis score.

Worsening of NASH is defined as increase ≥1 point in NAS for ballooning or inflammation.

6. Potential Covariates

There will be no adjustment for covariates.

7. Analysis Sets

The number of subjects in each analysis set will be summarized.

7.1. Full Analysis Set

The Full Analysis Set will consist of all enrolled subjects in Part 2 who received at least one dose of study intervention . The Full Analysis Set will also be used for safety summary and for PD endpoints, except for MRI and histology endpoints.

7.2. Pharmacokinetics Analysis Set

The PK Analysis Set will consist of all subjects in the Full Analysis Set who have received BIO89-100, and have at least one serum BIO89-100 concentration measurement collected with full dose, and can adequately characterize the trough serum BIO89-100 concentrations.

7.3. MRI Analysis Set

The MRI Analysis Set will consist of all subjects in the Full Analysis Set who have measurable post-baseline MRI data.

7.4. Histology Biopsy Analysis Set

The Histology Biopsy Analysis Set will consist of all subjects in the Full Analysis Set who have both baseline (screening or eligible historical) and post-baseline biopsies.

8. Methods of Statistical Analysis

8.1. General Considerations

In general, scheduled visits from baseline to Day 162 will be summarized. For summaries of worst post-baseline or post-baseline min/max, all visits will be considered, including unscheduled.

8.1.1. Statistical Notation and Presentation

All data collected from all subjects in the electronic data capture will be presented in the subject level listings. All continuous data will be listed with the same precision as presented in the

database. Data listings will be sorted by subject ID and time point. Missing values will be represented by an empty cell and no imputation will be made. If imputation is used for analysis, excluding treatment-emergent and concomitant medication determinations, the imputed values will be listed with a derivation type column in the listing indicating that origin of the imputed value.

Continuous data will be summarized in tables using number of subjects or sample size (n), mean, median, standard deviation (SD), minimum and maximum.

Categorical data will be summarized in two ways, by subject and by time point. Subject data will be summarized using the count of distinct subjects that fall in the category and the percentage of the total number of subjects. Population counts, either the number of subjects or the number of assessments at the time point, will be used as the denominator in the calculation of percentages unless specified otherwise.

The original units (conventional) and SI units will be presented in listings. In general, conventional units will be used for tables and figures, unless otherwise specified. Insulin will use the conventional unit of uU/mL; estimated glomerular filtration rate will be presented using SI units.

Minimum and maximum values will use the precisions of the original value. Means, least-squares (LS) means, and medians will be rounded to one decimal place greater than the precision of the original value up to a max of two decimal places. The limits of confidence intervals (CI), standard deviations (SD), and standard errors (SE) will be rounded to two decimal places greater than the precision of the original value. Derived PK and PD data (e.g., unit conversion) will be presented with three decimal places. Percentages will be rounded to the nearest tenth. Two-sided p-values will be presented with four decimal places and values less than 0.0001 will be presented as <.0001.

8.1.2. Inferential Statistical Analysis Methods

A mixed-model repeated measures (MMRM) analysis will be used to analyze the change from baseline and/or percent change from baseline for selected PD parameters. The model will include baseline value of the dependent variable as a covariate, and subjects as a random effect to account for repeated visits. A compound symmetric covariance structure will be used. The LS means will be derived from the model with their corresponding SE, p-values and two-sided 95% CI.

If strong evidence exists that the normality assumptions are violated for, but not limited to, triglycerides or MRI-PDFF, non-parametric methods will be considered such as the Wilcoxon Rank Sum test.

For proportion of various types or responders, the 95% exact binomial CI will be provided.

The Cohan-Kappa statistics, including the Kappa coefficient, 95% CI, and two-sided p-value will be applied when assessing the concordant and discordant between two raters, e.g., histology data central reader versus PathAI reader.

There will be no adjustments for multiplicity in this study.

8.1.3. Analysis Visits and Visit Windowing

In general, all scheduled visits will be used as analysis visit for descriptive analysis tables and listings.

If a scheduled visit is missing, an unscheduled visit may be mapped to take its place if and only if it is within the visit window of the missing scheduled visit. The following table describes the visit mapping of unscheduled post-baseline visits in the event that a scheduled visit is missing. If there are multiple unscheduled visits, the closest one to the projected date will be selected; if there are ties, the later measurement will be used.

Parameter	Analysis Visit/Time Point Window
Labs	Study Day ±3 days from Target Day Early termination (ET) visits are mapped to the nearest missing analysis visit, using the same window, after unscheduled visits are considered.
MRI	**Day 85:** Study Day >=78; ET visits with Study Day >=65 will be mapped to Day 85. **Day 141:** Study Day >=113
Histology Endpoints	**Day 141:** Any post-baseline
Fibroscan	**Day 141:** Any post-baseline
Vital Signs	Study Day ±3 days from Target Day; ET visits are mapped to the nearest missing analysis visit, using the same window, after unscheduled visits are considered.
Anthropometric Measures	Study Day ±3 days from Target Day (For body weight) Study Day ±14 days from Target Day (For waist-hip ratio related parameters) ET visits are mapped to the nearest missing analysis visit, using the same window, after unscheduled visits are considered
ECG	Study Day ±3 days from Target Day ; ET visits are mapped to the nearest missing analysis visit after unscheduled visits are considered using Study Day
PK	Depending on the time point, the window for each time point is specified in the PK sampling schedule. If multiple unscheduled records are available, the sample collected closest to the nominal time will be selected. If the distance is the same, the later one will be selected.

Measurements from all protocol planned visits will be summarized in descriptive tables and figures. For PD endpoints that are analyzed using MMRM analysis, only measurements taken at

analysis visits (e.g., Day 1, Day 8, 15, 29, 57, etc.) will be included in the analysis and corresponding data presentation. Analyses will utilize the measurements taken at the scheduled visits or the unscheduled visit that have been mapped to a scheduled visits, as described in Section 8.1.3. If there are duplicate results from the same sample are available, e.g., with the identical sampling date and time, the average value will be used for data analysis and both raw data and average value will be listed.

8.1.4. Assessments Below and Above the Limit of Quantification

For summarization of PK concentration values and data analysis, assessments that are below the lower limit of quantification (LLOQ) will be set to zero prior to summarization. For PK concentration graphs, assessments that are below the lower limit of quantification will be set to half of LLOQ prior to graphing. For PK concentration assessments that are above the upper limit of quantification (ULOQ), the record will be set to missing prior to summarization or graphing. For other exploratory PK analysis such as population PK, assessment that are below the LLOQ may be defined differently.

For all other assessments that are below the lower limit of quantification will be imputed to half of the LLOQ for summarization; assessments that are above the upper limit of quantification will be imputed to the ULOQ for summarization.

For listings, records that are LLOQ or ULOQ will be listed as such together with the imputed value in separate columns.

8.2. Pharmacokinetic Analyses

Trough serum concentration will be summarized using the PK Analysis Set.

The trough serum concentration of BIO89-100 over time will be listed and plotted by individual subject and also summarized by nominal study visit. Serum concentration data will also be presented using descriptive statistics. Mean and individual serum concentration vs. time plots will be produced on both the linear/linear scale and on the semi-logarithmic scale.

8.3. Study Subjects

Subject enrollment by site will be summarized. The number of subjects who were screened, enrolled, early discontinued from IP, early discontinued from study, and completers will be summarized.

8.3.1. Subject Disposition

Subject disposition will be presented for the Full Analysis Set. The number of subjects enrolled, included in each analysis set, who completed study or had early terminated from the study and the reason, who completed IP regimen or discontinued IP regimen prematurely and the reason will be summarized. The number of subjects who were screened will be summarized.

In addition, a listing will be provided for subjects who had been impacted by COVID-19, e.g., study interruptions and the duration of their study interruption, withdrew from IP, withdrew from study, or had protocol deviation.

8.3.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics data will be summarized descriptively using Full Analysis Set. Demographics and baseline characteristics include but not limited to, age (continuous and categories: <65, 65 to <75 years), sex, race and ethnicity, height, body weight, body mass index (continuous and categories: 25 to <30, 30 to <35, and ≥35 kg/m^2), [redacted], central obesity (waist circumference of >102 cm for males, >88 cm for females, or body mass index (BMI) >30 kg/m^2); [redacted], triglycerides (continuous and categories: <150, 150 to <200 and ≥200 mg/dL), non-HDL, HDL-c, LDL-c (continuous and categories: <130, ≥130 mg/dL), [redacted], ALT, increased ALT (ALT ≥40 U/L in males, ALT ≥30 U/L in females), AST, adiponectin, Pro-C3, Pro-C3 subgroup (<14.71, ≥14.71 ng/mL), [redacted]; MRI-PDFF, endogenous FGF21, T2D history (yes/no), HbA1c, fasting plasma glucose.

8.3.3. Baseline Biopsy

The number and percentage of subjects with biopsies within 24 weeks of baseline including qualified historical biopsy and on-study biopsy during screening will be summarized by fibrosis stage (F2, F3), NAS (continuous with range, categorical: score from 0 to 8), steatosis score (continuous with range, categorical), ballooning degeneration score (quartiles, categorical), lobular inflammation score (continuous with range, categorical) for the Full Analysis Set. The percentages for this table will be based on the number of subjects with biopsies within 24 weeks in the Full Analysis Set.

8.3.4. Medical History

The number and percentage of subjects will be summarized by medical history code with system organ class (SOC) and preferred term (PT) for the Full Analysis Set. Medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA version 23.1 – Sep 2020).

8.3.5. Inclusion/Exclusion Criteria

Inclusion and exclusion criteria failures will not be summarized, but will be listed for the Full Analysis Set.

8.3.6. Investigational Product Administration

IP administration data such as the number and percentage of subjects who were administered full doses of IP each time, the number and percentage of subjects who were administered at least one partial dose, total number of injections administered over the study, IP exposure, relative dose intensity and IP compliance over the entire study will be summarized for the Full Analysis Set.

All IP administration data including injection site, volume of incomplete injections -and reason for incompleteness, full or partial doses administered and total volume of injections will be listed by visit.

Relative dose intensity is the ratio of actual dose intensity (mg) to planned dose intensity (mg). Actual dose intensity (mg) is equal to the cumulative actual dose (mg) divided by 20. Dose compliance percentage is defined as the actual number of received doses divided by the expected number of doses to be received up to EOS. Partial doses contribute to the actual number of received doses.

8.3.7. Concomitant Medication

The World Health Organization Drug Dictionary (B3 WHO Drug Global – Mar 2019) will be used to code the verbatim descriptions of prior and concomitant medications into the Anatomic Therapeutic Chemistry (ATC) classification system. Each verbatim name will be classified by anatomical main group, ATC level 1, therapeutic subgroup, ATC level 2, pharmacological subgroup, ATC level 3, and chemical subgroup, ATC level 4.

The number and percentage of subjects receiving concomitant medications will be summarized by ATC classification level 2 and level 4 for the Full Analysis set.

Pre-treatment medications will not be summarized, but will be in listings.

Baseline medications will also be summarized by ATC classification level 2 and 4.

8.3.8. Concomitant Procedures

All procedures, pre-treatment and concomitant, will be listed.

8.3.9. Protocol Deviations

Protocol deviations will be summarized for the Full Analysis Set. All protocol deviations will be reviewed by study team to identify major deviations prior to database lock. Major protocol deviations will be flagged and summarized as well. All protocol deviations will be listed.

8.4. Pharmacodynamic Analyses

PD analysis will use Full Analysis Set, MRI Analysis Set, and Histology Biopsy Analysis Set.

8.4.1. Analysis of Histology

8.4.1.1. Histology Measurements from Central Reader

Endpoints of different histological responses will be summarized with the point estimates and 95% CIs of the proportions of subjects who meet the response criteria (defined in Sections 4.1.2, 4.2, and 4.4) at Day 141 using the Histology Biopsy Analysis Set.

Baseline, change from baseline in individual score including NASH CRN fibrosis score, ISHAK fibrosis score, NAS score, steatosis grade, lobular inflammation grade, and ballooning grade will be summarized using the Histology Biopsy Analysis Set and by subgroups. The proportions of

subjects who met ≥1-point improvement in steatosis, ≥1-point improvement in ballooning, ≥1-point improvement in inflammation will be summarized in tables and plotted in bar charts.

Shift of fibrosis stage from baseline to Day 141 in CRN and ISHAK fibrosis scores will be summarized. Shift of individual NAS components from baseline to Day 141 will be summarized.

Bar charts of CRN and ISHAK fibrosis scores with baseline and Day 141 side by side may be presented.

[redacted]

8.4.2. Analyses of Anthropometric Measurements

The observed values and the change from baseline and percent change from baseline for body weight, BMI, [redacted] will be presented by visit.

MMRM analysis will be performed on weight. Line plots (±SE) of the change from baseline mean over time may be presented.

8.4.3. Analyses of Laboratory Parameters

8.4.3.1. Lipids

The observed values and the change from baseline and percent change from baseline for triglycerides, non-HDL cholesterol, HDL-c, LDL-c, [redacted] will be presented by visit.

MMRM analysis will be performed on all lipids parameters. Only records where fasting is confirmed will be used for summary and analysis.

The following categories will be included in the descriptive summary by visit:

- Triglycerides <150, 150 - <200, and ≥200 mg/dL
- LDL-c <130 and ≥130 mg/dL

Additional shift tables for lipids based on the following cut points will be provided for baseline versus post-baseline values, by visit:

- Triglycerides <150, 150 - <200, and ≥200 mg/dL
- Triglycerides <150, ≥150 mg/dL
- LDL-c <130 and ≥130 mg/dL
- LDL-c <100 and ≥100 mg/dL
- HDL-c <40 and ≥40 mg/dL for males, and <50 and ≥50 mg/dL for females

Line plots (±SE) of the change from baseline mean over time may be presented.

In addition, waterfall plots for the individual percent change from baseline to Day 85, change from baseline to Day 85, percent change from baseline to Day 113, change from baseline to Day 113 will be generated.

8.4.3.2. Liver Biomarkers

The observed values and the change from baseline for ALT, AST, Pro-C3, and [redacted] will be presented by visit. MMRM analysis will be performed on all four endpoints.

A listing of only abnormal liver biomarker records will be provided.

Line plots (±SE) of the change from baseline mean over time may be presented.

8.4.3.3. Suspected Drug Induced Liver Injury

Suspected drug induced liver injury will be summarized in two ways.

For subjects with baseline ALT or AST are within normal range, then the proportion of subjects meeting the following criteria will be summarized by visit and over the entire study; for entire study summary all visits including unscheduled will be considered and the maximum value will be selected among all visits:

- ALT or AST >2x ULN
- ALT or AST >8x ULN
- ALT or AST >5x ULN for a duration of at least 2 weeks
- ALT or AST >3x ULN and (total bilirubin (TB) >2x ULN or international normalized ratio (INR) >1.5)

- ALT or AST >3x ULN (the protocol includes with the criteria the following that will not be considered in the summary table: with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%])

For subjects with baseline ALT or AST >ULN, then the proportion of subjects meeting the following criteria will be summarized:

- ALT or AST >2x ULN or bilirubin >1.5x ULN
- Baseline ALT or AST <2x ULN
  - ALT or AST >5x baseline value
- Baseline ALT or AST ≥2x ULN but <5x ULN
  - ALT or AST >3x baseline value
- Baseline ALT or AST ≥5x ULN
  - ALT or AST >2x baseline value
- ALT or AST increase >2x baseline value AND the increase is accompanied by a concomitant total bilirubin increase to >2x ULN OR the INR concomitantly increases by >0.2.
- ALT or AST increase >2x baseline value (the protocol includes with the criteria the following that will not be considered in the summary table: in the presence of signs and symptom(s) such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%])

An evaluation of drug induced serious hepatotoxicity (eDISH) plot will be generated. If there are subjects with Hy's law then these subjects' data will be listed.

Any subjects that meet the criteria for suspected drug-induced liver injury (DILI) will be summarized in a listing.

8.4.4. Analyses of MRI Measures

The observed values and the change from baseline and percent change from baseline in MRI-PDFF will be presented by visit. MMRM analysis will also be performed.

Number of subjects with MRI-PDFF ≥5% or <5% will be summarized at Day 85 and Day 141 based on observed data at each visit. The responder analysis will be performed for MRI-PDFF using the thresholds of reaching ≥30, ≥50, and ≥70 reduction in MRI-PDFF based on observed data at each visit. Ninety-five percent confidence intervals will be provided for the proportion of responders.

In addition, a bar chart will be generated including mean (±SE) percent change from baseline to Day 85, change from baseline to Day 85, percent change from baseline to Day 141, and change from baseline to Day 141 in MRI-PDFF.

[redacted]

[redacted]

8.5. Safety Analyses

Safety analysis will use the Full Analysis Set.

8.5.1. Adverse Events

All adverse events will be coded using the MedDRA (version 23.1 – Sep 2020).

The incidence and number of events of the following will be summarized:

- Overall TEAE Summary*
- TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- Serious TEAEs by SOC and PT
- Serious Related TEAEs by SOC and PT
- Serious TEAEs Leading to Study Discontinuation by SOC and PT
- Serious TEAEs Leading to IP Discontinuation by SOC and PT
- Related TEAEs by SOC and PT
- TEAEs Leading to Study Discontinuation by SOC and PT
- Fatal TEAE (will be provided in a listing)
- TEAEs by SOC, PT and Maximum CTCAE Grade
- TEAEs by SOC, PT and CTCAE Grade
- TEAEs Leading to IP Discontinuation by SOC and PT
- TEAEs by PT in Descending Frequency

When calculating incidence; subjects will only be counted once per SOC, PT, or grade.

When deriving relationship of AEs to study treatment, categories with the relationship of "definitely related", "probably related", and "possibly related" will be considered "related". If an AE has missing relationship, it will be assumed to be related to the IP for analysis purposes. If an AE has missing CTCAE grade, the missing grade will not be imputed. A separate category for "missing" will be included in the table. Any TEAE related to COVID19 will be provided in a listing.

*In the Overall TEAE summary, the most severe CTCAE grade will be summarized for each subject.

8.5.2. Clinical Laboratory Evaluations

The observed values and the change from baseline for labs (biochemistry, hematology, and urinalysis) will be summarized by visit. Pharmacodynamic endpoints summarized via descriptive efficacy summaries will not be presented in the safety lab change from baseline tables.

MMRM analysis will be performed on HbA1c and adiponectin.

A listing of only abnormal labs (biochemistry, hematology, and urinalysis) will be provided.

Shift tables will use the reference range result of low, normal, high to summarize lab (biochemistry and hematology) or normal and abnormal for select urinalysis shifts from baseline to each post-baseline visit. All labs with a reference range result will be included in shift tables. The percentage of the shifts will be derived using the number of subjects at the baseline range level as the denominator. The normal and abnormal reference range is included in Appendix 12.3 in the appendix section.

8.5.3. Physical Examination Findings

Physical examination findings will be listed.

8.5.4. Vital Signs

The observed values and the change from baseline for vital signs will be summarized by visit.

The number of subjects meeting the following criteria will be summarized considering all post-baseline visits including unscheduled:

- Absolute value of SBP <90 mm Hg
- Absolute value of DBP <50 mm Hg
- Pulse rate <50 bpm
- Pulse rate >120 bpm
- Maximum increase from baseline in SBP ≥30 mm Hg
- Maximum increase from baseline in DBP ≥20 mm Hg
- Maximum decrease from baseline in SBP ≥30 mm Hg
- Maximum decrease from baseline in DBP ≥20 mm Hg

Shift tables will be used to summarize clinically significant shifts from baseline to each post baseline visit in the following criteria:

- SBP and DBP:

Blood Pressure Category	Systolic mm Hg		Diastolic mm Hg
Hypotension	<90	Or	<60
Normal	<120	And	<80
Elevated	120-129	And	<80
Hypertension Stage 1	130-139	Or	80-89
Hypertension Stage 2	≥140	Or	≥90
Crisis	>180	And/or	>120

- HR (bpm): <50; 50-89; 90-99, ≥100

For the assignment of blood pressure category, since they are not mutually exclusive, the assignment priority is as follows: Crisis, Hypertension Stage 2, Hypertension Stage 1, Elevated, Normal and then Hypotension.

8.5.5. 12-Lead Electrocardiograms

The observed values and the change from baseline for 12-lead ECGs parameters will be summarized by visit. Only visits where ECGs were taken pre-dose will be summarized.

For corrected QT interval by Fridericia (QTcF), the number and percentage of subjects that have a change from baseline in QTcF >30 to 60 msec and >60 msec over the entire study considering all visits including unscheduled will be summarized.

Overall interpretation (Normal, Abnormal Not Clinically Significant and Abnormal Clinically Significant) will also be summarized.

The eCRF and central reader data will be listed in addition to a variable identifying if there is agreement between the PI and central reader (Y/N).

A shift table will be used to present the shifts from baseline to each post-baseline visit using the following criteria:

- QTcF <450 msec
- QTcF 450-480 msec
- QTcF 481-500 msec
- QTcF >500 msec
- Not Done/Missing

8.5.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation, intensity of ideation, suicidal behavior, and suicidal behavior lethality from C-SSRS will be listed.

8.5.7. Immunogenicity Analyses

Immunogenicity assessment will utilize a tiered approach (i.e., screen, confirm, titer, binding specificity and neutralizing activity). Results of immunogenicity assessment will be summarized by displaying the number and proportion of subjects with positive and negative tests. Antibody titers will be listed and summarized (i.e., n, mean, SD, median, min, max) by study visit. Available binding specificity and neutralizing immunogenicity results will be listed.

9. Changes to Planned Analysis in the Protocol

There are no changes to the planned analysis in the protocol.

10. Statistical Software

All statistical analyses will be performed using SAS version 9.4 or higher.

11. References

National Heart, Lung and Blood Institute (2020). *Low Blood Pressure*. Retrieved May 19, 2020, from https://www.nhlbi.nih.gov/health-topics/low-blood-pressure.

12. Appendix

12.1. Schedule of Activities for Part 2 (Cohort 7)

Cohorts 7 Assessments	Screening Period		Treatment Period		FU Period	
Study Visit	[redacted]					
Study Day (mandatory in clinic visits)						
Informed consent	X					
Medical history/demographics	X					
Percutaneous liver biopsy (optional)[b]	X				X	
Histology machine read (PathAI)	X				X	
Prior medications	X					
Inclusion and exclusion criteria	X		B			
Complete physical exam[c]	X				X	X
Symptom-directed physical exam[d]			B			
Body weight	X		B		X	X
Waist and hip circumference	X		B		X	
Lifestyle counseling	X	X	X			
Fibroscan[e]	X				X	
12-lead ECG (single)[f]	X		B		X	X
Urine drug screen and alcohol breath test	X		B[g]			
Clinical laboratory tests[h]	X	X	B		X	X
Urinalysis	X		B		X	X
HbA1c	X		B		X	X
Serology[i]	X					
TSH	X					
Pregnancy test in WOCBP only[j]	X(S)		B		X	X
Vital signs[k]	X		B		X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)	X					
Study intervention in-clinic (mandatory) administration[l]			X			
Home or in-clinic study intervention administration[m]						
PK blood collection[n]			B		X	
Pro-C3			B		X	
Adiponectin			B		X	
MRI-PDFF[o]	X				X	
Bone biomarkers analysis[p]			B		X	X

Cohorts 7 Assessments	Screening Period		Treatment Period			FU Period	
Study Visit	[redacted]						
Study Day (mandatory in clinic visits)							
Immunogenicity[q]			B			X	X
Endogenous FGF21[r]			B				
Adverse event monitoring[s]	X	X	X			X	X
Concomitant medication	X	X	X			X	X

Abbreviations: B = predose; D = Day; ECG=electrocardiogram; EOS = end of study; ET= early termination; FGF21 = fibroblast growth factor 21; FU = Follow-Up; HbA1c=hemoglobin A1c; MRI-PDFF = magnetic resonance imaging based proton density fat fraction; PK = pharmacokinetic; Pro-C3 = N-terminal propeptide of type III collagen; S = serum; TSH = thyroid stimulating hormone; WOCBP = women of child-bearing potential.

Footnotes

All ambulatory clinic visits will have a study window of ±1 day. Window for MRI-PDFF will be ±7 days. The first liver biopsy will be done during the screening period. The second liver biopsy will be performed within 14 days after the last dose of study intervention. Liver biopsies (first and second) will be done after MRI-PDFF.

a. For any subject who withdraws before completion of the study, an Early Termination (ET) visit willbe conducted, if possible; with the same assessments as the Day 141 visit.
b. A liver biopsy with NASH that meets study inclusion criteria, performed within 24 weeks from baseline visit with the sample deemed interpretable by the central reader is acceptable instead of the baseline liver biopsy. A second liver biopsy will be done within 14 days of the last dose of study intervention. Liver biopsies (first and second) will be done after MRI-PDFF. If out of a window, a liver biopsy should stillbe performed as close to the target date as possible, but a protocol deviation should be recorded.
c. Complete physical exam done at screening to include recording height, weight, and calculating BMI.
d. Physical examinations will be performed if clinically indicated.
e. Fibroscan should be performed during screening, prior to magnetic resonance imaging (MRI) forall subjects. Fibroscan will be repeated on D141/ET.
f. 12-lead safety ECGs will be recorded as single bedside measurements. Additional ECG maybe conducted if clinically indicated.
g. On Day 1, urine drug screen can be done at a local laboratory.
h. Clinical laboratory tests (performed under fasting conditions, ≥10 hours) will include biochemistry, hematology, and coagulation, and FSH for determination of post-menopausal status. For all subjects, alanine transaminase (ALT) and aspartate transaminase (AST) will be collected twice during the Screening period (at least 2 weeks apart), with the 2nd assessment to be collected at Day -7 to Day -3. A 3rd assessment, if required, will be collected via unscheduled visit (refer to Exclusion criterion 3).
i. Serology tests will include Hepatitis B surface antigen, Hepatitis C Virus, and HumanImmunodeficiency Virus (HIV) 1 and 2 antibodies.
j. Serum urine pregnancy test will be conducted at screening; at all other timepoints urine pregnancy test will be done to guide clinical decisions to dose on dosing days. On dosing days in the clinic, a urine pregnancy test will be obtained locally; in addition, a urine sample will be sent to the central lab. If urine test is positive, a confirmatory serum pregnancy test will be conducted.
k. Vital signs include blood pressure, pulse, body temperature, and respiratory rate; vital signs will be measured pre-dose (prior to scheduled blood draws and study intervention administration. Blood pressure and pulse will be measured in duplicate, the first measurement will be taken up to 15 minutes before the indicated timepoint. Additional vital signs measurement may be done if clinically indicated. Subjectsmust be in a supine or semi-erect/seated position and resting for at least 5 minutes prior to measurements.

l. Study intervention will be administered SC to the abdomen region by qualified study personnel or by the subject (under supervision) at ambulatory clinic visit and will be administered at home by the subject at the rest of the planned dosing days. Subjects will be observed for 15 minutes after each dose.
m. At the designated timepoints, study intervention will be administered at the subject's home. If home administration is not feasible, not desired by the subject, or deemed inappropriate option by the investigator for any reason, in-clinic study intervention administration may take place at some or all of these timepoints.
n. PK blood samples will be collected at the specified timepoints. Additional blood samples for PK analysis may be collected if clinically indicated (e.g., in case of SAE). For PK sample collection instruction/procedures, refer to the relevant manual.
o. At Screening, MRI-PDFF to be done within 35 days of baseline (Day 1). On Days 85 and 141, MRI-PDFF to be done within ±7 days of the planned visit date. If out of the window, MRI-PDFF should still be performed as close to the target day as possible, but protocol deviation should be recorded.
p. Samples for carboxy-terminal collagen crosslinks (CTX), N-terminal propeptide of type 1 collagen (P1NP) and osteocalcin will be obtained at the designated timepoints.
q. Subjects who test positive for neutralizing antibodies to BIO89-100 at the EOS visit (or at the ET visit if withdrawn from study) [redacted]
r. Baseline samples of endogenous FGF21 will be obtained in all subjects; [redacted]
s. The sites may take non-personally identifying photographs of potential injection site reactions (optional).

12.2. PK Sample Collection for Part 2 (Cohort 7)

Study Day	Dosing Day	Ambulatory Visit	Hours relative to 1st dose (Day 1)
[redacted]	X	X	[redacted]
	X	X	
	X	X	
	X	X	
	X	X	

12.3. Reference Ranges for Clinical Laboratory Tests

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Reference Ranges, Notable Values, and Critical Values

Sponsor: 89bio LTD

Protocol: BIO89-100-002

[redacted] 10-Dec-2020
Date(dd/mmm/yyyy)

Test Name	Subject Characteristics	Unit (Conventional)	Reference Range	Notable Values	Critical Values
Chemistry					
Albumin (SER)					
	Adult	g/dL	3.5 - 5.5	---	---
Alkaline Phosphatase (SER)					
	Adult	U/L	41 - 146	> 438	---
ALT/SGPT (SER)					
	Adult	U/L	10 - 53	> 159	> 212
Amphetamine and/or Methamphetamine (UR)					
	All	ng/mL	cutoff 1000	---	---
AST/SGOT (SER)					
	Adult	U/L	14 - 43	> 129	> 172
Barbiturates (UR)					
	All	ng/mL	cutoff 200	---	---
Benzodiazepines (UR)					
	All	ng/mL	cutoff 200	---	---
Bicarbonate (SER)					
	Adult	mmol/L	21 - 33	---	< 10 or > 40
Bilirubin (Direct) (SER)					
	Adult	mg/dL	<=0.24	---	---
Bilirubin (Indirect) (SER)					
	All	mg/dL	0.10 - 1.00	---	---
Bilirubin (Total) (SER)					
	Adult	mg/dL	0.25 - 1.21	> 2.00	---
BUN (SER)					
	Adult	mg/dL	5 - 22	---	> 80
Calcium (SER)					
	Adult	mg/dL	8.5 - 10.5	---	< 6.0 or > 13.0
Chloride (SER)					
	Adult	mmol/L	95 - 110	---	< 80 or > 120
Cocaine Metabolite (UR)					
	All	ng/mL	cutoff 300	---	---
Creatine Kinase (CK) (SER)					
	Adult	U/L	25 - 210	> 1050	> 2100

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Test Name	Subject Characteristics	Unit (Conventional)	Reference Range	Notable Values	Critical Values
Chemistry					
Creatinine (SER)					
	Adult Male	mg/dL	0.62 - 1.44	> 2.00	> 3.00
	Adult Female	mg/dL	0.49 - 1.12	> 2.00	> 3.00
Gamma Glutamyl Transferase (GGT) (SER)					
	Adult Male	U/L	11 - 52	> 156	---
	Adult Female	U/L	7 - 38	> 114	---
GFR - CKD-EPI Equation (SER)					
	18-49y	mL/min/1.73m²	> 60	---	---
	>= 50y	mL/min/1.73m²	> 53	---	---
Glucose (SER)					
	Adult	mg/dL	60 - 115	< 50 or > 180	< 40 or > 450
HDL - Cholesterol (ppt) (SER)					
	All	mg/dL	35 - 60	---	---
Lactate Dehydrogenase (LDH) (SER)					
	Adult	U/L	113 - 226	---	---
LDL - Cholesterol (ppt calc) (SER)					
	Adult	mg/dL	50 - 130	---	---
LDL-C (Direct) (SER)					
	Adult	mg/dL	50 - 130	---	---
Magnesium (SER)					
	Adult	mg/dL	1.8 - 2.4	---	< 1.0 or > 4.7
non-HDL Cholesterol (calc) (SER)					
	Adult	mg/dL	80 - 160	---	---
Opiates (UR)					
	All	ng/mL	cutoff 300	---	---
Phencyclidine (PCP) (UR)					
	All	ng/mL	cutoff 25	---	---
Phosphorus (SER)					
	Adult	mg/dL	2.5 - 4.8	---	< 1.0 or > 10.0
Potassium (SER)					
	Adult	mmol/L	3.5 - 5.1	< 3.0 or > 6.0	< 2.8 or > 6.2
Sodium (SER)					
	Adult	mmol/L	134 - 144	---	< 120 or > 160
THC (Marijuana) (UR)					
	All	ng/mL	cutoff 50	---	---
Total Cholesterol (SER)					
	Adult	mg/dL	100 - 200	---	---

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Reference Ranges, Notable Values, Critical Values, and Methodology
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Test Name	Subject Characteristics	Unit (Conventional)	Reference Range	Notable Values	Critical Values
Chemistry					
Total Protein (SER)					
	Adult	g/dL	6.0 - 8.0	---	---
Triglyceride (SER)					
	Adult	mg/dL	50 - 150	> 750	> 1000
Uric Acid (SER)					
	Adult Female	mg/dL	3.0 - 7.0	---	> 15.0
	Adult Male	mg/dL	4.0 - 8.5	---	> 15.0
Coagulation					
Activated Partial Thromboplastin Time (APTT) (PLAS)					
	All	Sec	23.9 - 40.0	---	> 70.0
International Normalized Ratio (INR) (PLAS)					
	All	(None)	0.8 - 1.2	---	> 2.5
EIA					
FGF-21 (SER)					
	All	pg/mL	31.3 - 914.0	---	---
Total Adiponectin (SER)					
	Adult	µg/mL	0.865 - 21.424	---	---
Hematology					
Basophil % (WHBLD)					
	All	%	0.0 - 4.0	---	> 7.0
	All	%	0.0 - 4.0	---	> 7.0
Basophil (Absolute) (WHBLD)					
	All	10^3/µL	0.0 - 0.3	---	---
	All	10^3/µL	0.0 - 0.3	---	---
Eosinophil % (WHBLD)					
	All	%	0.0 - 10.0	---	> 20.0
	All	%	0.0 - 10.0	---	> 20.0
Eosinophil (Absolute) (WHBLD)					
	All	10^3/µL	0.0 - 0.8	---	---
	All	10^3/µL	0.0 - 0.8	---	---
Hematocrit (WHBLD)					
	Adult Male	%	40 - 52	---	< 20 or > 60
	Adult Female	%	35 - 45	---	< 20 or > 60
Hemoglobin (WHBLD)					
	Adult Male	g/dL	13.6 - 18.0	---	< 7.0 or > 20.0
	Adult Female	g/dL	12.0 - 16.0	---	< 7.0 or > 20.0

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Test Name	Subject Characteristics	Unit (Conventional)	Reference Range	Notable Values	Critical Values
Hematology					
Hemoglobin A1c (WHBLD)					
	All	%	4.0 - 6.0	---	---
Lymphocyte % (WHBLD)					
	All	%	15.0 - 45.0	---	> 75.0
	All	%	15.0 - 45.0	---	> 75.0
Lymphocyte (Absolute) (WHBLD)					
	All	10^3/µL	1.0 - 5.0	---	---
	All	10^3/µL	1.0 - 5.0	---	---
MCH (WHBLD)					
	Adult	pg	27 - 34	---	---
MCHC (WHBLD)					
	All	g/dL	32.0 - 36.0	---	---
MCV (WHBLD)					
	Adult	fL	82.0 - 98.0	---	---
Monocyte % (WHBLD)					
	All	%	0.0 - 12.0	---	> 25.0
	All	%	0.0 - 12.0	---	> 25.0
Monocyte (Absolute) (WHBLD)					
	All	10^3/µL	0.0 - 1.0	---	---
	All	10^3/µL	0.0 - 1.0	---	---
Neutrophil % (WHBLD)					
	All	%	40.0 - 80.0	---	---
	All	%	40.0 - 80.0	---	---
Neutrophil (Absolute) (WHBLD)					
	All	10^3/µL	1.0 - 8.0	---	---
	All	10^3/µL	1.0 - 8.0	---	---
Platelet (WHBLD)					
	Adult	10^3/µL	140 - 400	---	< 40 or > 999
RDW (WHBLD)					
	All	%	11.6 - 14.8	---	---
Red Blood Cells (WHBLD)					
	Adult Male	10^6/µL	4.30 - 6.00	---	---
	Adult Female	10^6/µL	3.90 - 5.40	---	---
Reticulocyte (WHBLD)					
	All	%	0.3 - 2.3	---	---
White Blood Cells (WHBLD)					
	Adult	10^3/µL	3.5 - 11.0	---	< 2.0 or > 30.0

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Test Name	Subject Characteristics	Unit (Conventional)	Reference Range	Notable Values	Critical Values
Immunology					
Follicle Stimulating Hormone (FSH) (SER)					
	Male	mIU/mL	1.6 - 11.0	---	---
	Female	mIU/mL	20.0 - 122.0	---	---
HBsAg (SER)					
	All	(None)	Non-reactive	---	---
Hepatitis C Antibody (SER)					
	All	(None)	Non-reactive	---	---
HIV 1 and 2 Screen (SER)					
	All	(None)	Non-reactive	---	>
Osteocalcin (SER)					
	Adult Female	ng/mL	7.0 - 37.0	---	---
	Adult Male	ng/mL	7.2 - 31.0	---	---
P1NP (SER)					
	Adult Male	ng/mL	23.30 - 94.40	---	---
	Adult Female	ng/mL	(See Comments)	---	---
ß CrossLaps (CTX) (SER)					
	Male 18-24y	ng/mL	(None)	---	---
	Male 25-40y	ng/mL	0.150 - 0.800	---	---
	Male > 40y	ng/mL	0.100 - 0.700	---	---
	Female 18-29y	ng/mL	0.100 - 0.900	---	---
	Female 30-39y	ng/mL	0.050 - 0.900	---	---
	Female 40-49y	ng/mL	0.050 - 0.700	---	---
	Female >= 50y	ng/mL	0.050 - 0.900	---	---
ß-HCG (Pregnancy) (SER)					
	Female	IU/L	0 - 5	> 5	> 10
	Male	IU/L	(none)	---	---
Thyroid Stimulating Hormone (TSH) (SER)					
	Adult	µIU/mL	0.40 - 4.00	---	---
Molecular					
HCV RNA, Qualitative (by RT-PCR) (SER)					
	All	(None)	Not Detected	---	---
Hepatitis B DNA (SER)					
	All	log IU/mL	< 1.29	---	---
Special Chemistry (Quest)					
HIV-1 RNA (SER)					
	All	(None)	Not Detected	---	> Detected

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Test Name	Subject Characteristics	Unit (Conventional)	Reference Range	Notable Values	Critical Values
Urinalysis					
Bilirubin (UR)					
	All	mg/dL	Negative	---	---
Blood (UR)					
	All	mg/dL	Negative,0.03	---	---
Color (UR)					
	All	(None)	Colorless,Light Yellow,Yellow	---	---
Glucose (UR)					
	All	mg/dL	Normal,30,50	---	---
Ketone (UR)					
	All	mg/dL	Normal	---	---
Leukocyte Esterase (UR)					
	All	Leu/µL	Negative,25	---	---
Nitrite (UR)					
	All	(None)	Negative	---	---
pH (UR)					
	All	(None)	5.0 - 8.0	---	---
Protein (UR)					
	All	mg/dL	Negative,10,20	---	---
Specific Gravity (UR)					
	All	(None)	1.002 - 1.035	---	---
Turbidity (UR)					
	All	(None)	Clear	---	---
Urinary Red Blood Cells (UR)					
	All	per HPF	0 - 2	---	---
Urinary White Blood Cells (UR)					
	All	per HPF	0 - 5	---	---
Urobilinogen (UR)					
	All	mg/dL	Normal	---	---

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