Statistical Analysis Plan

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Explore the Efficacy and Safety of BIO89-100 in Subjects with Severe Hypertriglyceridemia

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviation	Term
[redacted]	[redacted]
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (SGPT)
[redacted]	[redacted]
ApoB	Apolipoprotein B100
[redacted]	[redacted]
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase (SGOT)
AUC	Area Under the Curve
AUC0-tau	Area Under the Curve During The Dosing Interval
[redacted]	[redacted]
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood urea nitrogen
CK	Creatine Kinase
C_{max}	Maximum Concentration
CMH	Cochran Mantel Haenszel
CRF	Case Report Form
[redacted]	[redacted]
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
EOT	End of Treatment
[redacted]	[redacted]
FGF21	Fibroblast Growth Factor 21
FSH	Follicle-Stimulating Hormone
GGT	Gamma-Glutamyl Transferase
[redacted]	[redacted]
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL-C	High Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
hsCRP	High-Sensitivity C-reactive Protein
[redacted]	[redacted]
INR	International Normalized Ratio
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System

Abbreviation	Term
LDL	Low Density Lipoprotein
LDL-C	Low Density Lipoprotein Cholesterol
[redacted]	[redacted]
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MedDRA	Medical Dictionary for Regulatory Activities
MRI-PDFF	Magnetic Resonance Imaging – Whole Liver Proton Density Fat Fraction
OLE	Open Label Extension
PD	Pharmacodynamic
PE	Physical Examination
PEG	Polyethylene Glycol
PI	Principal Investigator
[redacted]	[redacted]
PK	Pharmacokinetic
PT	Preferred Term
QW	Every Week
Q2W	Every 2 weeks
QTcF	Fridericia's-corrected QT interval
RBC	Red blood cell
RDW	Red Cell Distribution Width
RLP-C	Remnant Lipoprotein Cholesterol
RNA	Ribonucleic Acid
RR	Respiratory Rate
SAE	Serious Adverse Events
SC	Subcutaneous
SD	Standard Deviation
SHTG	Severe Hypertriglyceridemia
T½	Half-life
[redacted]	[redacted]
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Events
TG	Triglycerides
Tmax	Time to Maximum Concentration
TSH	Thyroid Stimulating Hormone
V	Visit
VLDL-C	Very Low Density Lipoprotein Cholesterol
VLDL-TG	Very Low Density Lipoprotein Triglycerides
WBC	White Blood Cell

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the statistical methods, data derivations and data summaries that will be used to analyze and report results for Protocol BIO89-100-221 Version 3.0.

The SAP will supersede the protocol in the event of any differences between the two documents in the plans for data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report.

2 STUDY OBJECTIVES

This Phase 2 study is designed to evaluate the efficacy, safety, and tolerability of different doses and dose regimens (every week [QW] or every 2 weeks [Q2W]), subcutaneous (SC) dosing of BIO89-100 compared to placebo in subjects with Severe Hypertriglyceridemia (SHTG).

2.1 PRIMARY OBJECTIVE

The primary objective is to determine the effect of BIO89-100 on serum Triglycerides (TG) levels in subjects with SHTG (TG ≥500 mg/dL).

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To determine the effect of BIO89-100 on selected serum lipids and lipoproteins
- To determine the effect of BIO89-100 on high sensitivity C-reactive protein (hsCRP)
- To determine the effect of BIO89-100 on metabolic markers
- To characterize BIO89-100 pharmacokinetics (PK)
- To characterize BIO89-100 pharmacodynamic (PD) profile as assessed by Magnetic Resonance Imaging – Whole Liver Proton Density Fat Fraction (MRI-PDFF)

2.3 OTHER OBJECTIVES

The other objectives of the study are:

- [redacted]
- [redacted]

The safety objectives of the study are:

- To evaluate the safety and tolerability of BIO89-100
- To determine the effect of BIO89-100 on [redacted]
- Other safety assessments

3 STUDY DESIGN

3.1 STUDY POPULATION

Study BIO89-100-221 is a randomized, double-blind, placebo-controlled, Phase 2 study to evaluate the efficacy, safety, tolerability, PK and PD profiles, and [redacted] of BIO89-100 administered QW or Q2W SC for 8 weeks and followed by a 4-week follow-up period.

The main cohort will include approximately 90 subjects with SHTG without concurrent fibrate therapy and will consist of 5 treatment groups to compare 4 dose levels/regimens of BIO89-100 versus placebo (Figure 1). The fibrate expansion cohort will include approximately 36 subjects with SHTG on stable background fibrate therapy and with a baseline MRI-PDFF ≥6% and will consist of 2 treatment groups comparing one dose regimen of BIO89-100 versus placebo (Figure 2).

The study includes Lifestyle Stabilization, TG Qualification, Treatment, and Follow-up periods.

3.2 DOSAGE AND ADMINISTRATION

Subjects enroll in the main cohort will be dosed with one of four doses of BIO89-100 (9 mg QW, 18 mg QW, 27 mg QW, or 36 mg Q2W) or placebo. The subjects enroll in the fibrate expansion cohort will receive BIO89-100 27 mg or placebo QW. Intensive PK is planned for a subset of subjects (optional participation with no more than 45 subjects).

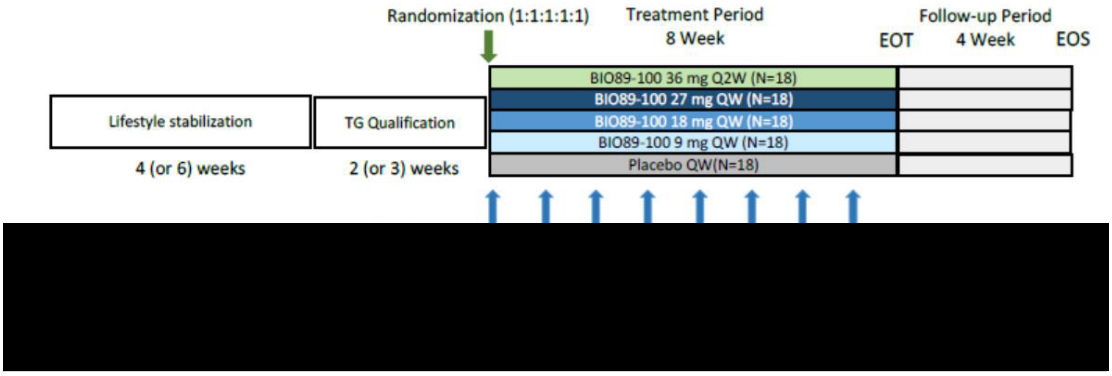


Figure 1. Study Schema: Main Cohort

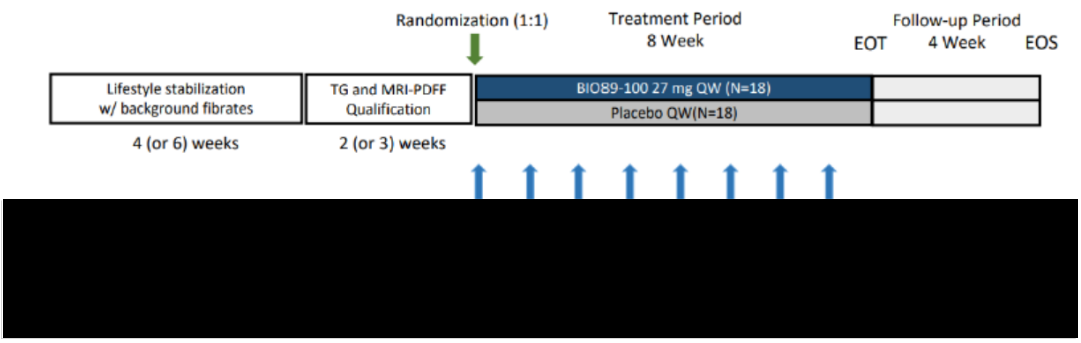


Figure 2. Study Schema: Fibrate Expansion Cohort

3.3 BLINDING AND RANDOMIZATION METHODS

Eligible subjects will be randomized in the order they are enrolled into the study. Subjects in the main cohort will be randomized in a 1:1:1:1:1 ratio to 1 of 4 doses of BIO89-100 (9 mg QW, 18 mg QW, 27 mg QW, or 36 mg Q2W) or placebo. Subjects in the fibrate expansion cohort will be randomized in a 1:1 ratio to BIO89-100 27 mg or placebo QW.

[redacted]

Randomization in the main cohort will be stratified by TG <750 mg/dL or ≥750 mg/dL (8.47 mmol/L) and by whether or not the subject is receiving background therapy (e.g., prescription fish oil and/or statins). [redacted] All subjects will be centrally assigned to randomized IP using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the log-in information and directions for the IVRS/IWRS will be provided to each site.

The study will be conducted under double-blind conditions. The subjects, PI , other study personnel involved with subject assessments, and 89bio will remain blinded to the actual treatment assignments of the subjects, post-baseline lipid panels (Triglycerides [TG], [redacted], Low Density Lipoprotein Cholesterol [LDL-C], High Density Lipoprotein Cholesterol [HDL-C], Non-high Density Lipoprotein Cholesterol [Non-HDL-C], Very Low Density Lipoprotein Cholesterol [VLDL-C], Very Low Density Lipoprotein Triglycerides [VLDL-TG], [redacted], Apolipoprotein B100 [ApoB]), [redacted], Remnant Lipoprotein Cholesterol [RPL-C], [redacted], and PK data. Blinded IP will be provided by a clinical supplies vendor and shipped to the study site. IP may be delivered to the subject's home for home administration by an HHP. The SC administration of the blinded IP will be performed by trained study staff, and only blinded staff will be involved with subject assessments.

3.4 STRATIFICATION FACTORS

Randomization in the main cohort will be stratified by (i) TG <750 mg/dL or ≥750 mg/dL (8.47 mmol/L) and (ii) whether the subject is receiving background therapy (e.g., prescription fish oil and/or statins) – Yes / No. [redacted]

3.5 SAMPLE SIZE CONSIDERATIONS

The effect of BIO89-100 on the percentage change from baseline in TG is estimated based on prior clinical studies evaluating BIO89-100 and other triglyceride lowering agents. [redacted]

Based on these results, it is estimated that the SD of the percent change in TG at Week 8 is approximately 40%. With 18 subjects in the placebo group and each BIO89-100 active treatment group, there would be at least 86% power to detect a 45% difference in TG between each BIO89-100 active treatment group and placebo at the 2-sided alpha level of 0.05, assuming 50% reduction in BIO89-100 dose group and 5% in the placebo group. This sample size assessment incorporates approximately 10% of subjects will be lost to follow-up.

Approximately 90 subjects are planned to be enrolled in the main cohort, with 18 subjects in each of the BIO89-100 active treatment groups (9 mg QW, 18 mg QW, 27 mg QW, or 36 mg Q2W) and in the placebo group. The study aims to enroll ~33% of subjects (~30 subjects total) in the main cohort with a baseline MRI-PDFF ≥ 6%. Approximately 36 subjects are planned to be enrolled in the fibrate expansion cohort (18 in each treatment group) with all subjects having baseline MRI-PDF ≥ 6%. Subjects who terminate early in either cohort may be replaced at Sponsor's discretion.

3.6 INTERIM ANALYSIS

No efficacy interim analysis is planned for this study.

3.7 DATA MONITORING COMMITTEE

No data monitoring committee is planned for this study.

4 STUDY ENDPOINTS AND COVARIATES

4.1 PRIMARY EFFICACY ENDPOINT

- Percentage change in serum TG from baseline to Week 8

4.2 SECONDARY EFFICACY ENDPOINTS

- The proportion of subjects who achieve TG < 500 mg/dL at Week 8
- Percentage change in VLDL-C, LDL-C, non-HDL-C, HDL-C, VLDL-TG, ApoB, remnant lipoprotein cholesterol (RLP-C), hsCRP from baseline to Week 8
- Percentage change in fasting plasma glucose, adiponectin, and body weight from baseline to Week 8
- The serum BIO89-100 concentrations and PK parameters
- Percentage change and change from baseline in hepatic steatosis using Magnetic Resonance Imaging – Whole Liver Proton Density Fat Fraction (MRI-PDFF)

4.3 OTHER EFFICACY ENDPOINTS

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
    - [redacted]
    - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]

- [redacted]

4.4 SAFETY ENDPOINTS

4.4.1 Adverse Events

The evaluation of adverse events (AE) will include only incidence of treatment-emergent AEs (TEAEs), defined as AEs with onset date and time after or identical to the date and time of the first dose of the investigational product until the last dose + 28 days or continuing AEs that worsen the grade post IP. When onset time is missing or partial missing, AE occurs on the same day as first dose date are considered as TEAE. The frequency of TEAEs, treatment-emergent serious AEs (TESAEs), and number of subjects who discontinue due to TEAEs will be summarized.

4.4.2 Clinical Safety Laboratories

The evaluation of clinical safety laboratories, including blood hematology, chemistry, 24-hour urine cortisol, and urinalysis will be based on the observed values. Observed values and changes from baseline will be summarized for all post-baseline study visits.

Incidence and shifts of laboratory abnormalities will be summarized.

Changes in liver function tests (i.e., alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin and Gamma-Glutamyl Transferase (GGT)) from baseline to Week 8 will be summarized. A summary of suspected liver injury cases according to drug induced liver injury (DILI) criteria will also be presented (Table 1).

Table 1. Suspected liver injury cases according to drug induced liver injury (DILI) criteria

Baseline Value of ALT/AST	Criteria to discontinue investigational product
>ULN and <2× ULN	ALT or AST >5× baseline value
>=2× ULN but <5× ULN	ALT or AST >3× baseline value
>=5× ULN	ALT or AST >2× baseline value
>ULN	ALT or AST >2× baseline value and (BILI >2× ULN OR INR >0.2)
Within Normal Range	ALT or AST >8× ULN
	ALT or AST >5× ULN
	ALT or AST >3× ULN and (BILI >2× ULN or INR >1.5)

[redacted]

4.4.3 Electrocardiogram, Vital Signs and Physical Examination

The evaluation of electrocardiogram (ECG) and vital signs (including body temperature,

pulse rate, respiratory rate [RR], and supine Blood Pressure [BP]), will be summarized by visits and by treatment group.

4.5 PHARMACOKINETICS ENDPOINTS

PK parameters will be calculated by non-compartmental methods from the BIO89-100 serum concentration data in Intensive PK subgroup, if the data are suitable.

- Maximal observed serum concentrations (C_{max}) within a dosing interval
- Area under the serum drug concentration by time curve within a dosing interval ($AUC_{0\text{-}tau}$)
- Time to achieve C_{max} (T_{max})
- Terminal elimination half-life ($t_{½}$)
- Trough concentration

Additional PK parameters may be calculated if also deemed appropriate.

PK parameters will be calculated separately by designee of 89BIO.

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

[redacted]

4.7 COVARIATES AND SUBGROUPS

- TG <750 mg/dL or ≥ 750 mg/dL
- Background lipid medication (Yes, No)
- Type of background lipid medication (use of statin (including combo therapy), use of fibrate therapy, use of prescription fish oil, Ezetimibe, and Bempedoic acid), provided there is sufficient number of subjects in the subgroup
- Type 2 diabetes (Yes, No)
- Age categories (21-<65, >=65).

- Sex (male, female)
- Baseline weight <median and ≥ median
- Region (US vs EU)
- TG responder at Week 8 (responder, non-responder)
- Use of background insulin medication (Yes/No) for insulin analysis only

Note, if the percentage of subjects within a certain subgroup is less than 33% (i.e., less than 6 of 18 subjects) of the overall cohort, only descriptive analysis will be performed.

More details of the analyses repeated in the above subgroups are described in Section 7.5.1.

5 DEFINITIONS

5.1 BASELINE DEFINITION

In general, baseline will be defined as the most recent non-missing measurement (scheduled or unscheduled) prior to the administration of the first dose of IP. For numerical measurements that have duplicates or triplicates (for the same visit), the arithmetic mean will be used. Some measurements have special definitions of baseline, which are defined below.

The mean TG value will be used for stratification factor [redacted]

Baseline Triglyceride is defined as the average of [redacted] and the preceding two lipid-qualifying visits collected in EDC. Fasting status is required for the TG values to be included.

The definition of baseline of other lipid panel labs is the average of last two non-missing screening fasting values and [redacted] value (Pre-dose, fasting).

The definition of baseline vital signs is the average of the last two non-missing screening values and [redacted] If there is Case Report Form (CRF) average value on duplicate measurements of BP and/or Pulse on [redacted], only the individual values will be included in the baseline derivation.

The baseline definition for MRI for subjects of the main cohort is the [redacted] value. The baseline definition for MRI for subjects of the fibrate expansion cohort is the value obtained between [redacted]

The baseline definition for safety numeric measurements (except for liver tests) is the average of last two non-missing screening values and [redacted]

The baseline definition of PK is the [redacted]. The details will be described in a

separate document.

5.2 ACTUAL TREATMENT GROUP

[redacted]

5.3 STUDY DAY

The day a subject receives their first dose of investigational product will be considered as [redacted]

If a subject is randomized but never dosed, study day will be calculated using the randomization date and randomization date will be set to [redacted]

If date of interest occurring on or after the relative date, relative day is calculated as: date of interest – relative date + 1, else if date of interest occurring prior the relative date, relative day is calculated as: date of interest – relative date. Data will be presented on listings in order of site number/subject number, assessment date and assessment (in order collected on CRF, unless specified otherwise). Dates will be presented in the format of YYYY-MM-DD.

For subjects with study interruptions due to COVID-19, post-interruption study day will be calculated as: (Index date) – (the date of [redacted] + 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.

5.4 END OF STUDY

A subject is considered to have completed the study if the subject has completed all phases of the study including the last scheduled procedure shown in Table 6. The EOS is defined as the date of the last visit of the last subject in the study.

5.5 STUDY SCOPE

For the efficacy analysis of the primary endpoint, results will be presented in two different formats as shown below:

1. A comparison between the pooled BIO89-100 group and the pooled Placebo group.

Subjects across all BIO89-100 dose groups will be pooled together to compare with all the placebo subjects. The table header is shown below (Table 2). The Total group will be presented as appropriate.

Table 2. Table Header for Pooled Analysis

<Description>	Placebo QW	BIO89-100	Total

	Pooled	Pooled	

2. A comparison between individual BIO89-100 dose group and the placebo group.

Each BIO89-100 dose group will be compared with the placebo group. Due to the low number of subjects enrolled in the fibrate cohort, subjects randomized to BIO89-100 in fibrate cohort will be combined with the 27mg QW main cohort as the pooled 27mg QW group. The subjects randomized to placebo in the fibrate cohort will be combined with the placebo group. The table header is shown below (Table 3). The Total group will be presented as appropriate.

Table 3. Table Header for Individual Dose Group Analysis

<Description>	Placebo QW Pooled	BIO89-100 9 mg QW	BIO89-100 18 mg QW	BIO89-100 27 mg QW Pooled	BIO89-100 36 mg Q2W	Total

For all other analyses, the results will be presented in a combined format as shown below (Table 3-1):

Table 4-1. Table Header for All Other Analysis

<Description>	Placebo QW Pooled	BIO89-100 pooled	BIO89-100 9 mg QW	BIO89-100 18 mg QW	BIO89-100 27 mg QW Pooled	BIO89-100 36 mg Q2W	Total

5.6 PRE-TREATMENT MEDICATION AND PRE-TREATMENT PROCEDURES

Any medication/procedure that starts and stops prior to [redacted].

5.7 BASELINE MEDICATION

Medications that have [redacted] within the duration of exposure will be considered baseline medications, i.e., medication taken prior to and/or on [redacted] and ongoing/stopped after [redacted].

5.8 CONCOMITANT MEDICATION AND CONCOMITANT PROCEDURES

Any medication/procedure that is taken any day on or after [redacted] is considered as concomitant medication/procedure. This includes medications/procedures that were started prior to administration of first dose and that were continued to be taken after [redacted].

5.9 ADVERSE EVENT AND SERIOUS ADVERSE EVENT

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of investigational product, whether or not considered as related to the investigational product. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of investigational product.

A Serious Adverse Events (SAE) is defined as any untoward medical occurrence that, at any dose 1) results in death; 2) is life-threatening; 3) requires inpatient hospitalization or prolongation of existing hospitalization; 4) results in persistent disability/incapacity; 5) is a congenital anomaly/birth defect; 6) medically or scientifically judged as serious in other situations.

5.10 TREATMENT EMERGENT ADVERSE EVENT

TEAEs are AEs with onset date and time after or identical to the date and time of the first dose of the investigational product until the last dose + 28 days.

6 ANALYSIS POPULATIONS

The following analysis populations are defined for the main and fibrate expansion cohorts.

Table 5. Analysis Population

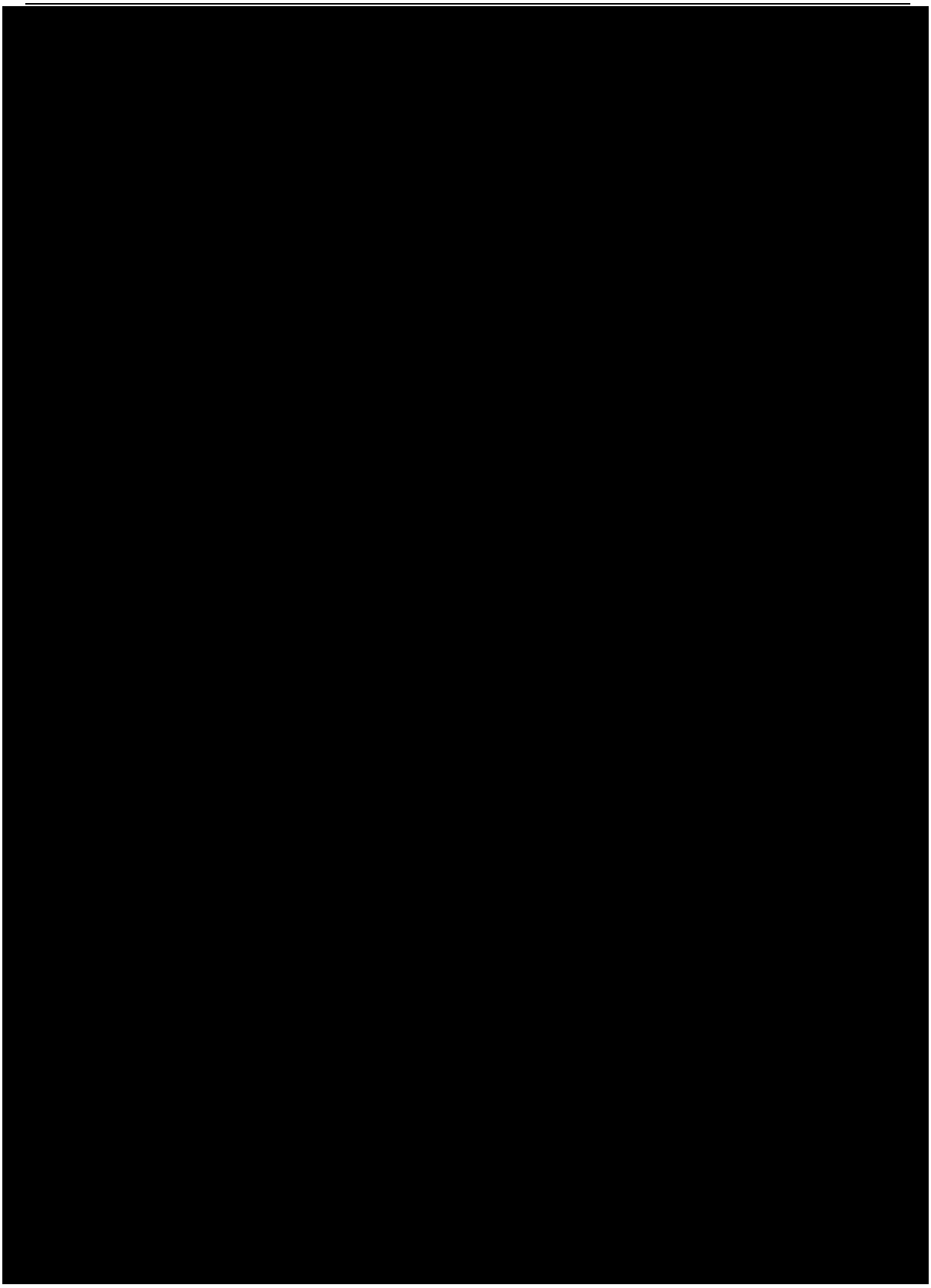
Population	Definition
Screened Analysis Set	All subjects who signed informed consent and have undergone screening.
Randomized Analysis Set	All subjects in screened analysis set who are assigned a randomization number in the study.
Full Analysis Set	All randomized subjects who received at least 1 dose of investigational product, have a baseline, and at least 1 post-baseline TG measurement not including EOS visit.
Safety Analysis Set	All subjects who received at least 1 dose of investigational product.
Trough PK Analysis Set	All subjects in the Safety Analysis Set, who have pre-dose and at least 1 post-dose trough PK measurements.
Intensive PK Analysis Set	All subjects in the Safety Analysis Set, who opted to participate in the Intensive PK scheme, and have at least 1 on-study PK measurement.
MRI-PDFF Analysis Set	All subjects in the Full Analysis Set who have baseline and a follow up MRI-PDFF assessments.

All primary, secondary, and exploratory efficacy endpoints will be assessed for all subjects in the Full Analysis Set. All safety assessments will be displayed and analyzed for all subjects in the Safety Analysis Set. Intensive PK endpoints will be displayed and analyzed for all subjects with applicable data in the Intensive PK Analysis Set.

6.1 HANDLING OF MISSING AND INCOMPLETE DATA

6.1.1 Missing Dates

For the missing or partially missing dates for the adverse event, prior/concomitant medication and procedures, the missing date will be imputed following the rules below.



6.1.2 Missing data for Efficacy Endpoints

Missing data handling will be explored as sensitivity analysis if there is more than 10% missing data for the primary efficacy endpoint. The details are described in Section 7.5.

6.2 ANALYSIS VISIT WINDOWS

In general, all screening visits will be combined as Screening Analysis Visit. Scheduled visits from randomization (except for EOT visit for early terminated subjects) through /Week 8 will be used as analysis visit for descriptive analysis tables and listings.

Unscheduled visits will be mapped according to the analysis visit window below. If a scheduled visit is missing, the unscheduled visit that is closest to the target study day may be used for analysis purpose.

For early terminated subjects, EOT visits will be remapped to scheduled visit week using the actual study day and analysis window. EOS visits will be analyzed separately.

Both nominal visits and analysis visits will be displayed in the listing.

The visit schedules and window are shown below.

Table 6. Analysis visit window

Nominal Visit/Time point	Analysis Visit Label	Target Study Day[a]	Analysis Window[a]
[redacted]			

6.3 SOFTWARE

All data processing, summarization and analyses will be performed using SAS Version 9.4 or later of the SAS ® statistical software package.

7 STATISTICAL METHODS OF ANALYSES

7.1 GENERAL CONSIDERATIONS

The statistical analysis for this study will be performed by combining the main cohort and the fibrate extension cohort. A single database lock will be implemented.

All the tables and figures will be based on the pooled data from both cohorts, unless otherwise specified. One set of listings will be generated for the whole study.

In general, summaries and analyses will be presented by dose/treatment group. Descriptive statistics will be presented for demographics and baseline characteristics, safety endpoints, and PK and PD parameters. Continuous variables will be summarized by number of subjects and mean, SD/standard error, median, minimum, and maximum values. Minimum

and maximum will be presented to the same number of decimal places as reported/collected. One additional decimal place will be presented for mean and median. Two additional decimal places will be presented for SD up to a max of three decimal places.

Categorical variables will be summarized by number and percentage of subjects. Percentage will be presented to one decimal place. The number of missing values will be presented as a separate category with no percentage, but only if 1 or more subjects are missing data for the summary. Otherwise, all categories will be presented (even if no subjects are counted in the category). Counts of zero in any category will be presented without percentage.

All statistical tests will be 2-sided and tested at a statistically significant level of 0.05 without adjustment for multiplicity. Confidence intervals will be 2-sided 95%, unless stated otherwise. Two-sided p-values will be presented with four decimal places and values less than 0.0001 will be presented as <.0001.

Both reported units (CN) and SI units will be presented in listings.

Both CN and SI units will be used in lipid panel (TG and other lipids) tables and figures.

For the rest, only CN units will be used for tables and figures, unless otherwise specified. Insulin will be presented with conventional unit of μIU/mL;

The listings will only present non-imputed data.

7.2 SUBJECT ACCOUNTABILITY

The number of subjects screened and the number (percentage) of subjects who failed screening (i.e., subjects who consented to participate in the clinical study but were not subsequently randomized) and the reasons for screen failure will be summarized.

In addition, the number of subjects who withdrew from the study and discontinued the investigational product will be summarized by discontinuation reason (including discontinuation due to COVID-19 pandemic).

The information including demography and screen failure details will be listed. Subjects with dose interruptions affected by the COVID-19 pandemic will also be noted in the listing.

7.3 PROTOCOL DEVIATIONS

A full list of protocol violations and deviations will be compiled and reviewed by the clinical team to identify important violations/deviations before final database lock. For violations at study entry, subjects will be assessed against the inclusion and exclusion criteria of the protocol. For on-study deviations, compliance with the protocol will be examined using blinded review of the database with regard to prohibited therapies, and timing and availability of planned assessments.

7.4 INVESTIGATIONAL PRODUCT ADMINISTRATION

7.4.1 Extent of Exposure and Treatment Compliance

The length of exposure to investigational product (as BIO89-100 or placebo) will be calculated as the number of days from the first dose to the last dose of double-blind investigational product administration +7, regardless of if the subject missed one or more doses of investigational product.

Total dose administered (mg) is calculated as number of injections received x dose (mg) of the investigational product contained in the injection.

Overall study treatment compliance will be calculated at the end of treatment as (total injections administered /total injections expected x 100%. Total injections expected is defined as the total number of injections protocol defined until the end of treatment.

The length of exposure, number of actual drug injections and number of missed injections, total dose administered, and overall study treatment compliance will be summarized by treatment group using descriptive statistics for the safety population. The investigational product administration and compliance data, including reasons for poor compliance, will be listed for each subject.

7.4.2 Medical History

General medical history and background therapy will be summarized by treatment group, as well as overall, for FAS population and presented in a by-subject listing. Where appropriate, terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher.

7.4.3 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by treatment group, as well as overall, for Safety Analysis Set and for Full Analysis Set:

- Age in years and by age group (21-<65, >=65-<75 and >=75)
- Gender
- Race
- Ethnicity
- Height (cm), weight (kg), weight group, body mass index (kg/m^2), BMI group (< 25, 25 -< 30, ≥ 30 kg/m^2), [redacted]
- systolic and diastolic blood pressure (mmHg),

- Serum lipids, lipoproteins and apolipoproteins (TG [mg/dL], [redacted] [mg/dL], VLDLC [mg/dL], VLDL-TG [mg/dL], LDL-C [mg/dL], HDL-C [mg/dL], non-HDL-C [mg/dL], [redacted] [mg/dL], ApoB [mg/dL], [redacted] [mg/dL], [redacted] [mg/dL], [redacted])
- hsCRP [g/dL]), Adiponectin, fasting plasma glucose, [redacted]
- ALT (U/L), AST (U/L)
- TG <750 mg/dL or ≥750 mg/dL (8.47 mmol/L)
- Whether or not the subject is receiving background therapy (e.g., prescription fish oil and/or statins)
- History of Type 2 Diabetes
- History of hypertension
- History of Non-alcoholic fatty liver disease (NAFLD)
- History of Nonalcoholic steatohepatitis (NASH)
- Estimated Glomerular Filtration Rate (eGFR) category (normal: ≥90 mL/min/1.73m^2; mild Renal Impairment: 60-89 mL/min/1.73m^2; moderate Renal Impairment: 30-59 mL/min/1.73m^2, and severe Renal Impairment: 15-29 mL/min/1.73m^2)
- MRI-PDFF [redacted]

Data will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables by treatment group and overall.

Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and serum pregnancy test (only for females of childbearing potential), follicle stimulating hormone (FSH) urine pregnancy test on Day 1 and thyroid-stimulating hormone (TSH) will be presented [redacted]

7.4.4 Prior, Baseline and Concomitant Medication/Procedure

Medications will be coded using WHO Drug (March, 2020 or later). The frequency of use of prior medications and use of concomitant medications will be summarized by treatment group, as well as overall, for the safety population according to Anatomical Therapeutic Chemical (ATC) class and preferred term. Prior and concomitant medications will be listed for each subject.

Prior and concomitant procedures will be listed.

7.5 EFFICACY ANALYSIS

The objective for the primary efficacy analyses is to evaluate the effect of BIO89-100 on TG reduction after the 8-week treatment period. The analyses consist of comparisons between the BIO89-100 groups and placebo as below:

1. A pooled BIO89-100 group combining all dose groups will be compared with the placebo to evaluate the overall effectiveness of BIO89-100

2. Individual BIO89-100 dose groups will be compared with the placebo group separately to evaluate the effectiveness of BIO89-100 at a specific dose

The study is considered positive and meeting the primary objective if any of the comparisons above is statistically significant.

All efficacy analysis will be performed using the FAS unless otherwise specified. Analyses comparing the placebo group and the pooled BIO89-100 group will be stratified if the sample size permits. The analyses comparing the placebo and individual dose group will not be stratified due to anticipated small size.

7.5.1 Analysis of Primary Efficacy endpoints

The primary endpoint is the percent change in TG at Week 8 from baseline. The TG value at week 8 is defined as the average of TG values at [redacted] In case of missing TG value at [redacted] the non-missing result will be used as the week 8 TG. The primary efficacy analysis will be performed using a mixed model with repeated measure (MMRM). The model includes the treatment group, baseline TG values, background therapy use, visit, visit and treatment interaction. The model will be fitted using all planned visits up to Week 8.

If the mixed model assumption of the MMRM method is severely violated, the non-parametric van Elteren test stratified by baseline TG level and background lipid therapy will be used to test the treatment difference using the pooled data. The location shift estimate, and Hodges-Lehmann 2-tailed 95% confidence interval will be presented. For the comparison between the individual dose group and the placebo, the unstratified Wilcoxon rank-sum test will be used instead due to the low sample size.

The primary efficacy analysis will be repeated in the subgroups (as noted in Section 4.7).

[redacted]

[redacted]

7.5.2 Analysis of Secondary Efficacy Endpoints

Full analysis set will be used for all secondary efficacy analyses. The proportion of subjects with TG <500 mg/dL at Week 8 will be summarized by treatment group and analyzed using Cochran Mantel Haenszel (CMH) method stratified by the 2 stratification. Unstratified Chi-square test will be performed for comparisons between the placebo and the individual dose group or if the sample size within a stratum is too small (< 5 subjects). In addition, responder analysis at Week 8 will be performed to ensure the consistency of the results. The following threshold will be used to calculate: the proportion of subjects with TG normalized; with TG reduction by ≥30%, ≥40%, ≥50%, ≥60%, ≥70%, ≥80%, and ≥90% from baseline.

Cumulative distribution function of both percentage changes from baseline and changes from baseline for TG at Week 8 by treatment group will be summarized descriptively and graphically.

Percentage change in VLDL-C, LDL-C, non-HDL-C, HDL-C, VLDL-TG, ApoB, hsCRP, fasting plasma glucose, adiponectin, and body weight from baseline to Week 8 will be analyzed similarly as the primary endpoints. For parameters that only have one post-baseline measurement, an ANCOVA model will be performed with treatment and background therapy as factors and baseline value as covariate.

7.5.3 Analysis of Other Efficacy Endpoints

Change, percent change in [redacted], ALT, body weight and MRI-PDFF at week 8 will be analyzed among those with TG reduction <30% vs. >=30%. MMRM or ANCOVA models will be used accordingly.

Tables of descriptive summary will be provided for the following.

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

7.6 SAFETY ANALYSIS

All safety analyses will be performed using the Safety Analysis Set. Safety data presented by treatment group will be summarized on an 'as treated' basis. Safety variables include treatment-emergent adverse events (TEAEs), concomitant medication use, physical examination, clinical laboratory parameters, vital signs, and ECG results. [redacted] for all safety analyses is defined as the date of the first dose of investigational product.

7.6.1 Adverse Events

Subject incidence of TEAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA, Version 23.0) system organ class, MedDRA preferred term, and

treatment groups. All TEAEs, all treatment-emergent related AEs, all TESAEs, and all treatment-emergent serious related AEs, the most severe CTCAE grade, TEAEs leading to IP discontinuation, and TESAEs leading to IP discontinuation will be summarized. Related is defined as "possibly related", "probably related", or "definitely related" to randomized investigational medicinal product. Subjects will be counted only once within a SOC and Preferred Term (PT), even if the subject experienced more than one TEAE within a specific SOC and PT, and PT only.

All AEs, TESAEs, TEAEs leading to IP discontinuation, Fatal TEAEs and COVID-19 related AEs will be listed.

7.6.2 Clinical Laboratory Parameters

The following laboratory assessments will be analyzed using the safety analysis set:

Hematology: White Blood Cell (WBC) with differential (Total Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils – absolute and %), Red blood cell (RBC) count, RBC Indices (Mean Corpuscular Volume [MCV], Mean Corpuscular Hemoglobin Concentration [MCH], Mean Corpuscular Hemoglobin Concentration [MCHC], Red Cell Distribution Width [RDW], Reticulocyte count) Hemoglobin, Hematocrit, Platelet count, Coagulation panel (including Prothrombin Time, International Normalized Ratio (INR), Activated Partial Thromboplastin Time [aPTT])

Lipid Assessment: [redacted], ApoB, [redacted] non-HDL-C, LDL-C, [redacted], TG, VLDL-C, VLDL-TG.

Clinical Chemistries: Alkaline Phosphatase (ALP), ALT, AST, Albumin, Bicarbonate, BUN (Blood urea nitrogen), Calcium, Creatinine, eGFR, Creatine Kinase (CK), Chloride, Fasting plasma glucose, Gamma-Glutamyl Transferase (GGT), Lactate dehydrogenase, Magnesium, Phosphorus, Potassium, Sodium, (Total bilirubin, Indirect/direct bilirubin), Total protein, Uric acid. For ALT, change and percent change from baseline at week 8 will be analyzed using MMRM method based on full analysis set.

Urinalysis: Basic urinalysis (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen); Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the screening and End of Study visits). A reflex microscopic urinalysis should be performed if the results of the urinalysis is abnormal or at the discretion of the Principal Investigator (PI) or delegate. A listing will be presented for Urinalysis results.

Other Study-Specific Laboratory Assessments:

- BIO89-100 level (to be evaluated by bioanalytical laboratory)
- TSH level
- Serum hCG pregnancy test, Urine hCG pregnancy test, FSH level

- Urine drug screen including amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, cannabinoids and phencyclidine

- Virology - Human Immunodeficiency Virus (HIV) antibody, hepatitis B surface antigen (HBsAg, and HCV antibody). To determine current infection status, if HBsAg positive Hepatitis B Virus (HBV) DNA will be measured or if HCV antibody positive, HCV Ribonucleic Acid (RNA) will be measured.

- 24-hour urine for cortisol, [redacted], [redacted], , total Insulin, hsCRP, [redacted], [redacted], Serum adiponectin, and [redacted].

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.

Laboratory results will be presented as received from the central laboratory (or kit provided by the central lab).

Descriptive summaries by treatment groups will be produced for the laboratory tests.

Shifts (low/normal/high) from the relevant baseline tables based on the normal ranges will be constructed. The shifts will be performed from the baseline to each post-baseline visit, and to minimum and maximum post-baseline visit.

7.6.3 Vital Signs

The observed values and the change from baseline for vital signs (body temperature, pulse rate, RR, and supine BP) will be summarized by visit and treatment group.

The number and percent 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

Clinically significant shifts for blood pressure from baseline to each post baseline visit will be summarized in the following criteria:

Table 7. Blood Pressure Category

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

Clinically significant shifts for pulse rate from baseline to each post baseline visit will be summarized using the category as <50 bpm; 50-99 bpm, ≥100 bpm

7.6.4 Physical Examinations

Physical examination (abdominal, cardiovascular, neurological, respiratory, skin, and general, etc) results will be summarized by visits and by treatment group.

Shift tables from baseline to end of the study will be summarized using the category as normal, abnormal but not clinically significant, and abnormal and clinically significant.

7.6.5 Electrocardiograms

The following quantitative ECG measurements will be taken during the study:

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

Descriptive summaries and changes from baseline will be presented by treatment group for the quantitative ECG measurements listed above and the qualitative overall ECG interpretation (categorized as normal; abnormal, insignificant; and abnormal, significant).

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to each post-baseline visit.

[redacted]

7.7 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.

7.8 PHARMACOKINETICS ENDPOINTS

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.

Individual and mean BIO89-100 serum concentrations for each nominal timepoints will be listed, summarized and plotted versus time. PK parameters will be listed for each subject in the analysis set and summary descriptive statistics will be presented.

If data are suitable, PK parameters include:

- Maximal observed serum concentrations (C_{max}) within a dosing interval
- Area under the serum drug concentration by time curve within a dosing interval ($AUC_{0\text{-}tau}$)
- Time to achieve C_{max} (T_{max})
- Terminal elimination half-life ($t_{½}$)
- Trough concentration

Additional PK parameters may be calculated if also deemed appropriate.

[redacted]

[redacted]

8 LIST OF PLANNED TABLES, FIGURES

The list of table, listing, and figure mockups are included in TLF Shell, as a separate document.

9 APPENDICES

Appendix 1 Schedule of Activities (SOA)

Study Period (Duration)	Screening/ Lifestyle Stabilization (Min 4 weeks to Max 6 weeks)	Screening/ TG Qualification (2 Week)	Screening/ TG Sample	Double-blind Treatment (8 Weeks)									Follow-up (4 Weeks)
Visits													
Study Day[b]													
Informed consent	x												
Inclusion/exclusion	x	x	x	x									
Randomization				x									
Demography, medical history	x												
Physical examination	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x	x
Body weight	x	x	x	x				x				x	x
Height[d]	x												
BMI (derived)	x											x	
Vital signs (BP[e], heart rate[e], RR) and body temperature	x	x		x				x				x	x

Study Period (Duration)	Screening/ Lifestyle Stabilization (Min 4 weeks to Max 6 weeks)	Screening/ TG Qualification (2 Week)	Screening/ TG Sample	Double-blind Treatment (8 Weeks)									Follow-up (4 Weeks)
Visits	[redacted]												
Study Day[b]													
Hematology, blood chemistry and coagulation panel	x[f]		x[f]	x[f]				x[f]				x[f]	x[f]
Urinalysis	x			x				x				x	x
[redacted]													
Thyroid panel (TSH, free T4, and free T3)	x		x									x	x
12-lead ECG	x			x				x				x	~~x~~
History of drug and/or alcohol abuse, urine drug test, and alcohol consumption test	x[g]		x[g,h]	x[h]				x[h]	x[h]		x[h]	x[h]	x[h]
Serum lipids, lipoproteins and apolipoproteins (TG, [redacted], VLDL-C, VLDL-TG, LDL-C, HDL-C, non-HDL-C, RLP-C, [redacted] ApoB, [redacted], [redacted])		x	x[i]	x				x	x[i]		x[i]	x	x
[redacted]													

Study Period (Duration)	Screening/ Lifestyle Stabilization (Min 4 weeks to Max 6 weeks)	Screening/ TG Qualification (2 Week)	Screening/ TG Sample	Double-blind Treatment (8 Weeks)									Follow-up (4 Weeks)
Visits	[redacted]												
Study Day[b]													
Inflammatory biomarker (hsCRP)				x				x				x	x
[redacted]													
[redacted] **and serum adiponectin, total**				x				x				x	x
[redacted]													
Intensive PK (optional)[k]				x	x	x	x	x	x	x	x	x	
Trough PK (for all subjects)[k]				x	x	x		x				x	
HIV, HCV and HBV Serology[l]		x											
FSH if required to determine menopausal status		x											
Serum pregnancy test (WOCBP)		x											x
Urine pregnancy test (WOCBP)			x	x				x				x	

Study Period (Duration)	Screening/ Lifestyle Stabilization (Min 4 weeks to Max 6 weeks)	Screening/ TG Qualification (2 Week)	Screening/ TG Sample	Double-blind Treatment (8 Weeks)									Follow-up (4 Weeks)
Visits	[redacted]												
Study Day[b]													
Jug dispensed for 24-hour urine collection for cortisol and creatinine[m]			x								x		
Archived serum and plasma samples[n]				x				x				x	
[redacted]													
Investigational product dosing[p]				x	x	x	x	x	x	x	x		
AE and SAEs including hypersensitivity-related AEs[q]	x	x		x				x				x	x
Concomitant medication	x	x		x				x				x	x
Review of lifestyle and alcohol use[r]	x	x	x	x				x	x		x	x	x
MRI-PDFF [s]				x								x	
FGF21				x									

Shaded columns indicate visits that can be conducted by home health providers.

Abbreviations: AE = adverse event; [redacted]; ALT = alanine aminotransferase; ALP = alkaline phosphatase; [redacted]; ApoB = apolipoprotein B100; [redacted] aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; [redacted] BP = blood pressure; BMI = body mass index; BUN = Blood urea nitrogen; CK = creatine kinase; CKD-EPI = chronic kidney disease epidemiology collaboration; [redacted]; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; EOT = end of treatment; [redacted]; FGF21 = fibroblast growth factor 21; FSH = follicle-stimulating hormone; GGT =

gamma-glutamyl transferase; [redacted]; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C Virus; HDL-C = high-density lipoprotein-cholesterol; HHP = home health provider; HIV = Human Immunodeficiency Virus; hsCRP = high-sensitivity C-reactive protein; [redacted] INR = international normalized ratio; LDL-C = low-density lipoprotein-cholesterol; [redacted] non-HDL-C = non-high-density lipoprotein-cholesterol; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MRI = Magnetic resonance imaging; MRI-PDFF = Magnetic Resonance Imaging – Whole Liver Proton Density Fat Fraction; [redacted]; PK = pharmacokinetics; PT = prothrombin time; RNA = ribonucleic acid; RR = respiratory rate; RLP-C = remnant lipoprotein-cholesterol; SAE = serious adverse event; SoA = Schedule of Assessments; T3 = triiodothyronine; T4 = thyroxine; [redacted]; TG = triglyceride; TSH = thyroid-stimulating hormone; V = Visit; VLDL-C = very low-density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides; WBC = white blood cell; WOCBP = women of childbearing potential.

Body posture during TG, BP, heart rate, RR and body temperature measurement needs to be the same (e.g., sitting, semi-erect, or supine) throughout the study with resting for at least 5 min prior to measurement at each study visit.

Fasting blood samples should be taken after at least 12 hours of fasting. (It is recommended that subjects fast no more than 14 hours.) Fasting includes food and all beverages except for non-mineral water.

Hematology: Hemoglobin, hematocrit, RBC count, reticulocyte count, MCV, MCH, MCHC, platelet count, WBC count, total neutrophils, eosinophils, monocytes, basophils, lymphocytes.

Blood chemistry: BUN, creatinine (eGFR using CKD-EPI equation), fasting plasma glucose, calcium, sodium, potassium, chloride, total CO2 (bicarbonate), AST (SGOT), ALT (SGPT), ALP, GGT, total bilirubin, direct (conjugated) bilirubin, indirect (unconjugated) bilirubin, CK, uric acid, albumin, total protein. Coagulation panel: INR, aPTT, PT.

Urinalysis: pH, glucose, protein, blood, ketones, nitrites, leukocyte esterase, urobilinogen, urine bilirubin, microscopy.

a = If [redacted] is required, only assessment at that visit is TG measurement.

b = [redacted]

c = Symptom-driven physical assessment for applicable reported AEs. Can be conducted on site during a scheduled or unscheduled visit or by a home health provider (HHP) if identified on the delegation log. d = Height at screening [redacted] only.

e = Starting from randomization, pre-dose BP and pulse will be measured in duplicate. The first measurement will be initiated before dosing with sitting/semi-erect or supine position and resting for at least 5 minutes prior to measurements. BP and pulse are to be repeated at least 1 minute apart. Additional vital signs measurements may be done if clinically indicated.

f = Coagulation panel will be done at [redacted] only.

g = History of drug and/or alcohol abuse taken at screening [redacted] only. Urine drug test will be performed at [redacted] only. h= Alcohol breathalyzers will be used. Results >0.01% will be considered as positive.

i = [redacted]

j = [redacted]

[redacted]

iii. [redacted]

k = Subjects will be included in either the Intensive PK scheme (optional) or Trough PK scheme (all subjects). Table 5 in the protocol details sampling times for the Intensive PK scheme. Intensive PK subjects will have additional visits on [redacted]. For the Trough PK scheme, blood samples will be taken within 4 hours prior to dosing on specified dosing days or during EOT visit ([redacted] for all subjects.
Note: Where the Intensive PK schedule overlaps with the Trough PK schedule, only 1 PK measurement should be taken at those time points.

l = Serology tests will include HBsAg, HCV, and HIV 1 and 2 antibodies. HBV and HCV determined by antibodies first and, if positive, by DNA/RNA.

m = Ambulatory 24-hour urine collection for analysis of cortisol and creatinine to be initiated the day prior to [redacted] Subject will start collection 24 hours before coming into the clinic and bring the sample to the visit. The 24-hour urine collection jug is dispensed at [redacted] so collection can be completed and brought to [redacted], respectively. The jug may be provided at the site or by an HHP.

n = Archived for possible analysis of additional biomarkers. This is optional and by subject consent.

o = [redacted]

p = Subjects randomized to BIO89-100 36 mg Q2W group will receive BIO89-100 at [redacted] and placebo at [redacted] to maintain the blind. Home health IP administration may occur on [redacted].

q = When IP is scheduled to be administered by an HHP, a subject's spontaneous reports of AE/SAE will be reported to the site staff who will follow-up and evaluate the need for an unscheduled visit for AE assessment. The sites/HHP may take non-personally identifying photographs of potential injection site reactions (optional).

r = Study coordinators should reinforce maintenance of eating and exercise habits without weight loss or gain of 5% for the duration of the study, and alcohol consumption restrictions 48 hours prior to fasting blood work.

s = After a consenting subject's [redacted], the site should preemptively schedule the baseline MRI-PDFF to occur within the following projected visit windows to ensure an MRI appointment is available to be performed after the [redacted] TG result ≥350 mg/dL is known. For the main cohort, MRI-PDFF is optional and should occur prior to [redacted]. For the fibrate expansion cohort, MRI-PDFF of ≥ 6.0% is required for enrollment and should be performed between [redacted]. The follow-up MRI at [redacted] should only be performed if the baseline liver MRI-PDFF value is ≥ 6.0%. MRI-PDFF is mandatory in the fibrate expansion cohort.

Appendix 2 SAS Sample Code