CLINICAL STUDY PROTOCOL

Title Page

Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Explore the Efficacy and Safety of BIO89-100 in Subjects with Severe Hypertriglyceridemia
Protocol Number:	BIO89-100-221
Compound Number:	BIO89-100
Study Phase:	Phase 2
Sponsor Name:	89bio, Inc.
Legal Registered Address:	142 Sansome Street, Second Floor. San Francisco, CA 94104, USA
Regulatory Agency Identifier Number(s):	IND: 146569
Sponsor Representative:	[redacted]
Approval Date:	03 May 2021
Version:	3.0

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States Code of Federal Regulations (CFR), and European Union Directives and Regulations (as applicable in the region of the study); national country legislation; and 89bio's Standard Operating Procedures.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Rationale: BIO89-100 is a glycoPEGylated analog of fibroblast growth factor 21 (FGF21), a metabolic hormone, regulated by nutritional status, that affects energy expenditure and glucose and lipid metabolism. It is secreted mainly by the liver, but also by white adipose tissue, skeletal muscle, and the pancreas. The activation of fibroblast growth factor receptors (FGFRs) by FGF21 requires the transmembrane protein cofactor β-Klotho, expressed predominantly in metabolic organs, including the liver, white adipose tissue, and the pancreas, conferring organ specificity to FGF21 (Li, et al. 2015; Ogawa, et al. 2007). Administration of exogenous FGF21 is being explored as a method to treat hypertriglyceridemia which is associated with increased risk of acute pancreatitis (AP) and cardiovascular disease (CVD). Severe hypertriglyceridemia (SHTG), defined as fasting triglyceride (TG) levels of greater than or equal to 500 mg/dL, is associated with an increased risk of AP, accounting for up to 10% of all AP episodes (de Pretis, 2018), and an increased risk of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and CVD (Grundy, et al. 2019). Clinical practice guidelines from both the American College of Cardiology/American Heart Association and from the American Association of Clinical Endocrinologists/American College of Endocrinology emphasize the importance of reducing TG in patients with levels above 500 mg/dL. Current treatments for hypertriglyceridemia include fibrates, fish oils, niacin, and statins. While these treatments can reduce TG levels, not all patients can reduce TG levels to below 500 mg/dL, signifying the need for additional therapies.

Several non-clinical and clinical studies have shown that administration of various FGF21 analogs had beneficial effects on serum lipid and insulin-resistance as well as on liver fat (Zhang, et al. 2014, Gaich, et al. 2013, Sanyal, et al. 2018). A pharmacodynamic (PD) effect of BIO89-100 on TGs has been demonstrated, with significant reductions in TG [redacted]

In Part 1 of the Phase 1b/2a study BIO89-100-002, subjects with NASH or NAFLD and high risk for NASH (hypertriglyceridemia was not an enrollment criterion) who received BIO89-100 at 27 mg QW for 12 weeks showed a significant beneficial effect on the lipid profile, evaluated as percent change at Week 13 (Day 92) (-28% decrease in TG, -16% reduction in non-HDL cholesterol and LDL cholesterol, $p<0.05$ for all comparisons).

The current data suggest that BIO89-100 achieves potent and rapid reductions in TG levels through pathways mediated by FGF21, offering novel mechanisms of action. Severe hypertriglyceridemia is associated with serious outcomes including risk of significant morbidity and mortality, and BIO89-100 has the potential for development as an important new therapy.

This Phase 2 study is designed to assess the efficacy, safety, and tolerability of different doses and dose regimens (QW or every 2 weeks [Q2W]), subcutaneous (SC) dosing of BIO89-100 compared to

placebo in subjects with SHTG. All subjects may be on a background therapy of prescribed fish oils or statins but not on niacin, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, or any supplements, including non-prescribed fish oils, used to alter lipid metabolism. Subjects who are not taking prescription therapy to lower serum TG may also be enrolled.

Subjects in the main cohort will not be on concurrent fibrate therapy. In contrast, subjects in the fibrate expansion cohort will remain on their current stable dose of fibrate therapy.

The objectives and endpoints are the same for the main cohort and the fibrate expansion cohort.

Objectives and Endpoints for Main and Fibrate Expansion Cohorts

Objectives	Endpoints
Primary	
• To determine the effect of BIO89-100 on serum TG levels in subjects with SHTG (TG ≥500 mg/dL)	• Percentage change in serum TG from baseline to Week 8
Secondary	
• To determine the effect of BIO89-100 on selected serum lipids and lipoproteins	• Achieve TG <500 mg/dL at Week 8 • Percentage change in very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein triglycerides (VLDL-TG), apolipoprotein B100 (ApoB), remnant lipoprotein cholesterol (RLP-C) from baseline to Week 8
• To determine the effect of BIO89-100 on high-sensitivity C-reactive protein (hsCRP)	• Percentage change in hsCRP from baseline to Week 8
• To determine the effect of BIO89-100 on metabolic markers	• Percentage change in fasting plasma glucose, adiponectin, and body weight from baseline to Week 8

Objectives	Endpoints
• To characterize BIO89-100 pharmacokinetics (PK)	• Serum BIO89-100 concentration • PK parameters in Intensive PK subgroup o Maximal observed serum concentrations (C_{max}) within a dosing interval o Area under the serum drug concentration by time curve within a dosing interval ($AUC_{0\text{-}tau}$) o Time to achieve C_{max} (t_{max}) o Terminal elimination half-life ($t_{½}$) Note: Additional PK parameters may be calculated if also deemed appropriate.
• To characterize BIO89-100 PD profile as assessed by MRI-PDFF	• Percentage change and change from baseline in hepatic steatosis using MRI-PDFF
Safety Endpoints	
• To evaluate the safety and tolerability of BIO89-100	• Frequency of treatment-emergent adverse events (TEAEs) • Frequency of treatment-emergent serious adverse events (TESAEs) • Number of subjects who discontinue due to TEAEs • [redacted]
• To determine the effect of BIO89-100 on liver function biomarkers	• Change in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) from baseline to Week 8
• Other safety assessments	• Incidence and shifts of clinically significant vital signs, physical examination findings, electrocardiogram (ECG) data, and laboratory abnormalities; safety laboratory evaluations include complete blood count (CBC), blood biochemistry, 24-hour urine cortisol, and urinalysis • [redacted]

Overall Design

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 SC for 8 weeks. The main cohort will include ~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. The fibrate expansion cohort will include ~36 subjects with SHTG on stable background fibrate therapy and with a baseline MRI-PDFF ≥ 6.0% and will consist of 2 treatment groups comparing one dose regimen of BIO89-100 versus placebo. Investigators whose sites are obtaining MRIs should assess if subjects on background fibrate therapy are appropriate for the main cohort (acceptable to washout fibrate therapy) or for the fibrate expansion cohort. For participation in the fibrate expansion cohort, investigators should first discuss the potential subject with the Medical Monitor.

The study includes lifestyle stabilization, TG qualification, treatment, and follow-up periods.

After signing the informed consent form and confirmation of general eligibility, subjects will undergo further screening assessments to confirm eligibility over a period of ~6 to 9 weeks. Generally, eligible subjects will enter a 4- or 6-week lifestyle stabilization period (maximum of 6 weeks for subjects stopping lipid-altering therapy, minimum of 4 weeks for subjects already on stable, protocol-accepted lipid-altering therapy), followed by a ~2-week TG qualification period with qualifying TG measurements [redacted]. If mean TG levels are not within the inclusion range, an additional week will be allowed for an additional measurement [redacted]

Individuals who do not meet the criteria for participation in this study (screen failures other than for TGs) may be re-screened, at least 7 days later, if the reason for screen failure is deemed temporary and is resolved prior to re-screening (e.g., respiratory infection). Re-screened subjects will sign a new consent and be assigned a new ID. Subjects can only re-screen once. Re-screening subjects who have maintained the lifestyle stabilization period may be allowed to forgo repeated tests [redacted] at the discretion of the Medical Monitor. Re-screening after COVID-19 infection requires Medical Monitor approval.

Subjects fulfilling all of the qualifying criteria and none of the exclusionary criteria will be randomized 1:1:1:1:1 for the main cohort [redacted] and enter a double-blind, 8-week treatment period during which they will be dosed with 1 of 4 doses of BIO89-100 (9 mg QW, 18 mg QW, 27 mg QW, or 36 mg Q2W) or placebo.

Subjects will be enrolled in the fibrate expansion cohort with randomization 1:1 [redacted] and similarly enter a double-blind, 8-week treatment period during which subjects will be dosed with BIO89-100 27 mg or placebo QW.

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). Randomization in the fibrate expansion cohort will be stratified by TG <750 mg/dL or ≥750 mg/dL (8.47 mmol/L) only.

Treatment with investigational product (IP) may be given at home by a home health provider (HHP) or at the Investigator site, QW, SC into the abdomen. To maintain the blind, all subjects will receive 2 SC injections at study [redacted]. Subjects randomized to 36 mg Q2W will receive placebo at visits between BIO89-100 Q2W administrations. Intensive PK is planned to be assessed in a subset of subjects (optional participation to include no more than 45 subjects). Treatment assignment and

results of the post-baseline lipid panels (TG, [redacted] LDL-C, HDL-C, non-HDL-C, VLDL-C, VLDL-TG, [redacted] ApoB, [redacted] RPL-C, [redacted]), post-baseline MRI-PDFF, [redacted], and PK data will be blinded to subjects, sites, study team and 89bio.

The efficacy, safety, and tolerability of the treatments will be monitored throughout the study as described in the objectives (Section 3).

Subjects who terminate treatment early will be requested to have an EOT [redacted] and an EOS visit 4 weeks later. All subjects who complete the treatment period will enter a 4-week follow-up period.

Disclosure Statement: This is a parallel treatment study in which subjects, Principal Investigators, study site personnel, and 89bio will be blinded to treatment during the double-blind treatment period.

Number of Subjects:

Approximately 90 subjects are planned to be enrolled in the main cohort, with 18 subjects in each of the BIO89-100 dose 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 [redacted]
Subjects who terminate early in either cohort may be replaced at Sponsor's discretion.

Intervention Groups and Duration:

The main cohort will consist of 5 treatment groups (details shown in Table 1), with subjects randomized 1:1:1:1:1 to receive 1 of 4 doses of BIO89-100 (9 mg QW, 18 mg QW, 27 mg QW, or 36 mg Q2W) or placebo. The fibrate expansion cohort will consist of 2 treatment groups randomized 1:1 to receive BIO89-100 27 mg or placebo QW. 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 they are receiving background lipid-modifying therapy, as defined by prescription fish oil and/or statins. Randomization in the fibrate expansion cohort will be stratified by TG <750 mg/dL or ≥750 mg/dL (8.47 mmol/L) only. In both the main and fibrate expansion cohorts, the total duration of treatment will be 8 weeks, followed by a 4-week follow-up period.

Table 1: Intervention Groups Across Main and Fibrate Expansion Cohorts

Treatment Group	Dose Level[a]	Frequency and Route of Administration	Number of Subjects
1	9 mg	QW, SC to abdomen [redacted] Main cohort only	18
2	18 mg	QW, SC to abdomen [redacted] Main cohort only	18
3	27 mg	QW, SC to abdomen [redacted] Note: 18 subjects in the main cohort and 18 subjects in the fibrate expansion cohort	36
4	36 mg	Q2W, BIO89-100: SC to abdomen [redacted] Subjects in the 36 mg treatment group will receive placebo at visits between BIO89-100 Q2W administrations to maintain the blind. Placebo: [redacted] Main cohort only	18
5	Placebo	QW, SC to abdomen [redacted] Note: 18 subjects in the main cohort and 18 subjects in the fibrate expansion cohort	36

Abbreviations: SC = subcutaneous; QW = weekly; Q2W = every 2 weeks

[a] The actual doses will be ±5% of 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 includes lifestyle stabilization, TG qualification, treatment, and follow-up periods.

Screening period:	~6 to 9 weeks
Lifestyle stabilization period:	~4 weeks (minimum) to ~6 weeks (maximum) (~6 weeks for subjects stopping lipid-altering therapy, ~4 weeks for subjects already on stable, protocol accepted, lipid-altering therapy)
TG qualification period	~2 weeks to ~3 weeks
Treatment period	8 weeks
Follow-up period	4 weeks

Data monitoring committee: No data monitoring committee is planned for this study.

Figure 1: Study Schema: Main Cohort

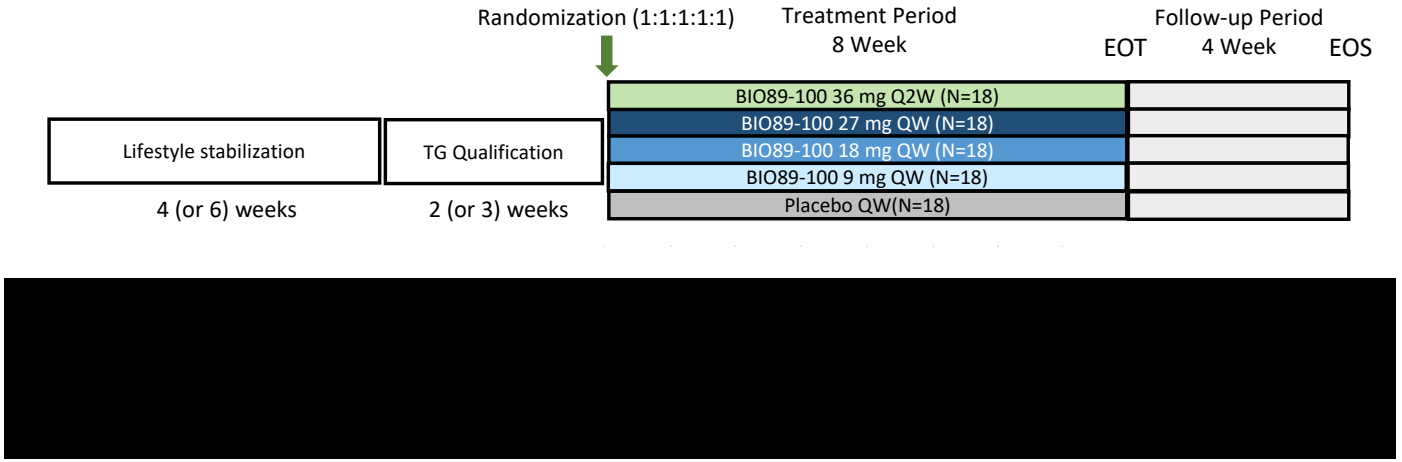
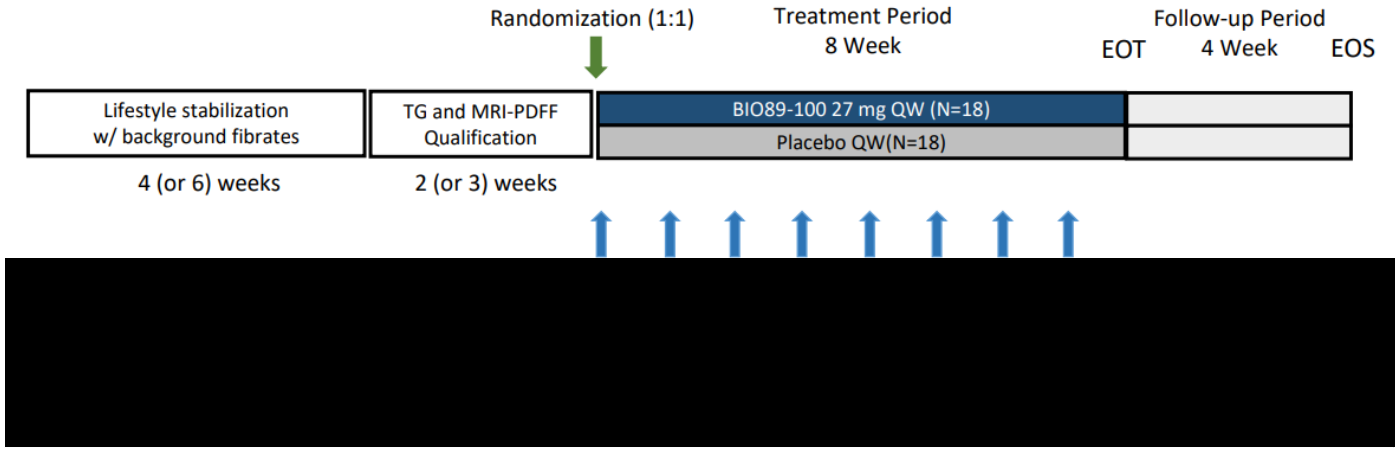


Figure 2: Study Schema: Fibrate Expansion Cohort



Abbreviations: EOT = end of treatment, EOS =end of study, N = number of subjects, QW = once weekly. Q2W = every 2 weeks, TG = triglyceride, V = visit, wk = week.

1.2. Schedule of Assessments (SoA)

Table 2: Schedule of Assessments

Schedule of Assessments													
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

Schedule of Assessments

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]													

Schedule of Assessments

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]													
Inflammatory biomarker (hsCRP)				x				x				x	x
and serum adiponectin, total				x				x				x	x
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	

Schedule of Assessments

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 CO_2 (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]

iii. [redacted]

k = Subjects will be included in either the Intensive PK scheme (optional) or Trough PK scheme (all subjects). Table 5 details sampling times for the Intensive PK scheme. [redacted] For the Trough PK scheme, blood samples will be taken [redacted]

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 [redacted]. 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]

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.

2. INTRODUCTION

2.1. Study Rationale

BIO89-100 is a glycoPEGylated analog of FGF21, a metabolic hormone, regulated by nutritional status, that affects energy expenditure and glucose and lipid metabolism. It is secreted mainly by the liver, but also by white adipose tissue, skeletal muscle, and the pancreas. The activation of FGFRs by FGF21 requires the transmembrane protein cofactor β-Klotho, expressed predominantly in metabolic organs, including the liver, white adipose tissue, and the pancreas, conferring organ specificity to FGF21 (Li, et al. 2015; Ogawa, et al. 2007). Administration of exogenous FGF21 is being explored as a method to treat hypertriglyceridemia, which is associated with increased risk of AP and CVD. Severe hypertriglyceridemia, defined as fasting TG levels of greater than or equal to 500 mg/dL, is associated with an increased risk of AP, accounting for up to 10% of all AP episodes (de Pretis, 2018), and an increased risk of NAFLD, NASH, and CVD (Grundy, et al. 2019). Clinical practice guidelines from both the American College of Cardiology/American Heart Association and from the American Association of Clinical Endocrinologists/American College of Endocrinology emphasize the importance of reducing TG in patients with levels above 500 mg/dL. Current treatments for hypertriglyceridemia include fibrates, fish oils, niacin, and statins. While currently approved therapies are proven to reduce TG levels, the treatment goal of alleviating SHTG, i.e., reducing TG levels to below 500 mg/dL remains a significant challenge. In the Phase 3 studies with Vascepa® and Epanova®, ~50% of subjects did not have TG level reductions below 500 mg/dL at the end of the 12-week studies (Chowdhury, 2012, Chowdhury 2014). Patients with TG levels above 500 mg/dL remain at risk for AP as well as cardiovascular and fatty liver diseases. Several non-clinical and clinical studies have shown that administration of various FGF21 analogs had beneficial effects on serum lipid and insulin-resistance as well as on liver fat (Zhang, et al. 2014, Gaich, et al. 2013, Sanyal, et al. 2018). A PD effect of BIO89-100 on TGs has been demonstrated, with significant reductions in TG levels in a non-human primate disease model and in the Phase 1a clinical study, TV47948-SAD-10122. [redacted] In Part 1 of the Phase 1b/2a study BIO89-100-002, subjects with NASH or NAFLD and high risk for NASH (hypertriglyceridemia was not an enrollment criterion) who received BIO89-100 at 27 mg QW showed a significant beneficial effect on the lipid profile, evaluated as percent change at Week 13 (-28% decrease in TG, -16% reduction in non-HDL cholesterol and LDL cholesterol, $p<0.05$ for all comparisons).

The current data suggest that BIO89-100 achieves potent and rapid reductions in TG levels through pathways mediated by FGF21, offering novel mechanisms of action. SHTG is associated with serious outcomes including risk of significant morbidity and mortality, and BIO89-100 has the potential for development as an important new therapy.

This Phase 2 study is designed to assess the efficacy, safety, and tolerability of QW or Q2W, SC dosing of BIO89-100 compared to placebo in subjects with SHTG. All subjects may be on a background therapy of prescribed fish oils or statins, but not on PCSK9 inhibitors, niacin, or any supplements, including non-prescribed fish oils, used to alter lipid metabolism. Subjects who are not taking prescription therapy to lower TG may also be enrolled. Subjects in the main cohort will not be on concurrent fibrate therapy. In contrast, subjects in the fibrate expansion cohort will remain on their current stable dose of fibrate therapy.

2.2. Background

2.2.1. Severe Hypertriglyceridemia

Hypertriglyceridemia refers to elevated TG concentrations in the blood, usually measured after fasting but occasionally non-fasting. High TGs are defined as TG = 200 to 499 mg/dL and very high triglycerides, or SHTG as TG ≥500 mg/dL (Berglund, et al. 2012; Jellinger, et al. 2017). Subjects with elevated levels of serum TGs (≥500 mg/dL) are at increased risk of AP, NASH, NAFLD and CVD (Grundy, et al. 2019). Persistent hypertriglyceridemia is associated with the development of AP and CVD. For example, people with high versus low, non-fasting TG (580 mg/dL vs 70 mg/dL) were at 5.1-fold higher risk for myocardial infarction, 3.2-fold higher risk of ischemic heart disease, 3.2-fold higher risk for ischemic stroke, and 2.2-fold higher risk for all-cause mortality (Nordestgaard, 2016). Patients with SHTG are at increased risk of AP with a reported 5% and 10% to 20% lifetime risk of AP in patients with TG >1000 and >2000 mg/dL respectively (Blom, et al. 2018, Scherer, et al. 2014). Kiss et al., reported that elevated TG worsens the severity of AP and increases the risk for local and systemic complications, however, they reported no specific correlation of AP severity with extent of hypertriglyceridemia (Kiss, et al. 2018). The mechanisms by which SHTG causes pancreatitis are not fully understood but may relate to impairment of capillary perfusion in the pancreas, pancreatic cell necrosis and subsequent release and activation of pancreatic enzymes (Blom, et al. 2018). If and when pancreatitis will occur in an individual patient is unpredictable. Episodes of acutely-elevated TG levels, associated for instance with alcohol use or meals with excessive fat, could increase risk in patients with chronically high TG levels. In most patients who develop AP secondary to SHTG, the condition is mild and self-limiting, but ~20% of patients suffer severe attacks associated with prolonged hospitalization and significant morbidity and mortality.

Given the high risk of AP associated with SHTG, early diagnosis is essential so that treatment can be initiated, including simple carbohydrate- and fat-restricted diet, use of medium-chain TG-rich foods and alcohol abstinence (Berglund, et al. 2012; Jacobson, et al. 2015).

Current approved therapies for SHTG, as an adjunct to diet, include multiple fibrates (approved by the FDA from 1993 to 2009), niacin (extended release approved by the FDA in 1997), and omega-3 fatty acids (approved in 2004, 2012, and 2014). Fibrates, niacin, and prescription omega-3 fatty acids, alone or in combination, can reduce TG by 20% to 50% in some patients with moderate to severe hypertriglyceridemia. However, minimal effects are seen in other patients, especially those with mutations in genes in the lipoprotein lipase pathway (Brisson, et al 2010). Statins have a modest TG lowering effect and are used in patients with moderately elevated TG levels, but they should not be used alone in patients with severe or very severe hypertriglyceridemia.

In patients at high risk for pancreatitis, fibrates remain first line drug treatment, but LDL-C levels may increase during therapy with fibrates which is a detrimental effect in this patient population. Fibrates are associated with an increase in the incidence of cholesterol gallstones, increases in transaminases and creatinine, among other safety and tolerability concerns (Lopid US Package Insert, 2017; Tricor US Package Insert, 2018). Further, due to increased risk of myopathy, the combination of gemfibrozil and statins should be avoided (Berglund, et al. 2014).

The approvals of the omega-3-acids (namely Vascepa® and Epanova®) represent advances in the therapeutic options with improved risk:benefit profiles as compared to the fibrates and niacin formulations. While currently approved therapies are proven to reduce TG levels, the treatment goal of alleviating SHTG, i.e., reducing TG levels to below 500 mg/dL remains a significant challenge. In the Phase 3 studies with Vascepa® and Epanova®, ~50% of the subjects did not have TG level reduction below 500 mg/dL at the end of the 12-week studies (Chowdhury, 2012; Chowdhury, 2014). Patients with TG levels above 500 mg/dL remain at risk for AP as well as cardiovascular and fatty liver diseases. There remains a critical need for new therapies that will reliably reduce TG levels below 500 mg/dL rapidly after diagnosis.

2.2.2. FGF21

FGF21 is a peptide hormone, which is secreted mainly by the liver. The activation of FGFRs by FGF21 requires the transmembrane protein cofactor β-Klotho, expressed predominantly in metabolic organs, including the liver, white adipose tissue, and the pancreas, conferring organ specificity to FGF21 (Li, et al. 2015; Ogawa, et al. 2007).

In patients with hypertriglyceridemia, circulating and/or tissue levels of FGF21 are increased, indicating the presence of FGF21 resistance, which can be overcome by administration of pharmacological doses of FGF21 (Galman, et al. 2008). On this basis, administration of exogenous FGF21 has been explored as a method to treat obesity-associated insulin-resistance disorders, including hypertriglyceridemia (Gaich, et al. 2013).

Native FGF21 has a short life (~2 hours), limiting the potential to use it as a therapeutic agent. Consequently, various methods have been developed to extend the half-life of FGF21, including PEGylation. PEGylated FGF21 was shown to provide comparable efficacy to wild-type FGF21 despite lower dosing frequency and total cumulative dose, which is likely a result of greatly increased *in vivo* half-life (Mu, et al. 2012). In 2 studies in humans, the effects of pegbelfermin (BMS-986036; a PEGylated analog of FGF21, which differs from BIO89-100 in PEG size, PEGylation site and technology, and location of mutations) were assessed separately in NASH or obese subjects. NASH subjects treated for 16-weeks with pegbelfermin experienced a statistically significant reduction in serum TGs versus placebo of 4.8% and 4.7% with doses of 10 mg/d and 20 mg/week, respectively (Sanyal, et al. 2018). Obese subjects treated for 12 weeks with pegbelfermin experienced a ~20% reduction of serum TGs($p=0.037$) at a dose of 20 mg/day (Charles, et al. 2019).

Improvements in LDL-C, and HDL-C were also noted in the NASH study primarily with the 10 mg daily dose. Finally, safety was considered favorable, with no deaths, treatment-related serious adverse events (SAEs), or discontinuations due to AEs reported. The most frequently reported AEs were diarrhea, nausea, and frequent bowel movement; most of these were mild, and none were considered severe in intensity.

2.2.3. BIO89-100

BIO89-100 is a glycoPEGylated analog of FGF21 that has an N-terminal methionine residue, 2-point mutations, and a single 20 kDa linear PEG covalently attached via a glycosyl moiety. Both point mutations are less likely to be exposed due to steric hindrance by the PEG domain, and thereby less likely to trigger an immune response. It has been evaluated in non-clinical pharmacology, PK, and toxicology studies and in a recently-completed, first-in-human, single ascending dose (SAD) study (TV47948-SAD-10122).

[redacted]

TV47948-SAD-10122, a Phase 1, first-in-human, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK properties of BIO89-100 following SC administration of SAD, has recently been completed. [redacted] No significant safety issues have been identified. The most common reported AEs (≥2 in the pooled BIO89-100 group) were injection site reactions (all common terminology criteria for adverse events [CTCAE] Grade 1), headache, contact dermatitis, and nausea. There were no deaths, SAEs, or discontinuations, and review of ECG, clinical laboratories, and vital sign data did not reveal any concerning trends. There was a single CTCAE Grade 3 TEAE that was considered not treatment-related (elevated creatine phosphokinase level at EOS in a physical laborer). No other CTCAE Grade 3 or above TEAE was reported.

Part 1 of 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 [redacted] of BIO89-100 administered SC in subjects with NASH or with NAFLD who are at a high risk of NASH. Subjects were treated at QW SC doses of 3 mg, 9 mg, 18 mg, and 27 mg, and Q2W SC doses of 18 mg and 36 mg of BIO89-100 or placebo. Data from the MAD study Part 1 demonstrated favorable safety and tolerability with repeated dosing of BIO89-100 for 12 weeks with evidence of clinical efficacy in NASH (clinically meaningful reductions in liver fat assessed by MRI-PDFF and in ALT).

A detailed description of the chemistry, pharmacology, efficacy, and safety of BIO89-100 is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

[redacted]

2.3.1. Risk Assessment

[redacted]

BIO89-100 is administered subcutaneously; ISRs are well-recognized with SC administration of biological agents. As with any biologic drug, exposure to BIO89-100 may potentially provoke an immune response with formation of [redacted] that may lead to loss of efficacy, neutralization of endogenous FGF21, or adverse effects (e.g., hypersensitivity reaction).

[redacted]

[redacted]

Increased appetite, which has been reported with other FGF21 analogs, occurred in 15.9% of BIO89-100-treated subjects and no placebo-treated subjects in Study BIO89-100-002 (Part 1) without a clear dose response.

In a clinical study of another FGF21 analog, increased blood pressure and heart rate were reported. No clinically significant changes in vital signs or ECGs were observed in study TV47948-SAD-10122 or study BIO89-100-002 (Part 1).

[redacted]

- [redacted]

2.3.2. Benefit Assessment

Patients with SHTG are at increased risk of AP and cardiovascular comorbidities and require significant reductions in TG to lower the risk of AP. As a substantial proportion of patients have persistent hypertriglyceridemia despite the use of TG lowering medications, there remains a critical need for new therapies that will reliably reduce TG levels below 500 mg/dL rapidly after diagnosis.

Long-acting FGF21 analogs are a promising mode of action for the treatment of SHTG; multiple FGF21 analogs have been shown to reduce levels of TG and other lipids in studies of subjects with NASH or obesity and Type 2 diabetes mellitus (Charles ED, 2019, Gaich G, 2013, Sanyal A, 2019, Talukdar S, 2016). A PD effect of BIO89-100 on TGs has also been demonstrated with significant reductions in TG levels in the Phase 1a clinical study, TV47948-SAD-10122, and in a non-human primate disease model. Furthermore, BIO89-100 also offers the potential for broader metabolic benefits, including amelioration of fatty liver disease, reduction in LDL-C, increase in HDL-C, and improvements in glycemic control that may confer an additional advantage in patients with SHTG , many of whom have metabolic comorbidities.

Taken together, treatment with BIO89-100 may have a positive impact on serum TG concentrations and other metabolic parameters in treated subjects.

2.3.3. Overall Benefit-Risk Assessment

Considering the potential benefits, potential risks, and risk mitigation measures that have been implemented, the benefit-risk profile of administering BIO89-100 to subjects with SHTG in study BIO89-100-221 is considered to be favorable. The overall benefit-risk associated with administration of BIO89-100 will be continually re-assessed with the emergence of additional data.

Safety of trial participants is of primary importance. Subject participation in the trial during the COVID-19 pandemic requires that site personnel and study subjects follow key protective measures against COVID-19 infection, aligned with local requirements and recommendations. 89bio and participating study sites will continually monitor the conditions of the pandemic as they may affect the subjects' safe participation in the trial. 89bio and participating study sites may

implement changes to the protocol based on an overall risk assessment that includes considerations related to COVID-19 that may result in changes or alternatives regarding in-clinic visits, methods of performing assessments, monitoring, data collection, and/or trial participation. Provisions concerning IP administration related to potential impacts due to COVID-19 are described in Section 7.1.

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints are the same for the main cohort and fibrate expansion cohort.

Objectives	Endpoints
Primary	
• To determine the effect of BIO89-100 on serum TG levels in subjects with SHTG (TG ≥500 mg/dL)	• Percentage change in serum TG from baseline to Week 8
Secondary	
• To determine the effect of BIO89-100 on selected serum lipids and lipoproteins	• Achieve TG <500 mg/dL at Week 8 • Percentage change in VLDL-C, LDL-C, non-HDL-C, HDL-C, VLDL-TG, ApoB, RLP-C from baseline to Week 8
• To determine the effect of BIO89-100 on hsCRP	• Percentage change in hsCRP from baseline to Week 8
• To determine the effect of BIO89-100 on metabolic markers	• Percent change in fasting plasma glucose, adiponectin, and body weight from baseline to Week 8
• To characterize BIO89-100 PK	• Serum BIO89-100 concentration • PK parameters in Intensive PK subgroup o C_{max} within a dosing interval o $AUC_{0\text{-}tau}$ within a dosing interval o t_{max} o $t_{½}$ • Additional PK parameters may be calculated if also deemed appropriate.
• To characterize BIO89-100 PD profile as assessed by MRI-PDFF	• Percentage change and change from baseline in hepatic steatosis using MRI-PDFF

Objectives	Endpoints
Exploratory	
• [redacted]	[redacted]

Objectives	Endpoints
Safety Endpoints	
• To evaluate the safety and tolerability of BIO89-100	• Frequency of TEAEs • Frequency of TESAEs • Number of subjects who discontinue due to TEAEs • [redacted]
• To determine the effect of BIO89-100 on liver function biomarkers	• Change in ALT and AST from baseline to Week 8
• Other safety assessments	• Incidence and shifts of clinically significant vital signs, physical examination findings, ECG data and laboratory abnormalities; safety laboratory evaluations include CBC, blood biochemistry, 24-hour urine cortisol, and urinalysis. • [redacted]

4. STUDY DESIGN

4.1. Overall Design

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 SC for 8 weeks. The main cohort will include ~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 ~36 subjects with SHTG on stable background fibrate therapy and with an MRI-PDFF ≥6.0% and will consist of 2 treatment groups comparing one dose regimen of BIO89-100 versus placebo (Figure 2). Investigators whose sites are obtaining MRIs should assess if subjects on background fibrate therapy are appropriate for the main cohort (acceptable to washout fibrate therapy) or for the fibrate expansion cohort. For participation in the fibrate expansion cohort, investigators should first discuss the potential subject with the Medical Monitor

The study includes lifestyle stabilization, TG qualification, treatment, and follow-up periods.

After signing the informed consent form and confirmation of general eligibility, subjects will undergo further screening assessments to confirm eligibility over a period of ~6 to 9 weeks. Generally, eligible subjects will enter a 4- or 6-week lifestyle stabilization period (maximum of 6 weeks for subjects stopping lipid-altering therapy, minimum of 4 weeks for subjects already on stable, protocol-accepted lipid-altering therapy), followed by a ~2-week TG qualification period with qualifying TG measurements [redacted]

Individuals who do not meet the criteria for participation in this study (screen failures other than for TGs) may be re-screened, [redacted], if the reason for screen failure is deemed temporary and is resolved prior to re-screening (e.g., respiratory infection). Re-screened subjects will sign a new consent and be assigned a new ID. Subjects can only re-screen once. Re-screening subjects who have maintained the lifestyle stabilization period may be allowed to forgo repeated tests [redacted] at the discretion of the Medical Monitor. Re-screening after COVID-19 infection requires Medical Monitor approval.

Subjects fulfilling all of the qualifying criteria and none of the exclusionary criteria will be randomized 1:1:1:1:1 for the main cohort [redacted] and enter a double-blind, 8-week treatment period during which they will be dosed with 1 of 4 doses of BIO89-100 (9 mg QW, 18 mg QW, 27 mg QW, or 36 mg Q2W) or placebo.

Enrollment will begin in the fibrate expansion cohort, with randomization 1:1 [redacted] to a double-blind, 8-week treatment period during which subjects will be dosed with BIO89-100 27 mg or placebo QW.

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). Randomization in the fibrate expansion cohort will be stratified by TG <750 mg/dL or ≥750 mg/dL (8.47 mmol/L) only.

Treatment with IP will be given at the Investigator site, QW, SC into the abdomen. To maintain the blind, all subjects will receive 2 SC injections [redacted]. Subjects randomized to 36 mg Q2W will receive placebo at visits between BIO89-100 Q2W administrations. Intensive PK is planned to be assessed for a subset of subjects (optional participation with no more than 45 subjects). Treatment assignment and results of the post-baseline lipid panels (TG, [redacted], LDL-C, HDL-C, non-HDL-C, VLDL-C, VLDL-TG, [redacted], ApoB, [redacted], RPL-C, [redacted]), post-baseline MRI-PDFF, [redacted], and PK data will be blinded to subjects, sites, study team, and 89bio.

The efficacy, safety, and tolerability of the treatments will be monitored throughout the study as described in the objectives (Section 3).

Subjects who terminate treatment early will be requested to have an EOT visit [redacted] and an EOS visit 4 weeks later. All subjects who complete the treatment period will enter a 4-week follow-up period.

4.2. Scientific Rationale for Study Design

BIO89-100-221 a Phase 2, randomized, double-blind, placebo-controlled study designed to assess the efficacy, safety and tolerability of different doses and dose regimens (QW or Q2W) of SC BIO89-100 compared to placebo in subjects with SHTG. The study will separately evaluate the response to BIO89-100 in subjects who are not on concurrent fibrate therapy and subjects who remain on their current fibrate therapy. The primary and secondary efficacy endpoints, safety, and PK are characteristic for this type of study. Results from this study will provide proof-of-concept data to inform dose selection in the future Phase 3 clinical program.

Fibrate therapy is commonly used to lower TGs in patients with SHTG. Fibrates act by agonizing PPARα, which stimulates the release of FGF21 in the liver. It is unknown if the levels achieved by exogenous FGF21 supplementation with BIO89-100 will be greater than, or have an add-on effect to, those achieved by fibrate-induced PPARα agonism alone.

One potential additional benefit of BIO89-100 is reduction in liver fat content. Fatty liver has been shown to be significantly associated with moderately severe or severe acute pancreatitis (Yoon, et al. 2017). In Study BIO89-100-002 (Part 1), BIO89-100 (27 mg QW) reduced liver fat as assessed by MRI-PDFF up to 60%. Fibrates do not reduce liver fat content. To evaluate this additional potential benefit, only subjects with liver fat content ≥6.0% by MRI-PDFF at baseline will be enrolled into the fibrate expansion cohort.

4.3. Justification for Dose

Five groups of SHTG subjects are planned to be dosed, SC × 2 per visit, into the abdomen, with either placebo or 1 of 4 doses of BIO89-100 (9 mg QW, 18 mg QW, 27 mg QW, or 36 mg Q2W) (Figure 1).

These dose regimens were selected based on non-clinical pharmacological and PK models mainly in spontaneously diabetic monkeys, review of clinical PK, and efficacy data from the single ascending dose clinical study TV47948-SAD-10122 and PK modeling.

[redacted]

[redacted]

The selected dose of 27 mg QW was chosen for the fibrate expansion cohort based on the results observed in subjects with NASH or NAFLD and high risk for NASH in Study BIO89-100-002 (Part 1), in which 10 subjects were randomized to that dose. [redacted]

The benefit/risk assessment for BIO89-100 at the chosen doses is presented in Section 2.3. Based on these data, the dose regimens are anticipated to be safe, and of sufficient duration to reach steady state, to maintain PD responses over the dosing intervals, and to cover the dose range where key PD responses are predicted to be associated with important clinical outcomes to be assessed in subsequent studies.

4.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Assessments (SoA) (Table 2). The EOS is defined as the date of the last visit of the last subject in the study.

5. STUDY POPULATION

5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Subject understands the study design and has been informed of the investigational nature of the study. Subject has given voluntary, written, informed consent to take part in this study.
2. Subject agrees to be compliant and is capable of completing the required study assessments.
3. Male or female age ≥21 to ≤75 years at time of signing informed consent.
4. All subjects (male or female) who are of childbearing potential must agree to use highly-effective, double contraception (with male/female partners) during the study. Double contraception is defined as use of a condom by the male partner, combined with use of 1 of the following forms of highly-effective contraception by the female partner:
   a. Oral contraceptive pills
   b. Depot or injectable contraceptive
   c. Intrauterine device (IUD)
   d. Contraceptive patch (e.g., Xulane®) or NuvaRing®
   e. Documented evidence of tubal ligation at least 6 months prior to the screening visit).

   Male subjects with a history of vasectomy should also use condoms as double contraception during the study. Use of highly-effective, double contraception must continue for 30 days or 5 half-lives (whichever is longer) after the last dose of IP. Female subjects must not donate oocytes during this time. Male subjects must not donate sperm during this time. Rhythm methods are not considered as highly-effective methods of birth control. Subject abstinence for the duration of the study and 30 days or 5 half-lives (whichever is longer) after last dose of IP is acceptable if it is the subject's regular practice.
5. Females of childbearing potential must have a negative serum pregnancy test at screening [redacted] and agree to undergo a urine pregnancy test at [redacted], and a serum pregnancy test at end of the study [redacted].
6. Females not of childbearing potential will be defined for this study as postmenopausal (defined as cessation of regular menstrual periods for at least 12 months) and confirmed by follicle-stimulating hormone (FSH) level OR surgically sterile (e.g., total hysterectomy, partial hysterectomy, or oophorectomy).
7. Serum TG criteria meeting <u>all</u> of the following criteria:
   a. A historical documented TG ≥400 mg/dL (4.52 mmol/L) in the past 5 years from screening [redacted] or currently on lipid-modifying therapy due to SHTG at screening [redacted].
   b. Mean of 2 screening fasting serum TGs ≥500 mg/dL (5.65 mmol/L) and ≤2000 mg/dL (22.60 mmol/L). The target for the study is 500 mg/dL. Due to TG variability, up to 10% of subjects enrolled may have a mean qualifying TG level between 475 and 500 mg/dL. Mean screening fasting serum TG is defined as the mean of TG [redacted] if the average of TG at [redacted] is <500 mg/dL, or

>2000 mg/dL. The repeat measure of TG is permitted at a minimum of 7 days apart at [redacted].

c. If 1 of the 2 qualifying TGs is <400 mg/dL, the difference between 2 TG should be <300 mg/dL. Note: If a subject has an individual fasting TG value of <350 mg/dL at any one visit or mean of two fasting TG levels <475 mg/dL, they will be considered a screen fail and not eligible to be re-screened.

8. Willing to maintain current eating and exercise habits from time of signing the informed consent and for the duration of the study. (See also Inclusion Criterion #11 and Exclusion Criterion #10 regarding alcohol consumption and Exclusion Criterion #4 regarding weight changes.)
9. Concomitant medication may include prescription fish oil (including purified eicosapentaenoic acid [EPA] with or without docosahexaenoic acid [DHA]) and/or statin with or without ezetimibe (none of which will be supplied as part of study) as long as the subject has been clinically stable (per Principal Investigator [PI] judgment) while on stable dose for [redacted].
10. Medicines known to exacerbate hypertriglyceridemia (such as certain beta blockers, thiazides, estrogens, bile acid sequestrants) should be stable [redacted]) and remain stable during the study.
11. Subject is willing to refrain from alcohol consumption for ≥48 hours before each study visit.
12. MRI-PDFF of ≥ 6.0% for subjects screened for the fibrate expansion cohort. Note: Those who cannot undergo MRI for any reason (e.g., claustrophobia, metal implants) cannot participate in the fibrate expansion cohort.

5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Females who are pregnant or breastfeeding, or planning to become pregnant, or breastfeed while enrolled in the study or within 30 days or 5 half-lives (whichever is longer) after last dose of IP.
2. Uncontrolled or newly diagnosed (< 3 months since diagnosis at time of Screening) **hypertension**. Subjects with well controlled hypertension who are clinically stable may enroll if they have been on a stable dose of antihypertensive medications for at least 2 months before Screening. Subjects who are taking >2 antihypertensive medications may be eligible with Medical Monitor (or designee) approval.
3. Body mass index (BMI) >45 kg/m^2 at screening [redacted].
4. Weight change ≥5% in 3 months prior to screening [redacted] or weight change ≥5% between screening [redacted].
5. Central laboratory hemoglobin levels below the lower limit of normal (<12.0 g/dL for males, <11.0 g/dL for females), or dialysis, lipid apheresis, plasma exchange, blood transfusion, or blood donation/blood loss of ≥400 mL at least a month prior to and during

the screening period or anticipation of these procedures during the period of the study and up to 30 days afterwards.

6. A history of symptomatic gallstone disease unless treated with cholecystectomy and/or pancreatitis within 5 years from screening will be excluded from the study.
7. ALT or AST >3× upper limit of normal (ULN) at screening [redacted].
8. Total bilirubin exceeds ULN at screening [redacted], unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤3 mg/dL.
9. Creatine kinase (CK) > 5 × ULN at screening [redacted].
10. Risky drinking (defined as alcohol intake >14 standard drink units per week or 4 standard drinks on a single occasion in men; and alcohol intake >7 standard drink units per week or 3 standard drinks on a single occasion in women) within the 24 months before screening [redacted] or had positive alcohol test at screening [redacted]. A unit of alcohol is defined as 14 gram or as 355 mL of beer (5% alcohol by volume [ABV]), 1 glass of wine (150 mL; 12% ABV), or 1 shot of hard liquor (45 mL; 40% ABV). During the study, subjects will receive counseling and will be encouraged to abstain from alcohol.
    Alcohol intake will be limited to 2 units of alcohol per day for men and 1 unit of alcohol per day for women. Subjects must be willing to abstain from alcohol use 48 hours prior to study visits.
11. Concomitant use of PCSK9 inhibitors, niacin, or any supplements, including non-prescription, non-pharmaceutical strength fish oils, used to alter lipid metabolism. Previous treatment with a PCSK9 inhibitor will need to have ceased >12 weeks before screening with no intention to reinitiate treatment for the duration of the trial. Other lipid-modifying supplements including, but not limited to, red rice yeast supplements, garlic supplements, soy isoflavone supplements, sterol/stanol products, or policosanols are not permitted.
    a. Subjects participating in the main cohort previously treated with a fibrate will need to agree to cease fibrate treatment for the duration of this trial.
    b. Subjects enrolled in the fibrate expansion cohort will need to maintain their current stable dose of fibrate therapy (≥4 weeks before screening [redacted]).
12. Previous long-term (>4 weeks) use of systemic steroid (glucocorticoid) medications such as prednisone within 12 months of screening [redacted]. Inhaled or topical corticosteroids are permitted.
13. Reduced renal function (eGFR ≤ 55 mL/min/1.73 m^2 calculated using chronic kidney disease epidemiology collaboration [CKD-EPI] equation).
14. Positive for hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV). HIV, HBV and HCV determined by antibodies first and, if positive, confirmed by DNA/ribonucleic acid (RNA). Subjects who have tested positive for COVID-19 who are asymptomatic or who have active COVID-19 infection are excluded. Note: subjects who had COVID-19 and recovered without sequelae or tested positive without symptoms at least 8 weeks prior to screening may be included.

15. History of substance use disorder, or any other substance dependence (with the exception of caffeine) as defined by the Diagnostic and Statistical Manual of Mental Disorders 4th edition Text Revision (DSM-IV-TR) in the past 2 years prior to Screening. Subjects without a history of substance use disorder who have a positive drug screen test at Screening may be considered for enrollment with Medical Monitor (or designee) approval.
16. Participation in a previous clinical trial or exposure to another investigational drug within 12 weeks or 5 half-lives, whichever is longer, prior to screening.
17. Previous exposure to an FGF21 analog [redacted] r FGFR1 activating product or known sensitivity to PEG or any of the excipients.
18. Type 1 diabetes mellitus (T1DM).
19. Diagnosis of Type 2 diabetes mellitus (T2DM) <6 months prior to screening.
20. Subjects with T2DM diagnosed ≥ 6 months prior to screening must have a HbA1c < 9.5% and if receiving antidiabetic medications, must be on a stable regimen before screening. A stable regimen is defined as no addition or discontinuation of antidiabetic medications, but dose adjustments or switching to another medication in the same class at the same relative dose per standard of care are allowed. Insulin, dipeptidyl peptidase IV (DPP-IV) antagonists and other oral medications are allowed if subject has been on a stable regimen for at least 3 months. Glucagon-line peptide 1 (GLP-1) agonists and sodium glucose co-transporter 2 (SGLT2) inhibitors are allowed if subject has been on stable doses for 6 months. Use of thiazolidinediones such as pioglitazone, which can reduce serum TGs, are NOT allowed in this study.
21. History of malignancy within 5 years prior to screening [redacted] other than successfully treated basal or squamous cell carcinoma or localized cervical carcinoma.
22. Inadequately controlled thyroid disorders. Subjects on thyroid replacement should be on stable doses for at least 2 months prior to screening.
23. Subjects with known lipoprotein lipase impairment or deficiency (Fredrickson Type 1), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type 3).
24. Clinically or otherwise documented cardiovascular or cerebrovascular disease including clinically significant anomalies of rhythm or pattern of ECG or New York Heart Association Class II to IV heart failure within 12 months of screening [redacted] that, in the judgment of the Investigator, could affect the safety of the subject or their ability to comply with the study requirements.
25. History of bone trauma, fracture, or surgery within 2 months of screening or other bone disorders, such as osteoporosis, osteomalacia, and known untreated severe vitamin D deficiency (serum 25-hydroxy-vitamin D ≤5 ng/mL).
26. Subject who cannot fast for study procedures for any reason per Investigator's assessment will be excluded. Subjects with T2DM who are treated by insulin secretagogues will need to consult their treating physician about the optimal timing to take these medications to enable them to fast safely for study procedures.

27. An employee of the investigational center or has a family member who is involved with the conduct of this study.
28. Any other condition(s) that would compromise the safety of the subject or compromise the quality of the clinical study, as judged by the Investigator.

5.3. Lifestyle Considerations

Beginning at the screening visit, all subjects will enter a diet, lifestyle, and medication stabilization period. Subjects should maintain their current eating and exercise habits as of the time they signed the ICF for the duration of the study. All subjects should be instructed to refrain from excessive alcohol consumption.

5.3.1. Meals and Dietary Restrictions

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. All subjects will be required to fast for at least 12 hours (it is recommended that subjects fast no more than 14 hours) before visits requiring fasted blood sampling. Subjects will be instructed to attempt to remain consistent in how long they fast for the duration of the study. For the purposes of this study, fasting is defined as nothing by mouth except non-mineral water (and any essential medications).

5.3.2. Alcohol

Beginning at the screening visit, all subjects should be instructed to refrain from excessive alcohol consumption, limited to 2 units of alcohol per day for men and 1 unit of alcohol per day for women. Subjects will abstain from alcohol for 48 hours before each study visit. If the subject's alcohol test is positive at a scheduled visit where lipid panels will be measured, the subject will be instructed to come back for an unscheduled visit for lipid panel measurement prior to or at the next scheduled visit.

5.3.3. Activity

Beginning at the screening visit, all subjects should not alter their normal activity routines for the duration of the study.

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failures other than for TGs) may be re-screened, at least 7 days later, if the reason for screen failure is deemed temporary and is resolved prior to re-screening (e.g., high blood pressure). Re-screened subjects will sign a new consent and be assigned a new ID. Subjects can only re-screen once. Re-screening subjects who have maintained the lifestyle stabilization period may be allowed to forgo repeated

tests [redacted] at the discretion of the Medical Monitor. Re-screening after COVID-19 infection requires Medical Monitor approval.

Retesting of laboratory tests is allowed when results are deemed spurious or incomplete.

6. INVESTIGATIONAL PRODUCT

Investigational product is defined as BIO89-100 or matching placebo, intended to be administered to a study subject according to the study protocol.

6.1. Investigational Product(s) Administered

Investigational product will be administered SC to the abdomen by qualified study personnel. Each administration will consist of 2 SC injections.

Arm	**Active arm**	**Placebo arm (control)**
Intervention	BIO89-100	Matching Placebo
Type	Biologic	Chemical solution
Dose Formulation	[redacted]	[redacted]
Unit Dose Strength(s)	Mg	Not applicable
Dosage Level(s)[a]	9 mg, 18 mg, 27 mg QW 36 mg Q2W	NA; matching placebo will be injected at matching frequency per protocol.
Route of Administration	SC injection	SC injection
Sourcing	Provided centrally by 89bio	Provided centrally by 89bio
Packaging and Labeling	BIO89-100 is supplied as a sterile, preservative-free, frozen liquid formulation in a single-use Type 1 clear glass vial for SC injection. Each vial will be labeled as required per country requirement.	Placebo will be supplied as a sterile, preservative-free, frozen liquid formulation in a single-use Type 1 clear glass vial for SC injection. Each vial will be labeled as required per country requirement.

Abbreviations: QW = every week; Q2W = every 2 weeks.

[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.

6.2. Administration Instructions

On-site administration: The SC injection of the IP should be performed by a limited number of site staff specifically trained in the administration of SC injections. Injections will be administered in the abdominal area only. Details on injection of IP will be provided in the relevant study manual.

After administration of the IP, the subject should remain resting for ~15 minutes. For additional doses in the same subject, the injection site should be rotated within the abdominal area by at least 2 inches. Injections should be at least 2 inches from the umbilicus (belly button).

Home administration: Home administration of IP may occur on [redacted]. Home health visits conducted by qualified HHPs for IP dosing will follow the above administration protocol. Further details are provided in the relevant study manual.

6.3. Preparation/Handling/Storage/Accountability

BIO89-100 will be stored and prepared in appropriate conditions as indicated in the relevant study manual.

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.
- Only subjects enrolled in the study may receive IP and only authorized study staff or HHPs may supply or administer IP. All IP on site must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for on-site IP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for IP shipping, preparation, and administration and the final disposition of unused IPs are provided in the relevant manuals for on-site and home administration.

6.4. Measures to Minimize Bias: Randomization and Blinding

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.

To maintain the blind, each subject will receive 2 injections QW including subjects randomized to 36 mg Q2W who will receive placebo injections at alternate Q2W visits.

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). Randomization in the fibrate expansion cohort will be stratified by TG <750 mg/dL or ≥750 mg/dL (8.47 mmol/L) only. 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 (TG, [redacted], LDL-C, HDL-C, Non-HDL-C, VLDL-C, VLDL-TG, [redacted], ApoB, [redacted], RPL-C, [redacted]), [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.

6.5. Emergency Unblinding

At the initiation of the study, Investigators will be instructed on the method for breaking the blind. The method will be an electronic process in the IWRS/RTSM system. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is essential for further management of the subject. Investigators are encouraged to discuss with the Medical Monitor if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and subject will need to discontinue study drug and complete the final study procedures.

6.6. Investigational Product Compliance

The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of IP and study subject identification will be confirmed by a member of the study site staff other than the person administering the IP. For doses administered by an HHP, administration details will be provided to the study staff for documentation.

In cases in which a dose is administered outside of the allowed visit time window, adjustments to the remaining visit dates may be required. The Investigator should discuss with the Medical Monitor if the dosing schedule changes markedly compared to the original schedule.

6.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the subject has received within 3 months from Screening [redacted] (prior therapy), is receiving at the time of enrollment, or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Concomitant medication may include prescription fish oil (including purified EPA with or without DHA) and/or statin with or without ezetimibe (none of which will be supplied as part of study) as long as the subject has been clinically stable (per PI judgment) while on stable dose for ≥4 weeks before screening [redacted] and will maintain stable dose during the duration of the study.

Elevated levels of FGF21 have been linked to reduced cytochrome P450 3A (CYP3A) mRNA expression and activity in NAFLD patients (Woolsey et al, 2016). The underlying mechanism has not been fully elucidated and whether such effects will be observed in SHTG patients is unknown. However, subjects receiving concomitant administration of CYP3A4 substrates with narrow therapeutic index should be closely monitored for any potentially related safety events, and dose adjustment of the CYP3A4 substrate should be considered as needed.

COVID-19 vaccine, if available, will be allowed but subjects are prohibited from participation in interventional COVID-19 vaccine clinical trials.

6.7.1. Prohibited Medications/Therapies

Subjects must abstain from taking lipid-modifying supplements after the start of screening until completion of the EOS visit, unless, in the opinion of the Investigator and the Medical Monitor, the medication is required.

Other prohibited therapies include:

- Use of PCSK9 inhibitors, niacin, or any supplements, including non-prescription, non-pharmaceutical strength fish oils, used to alter lipid metabolism. For subjects enrolled in the main cohort, use of fibrates is prohibited.
- Medicines known to exacerbate hypertriglyceridemia (such as certain beta blockers, thiazides, estrogens, bile acid sequestrants) should be stable (≥4 weeks before screening [redacted] and remain stable during the study.
- Other lipid-modifying supplements including, but not limited to, red rice yeast supplements, garlic supplements, soy isoflavone supplements, sterol/stanol products, or policosanols.
- Long-term (>4 weeks) use of systemic steroid (glucocorticoid) medications such as prednisone. Inhaled and topical steroids are acceptable.
- Use of thiazolidinediones such as pioglitazone
- Any IP, FGF21 analog [redacted] or FGFR1 activating product.

6.7.2. Blinded Alerts and Rescue Medications/Therapies

Lipid panel results including TG are blinded during the study. If a subject has a measured fasting TG >2000 mg/dL, a blinded alert will be sent to the Investigator noting that the TG alert criteria has been met for that subject. The Investigator will contact the subject for the following:

- Investigator to confirm and ensure the subject is managed and compliant with the allowed standard of care therapies for optimal hypertriglyceridemia management.
- Investigator to confirm the subject was fasting for at least 12 hours and was absent from alcohol for 48 hours prior to the TG triggered blinded alert was measured.
- Investigator to schedule the subject for an unscheduled fasting TG measurement. The subject should fast for at least 12 hours (and recommended no more than 14 hours) and

have no alcohol 48 hours prior to the planned unscheduled visit TG measurement. The subject should have the unscheduled fasting TG measurement prior to or at the next scheduled visit.

If the subject has 2 consecutive blinded TG alerts, the Investigator should assess whether it is clinically safe for the subject to continue receiving IP.

6.8. Stopping Rules

The Sponsor may suspend or terminate the study in the event of:

- New toxicological or pharmacological findings or clinical safety findings that invalidate the earlier positive benefit-risk assessment;
- Discontinuation of the development of BIO89-100;
- External circumstances that do not enable the study to be properly conducted under the existing protocol, including potential circumstances related to the COVID-19 pandemic.

6.8.1. Monitoring and Discontinuation for Suspected Drug-induced Liver Injury (DILI) Criteria

A subject will be additionally monitored if they meet any of the following liver-related criteria. Baseline value is defined as the last ALT and AST values performed prior to or on the [redacted].

New transaminase elevations in subjects with baseline value within the normal range:

For new elevations in transaminases greater than 2× ULN, repeat measurement should be performed within 48 to 72 hours. If elevations persist, subjects should be evaluated for other causes of transaminase elevations and with tests of hepatic function. If no other cause is identified, then the subjects need to be monitored closely (see below), and discontinuation of the study drug should be considered.

Drug should be discontinued, and the subject followed until resolution of symptoms or signs in the following situations:

- ALT or AST >8× ULN
- ALT or AST >5× ULN for more than 2 weeks
- ALT or AST >3× ULN and (TB >2× ULN or INR >1.5)
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

New transaminase elevations in subjects with baseline ALT or AST > ULN:

For new elevations in transaminases greater than 2× baseline value or total bilirubin >1.5× ULN, repeat measurement should be performed within 48 to72 hours. If elevations persist, subjects should be evaluated for other causes of transaminase elevations and with tests of hepatic function. If no other cause is identified, then the subjects need to be monitored closely (see below), and discontinuation of the study drug should be considered.

Drug should be discontinued and the subject followed until resolution of symptoms or signs in the following situations described in Table 3:

Table 3: Discontinuation Criteria in Subjects with Abnormal Baseline ALT or AST Values

Baseline value of ALT/AST	Criteria to discontinue investigational product
<2× ULN	if ALT or AST increases to >5× baseline value
≥2× ULN but <5× ULN	if ALT or AST increases to >3× baseline value
≥5× ULN	if ALT or AST increases to >2× baseline value
Other	if 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
	if ALT or AST increase >2× baseline value in the presence of signs and symptom(s) such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophil (>5%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = International Normalized ratio; ULN = Upper limit of normal

Close monitoring for suspected DILI includes:

- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of repeat testing can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E, autoimmune or alcoholic hepatitis, hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

Note: If a subject lives in a remote area, laboratory testing can be performed locally, and the results should be promptly communicated to the Investigator site.

7. INTERRUPTION OR DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. COVID-19-Related Risk Mitigation and Interruption of Investigational Product Administration

The following are provided as mitigations in the event of potential disruptions to study conduct secondary to COVID-19 infection or related control measures:

- Dose interruption resulting in missing 1 dose is acceptable at any time during the dosing period.
- Interruption in IP administration and other study procedures (collectively "study interruption") will be allowed for up to 2 weeks up to Week 5.
- Dose interruption for 2 weeks after Week 5 is not allowed and will require discontinuation of treatment as resuming the dose would impact the interpretation of the primary endpoint.
- Study interruptions longer than 2 weeks at any time during the dosing period will lead to discontinuation of treatment and the subject's participation in the study.
- For subjects who have a study interruption, prior to resuming dosing, the Investigator will assess whether the subject is clinically stable to continue participation in the study and will discuss the assessment with the Medical Monitor.
- Upon resumption of dosing, the subject will continue at the next planned visit relative to the last visit performed prior to study interruption and will be administered all remaining planned doses.
- If clinical laboratory tests are not part of the protocol-defined procedures for the first dosing visit after study interruption, unscheduled hematology and clinical biochemistry panels may be obtained prior to dosing as needed and at Investigator discretion and sent to the central lab. Results from both local and central labs should be documented in EDC.
- If circumstances related to the COVID-19 pandemic or other extenuating circumstances preclude a visit to the investigative site, alternative means for completing study procedures and assessments may be considered at Investigator discretion, in accordance with local guidance/regulations and with Medical Monitor approval. For example, remote verification of source data may be instituted. Also, safety assessments may be conducted via telemedicine or phone contact or laboratory tests may be obtained at a certified local lab. Local analysis can be used for safety decisions.

Efforts should be made to obtain EOT assessments in subjects who are not willing or able to return to the study after study interruption, who are deemed not clinically stable to continue participation by the Investigator, or who are lost to the study due to disruptions because of the COVID-19 pandemic. The EOT visit should be scheduled as soon as possible in these scenarios, whenever possible.

- Study interruption will be allowed as long as COVID-19 pandemic-related circumstances are ongoing and will not be allowed when these circumstances are no longer applicable, as determined by the Sponsor.
- For newly qualified subjects who have not yet received their first dose at a site and that can foresee a near-term disruption by the COVID-19 pandemic, the Investigator should discuss with the Sponsor whether the initiation of dosing should be postponed. In this situation, study interruption should not apply, and the subject will initiate and finish all planned doses when the Investigator deems it is safe to start dosing. Re-screening or retest of certain laboratory tests may be required prior to start of dosing, pending Medical Monitor evaluation.

Changes in study visit schedules, missed visits, or patient discontinuations may lead to missing information (e.g., for protocol-specified procedures). Specific information will be captured in the eCRF that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19).

7.2. Discontinuation of Investigational Product

In rare instances, it may be necessary for a subject to permanently discontinue IP. If IP is permanently discontinued, subjects will be requested to have an EOT visit within 7 days of terminating the treatment and an EOS visit 4 weeks later. The subject will remain in the study to be evaluated for safety tolerability, and PK/PD assessments. The reason for subject withdrawal from the IP will be recorded in the eCRF. See the SoA (Table 2) for data to be collected at the time of discontinuation of IP (EOT visit).

7.3. Subject Discontinuation/Withdrawal from the Study

A subject may withdraw or be withdrawn from the study for the following reasons:

- Investigator decision
- AE or intercurrent illness
- Noncompliance with protocol requirements
- Subject's withdrawal of consent
- Sponsor termination or suspension of the study
- Lost to follow-up
- A COVID-19-related dose interruption for 2 weeks or longer after [redacted] or study interruptions longer than 2 weeks at any time during the dosing period

The reason for subject's withdrawal from the study will be recorded in the eCRF.

At the time of withdrawal from the study, subjects will be requested to have an EOT visit within 7 days of terminating the treatment, and an EOS visit 4 weeks later, as shown in the SoA (Table 2).

7.4. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study is handled as part of Appendix 1 (Section 10.1.8).

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 2). Protocol waivers or exemptions are not allowed.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- If multiple assessments are scheduled at the same timepoint, it is recommended that procedures be performed in the following sequence: 12-lead ECGs, vital signs, sample collection for lipids, other laboratory and PD biomarker tests, sample collection for PK and [redacted], prior to administration of study drug.
- Immediate safety concerns should be discussed with study Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue IP.
- Adherence to the study design requirements, including those specified in the SoA (Table 2), is essential and required for study conduct.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for subject management and pre-screening, however screening and baseline assessments must be obtained by central laboratory and as defined by the protocol.
- Any situation at the site level with potential impact on subject safety or study conduct, including situations related to COVID-19 infection or control measures, should be discussed with the Sponsor/contract research organization (CRO) immediately upon occurrence or awareness to determine potential impact on study subject/s or study conduct.

8.1. Efficacy Assessments

Fasting blood samples will be collected at the time points specified in the SoA for the measurement of serum total lipids, lipoprotein profiles, and apolipoproteins. Efficacy assessments in this study are the PD and biomarker assessments, which are described in Section 8.6.

8.2. Safety Assessments

Safety assessments include AEs (either reported by the subject or observed by the Investigator), concomitant medication use, physical examination, ECG, vital signs, and laboratory assessments.

Any clinically significant safety assessment findings, including physical examination, ECG, vital signs, laboratory assessments, and AEs that are considered to be related to COVID-19 infection should be documented as such in the AE term reported (e.g., COVID-related pneumonia).

All safety analyses will be performed using the Safety Analysis Set (Section 9.4.5). Planned time points for all safety assessments are provided in the SoA (Table 2).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, abdominal and a neurological exam. Height (only collected at screening) and weight will also be measured and recorded.
- A symptom directed physical examination will include, at a minimum, assessments of the skin, respiratory, cardiovascular system, and abdomen (liver and spleen).

8.2.2. Vital Signs

- Vital signs including body temperature, pulse rate, RR, and supine BP will be assessed.
- Planned time points for vital signs assessment are provided in the SoA (Table 2).
- Starting from randomization, 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 measurement may be done if clinically indicated.

8.2.3. Electrocardiograms

- 12-lead ECG will be recorded as single bedside measurements using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT (QTcF) intervals.
- Subject to be resting for at least 2 minutes prior to ECG.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) or the list of clinical laboratory tests to be performed and the SoA (Table 2) for the timing and frequency. Laboratory tests should be performed under fasting conditions (for at least 12 hours; it is recommended that subjects fast no more than 14 hours). Subjects should be instructed to attempt to remain consistent in how long they fast prior to blood draws for the duration of the study.
- Fasting is defined as taking nothing by mouth except non-mineral water (and any essential medications). It is required that subjects abstain from consumption of alcoholic beverages for at least 48 hours before laboratory test assessments.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- Retesting of laboratory tests is allowed when results are deemed spurious or incomplete.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of IP should be repeated

until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or the Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator and remain clinically significant, the etiology should be identified and the Medical Monitor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the relevant study manual and the SoA (Table 2).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or skipping of dose), then the results must be recorded in the eCRF and the Medical Monitor should be notified.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IP or study procedures, or that caused the subject to discontinue the study or IP (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The timing and frequency of collection of all AEs and SAEs is specified in the SoA (Table 2).

Table 4 summarizes the different reporting periods for AEs, SAEs and events to monitor. Events to monitor are defined in Section 10.3.3.

Table 4: Adverse Event Reporting Periods

Type of Event	Adverse Event	Serious Adverse Event	Events to Monitor with Investigational Product
Reporting period	From consent until 28 days after last dose of investigational product	From consent until 28 days after the last dose of investigational product	From consent until 28 days after the last dose of investigational product
Reporting Timelines to 89bio	Entered into the clinical database on an ongoing basis	Within 24 hours	Within 24 hours

All SAEs will be recorded and reported to 89bio or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The

Investigator will submit any updated SAE data to 89bio or designee within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the IP or study participation, the Investigator must promptly notify 89bio or designee.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to 89bio or designee of an SAE is essential so that legal obligations and ethical responsibilities regarding the safety of subjects and the safety of the IP under clinical investigation are met.
- 89bio has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the IP under clinical investigation. 89bio will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and 89bio policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from 89bio will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female subjects and in female partners of male subjects will be collected after the start of IP and until 90 days after last dose of IP.
- If a pregnancy is reported, the Investigator should inform 89bio within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

There is no experience with overdose of BIO89-100 in humans.

For this study, any dose of BIO89-100 greater than the protocol-specified dose will be considered an overdose.

89bio does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Monitor the subject's vital signs and institute supportive measures as indicated by the subject's clinical state.
3. Obtain a plasma sample for PK analysis within 2 days from the date of the overdose if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the incidence of the overdose in the eCRF.

8.5. Pharmacokinetics

Blood samples for analysis of BIO89-100 serum levels will be collected at the timepoints designated in the SoA (Table 2).

Blood samples will be processed for collection of serum fractions for determination of BIO89-100 serum concentrations. BIO89-100 metabolites may be analyzed. Serum samples will be shipped to the bioanalytical laboratory for analysis.

The trough serum BIO89-100 concentrations will be summarized by treatment group and nominal sampling time using descriptive statistics.

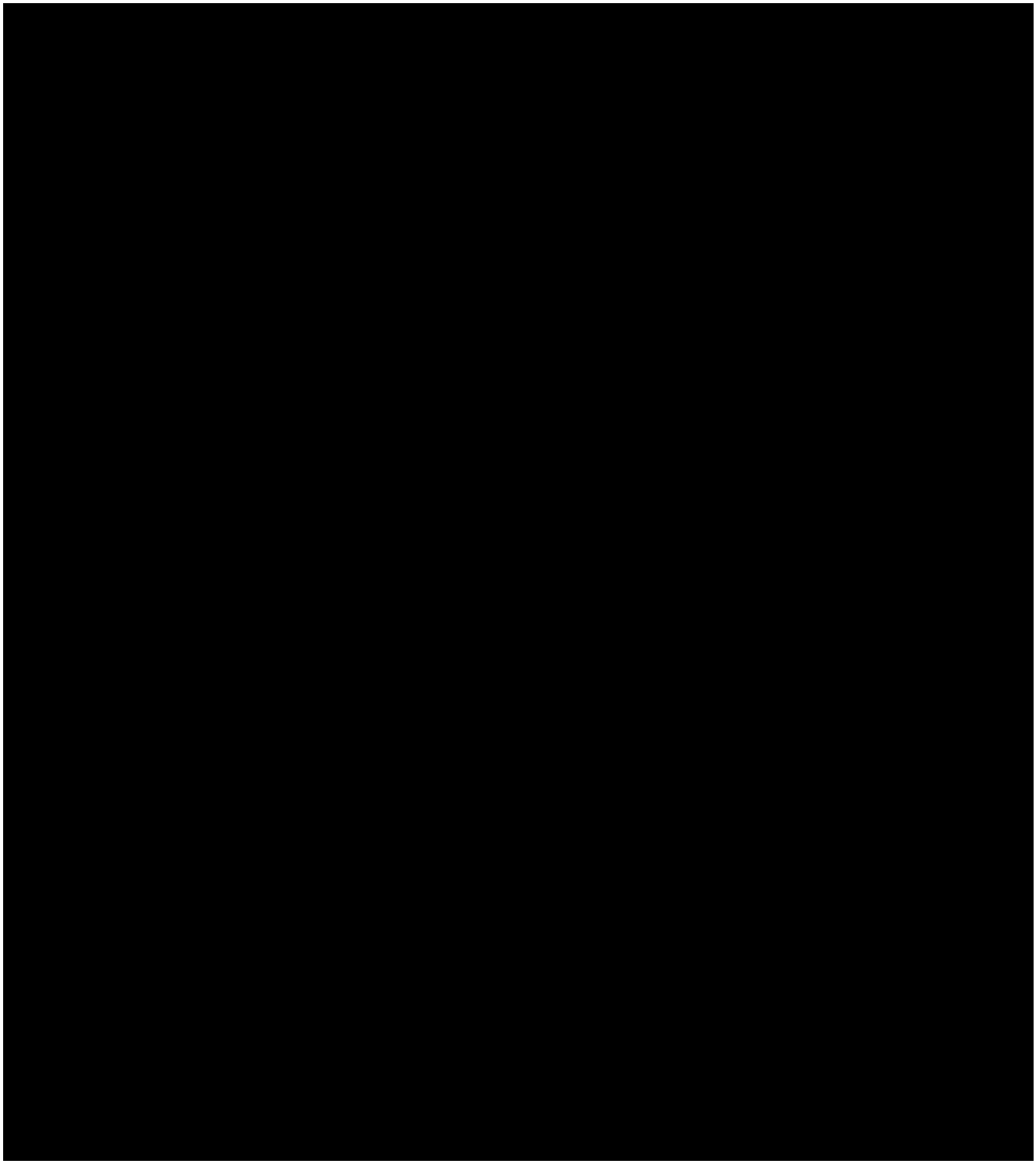
When appropriate, pharmacokinetic parameters calculated by non-compartmental methods from the BIO89-100 serum concentration data will include:

- C_{max}
- $AUC_{0\text{-}tau}$
- t_{max}
- $t_{½}$

Subjects may choose to participate in the Intensive PK scheme. All subjects will be included in the Trough PK scheme. Table 5 details sampling times for the Intensive PK scheme. For subjects in the Trough PK scheme, blood samples will be taken within 4 hours prior to dosing on specified dosing days or during EOT visit [redacted].

Table 5: Intensive PK Scheme for Sample Collection

Note: Where the Intensive PK schedule overlaps with the Trough PK schedule, only 1 PK measurement should be taken at those timepoints.



Additional PK parameters may be calculated if deemed appropriate.

8.6. Pharmacodynamics and Biomarkers

8.6.1. Pharmacodynamics

The following biomarkers/PD parameters will be evaluated at timepoints designated in the SoA (Table 2).

Laboratory parameters:

- TG
- [redacted]
- VLDL-C
- VLDL-TG
- LDL-C
- HDL-C
- Non-HDL-C
- ApoB
- RLP-C
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- ALT
- AST
- Adiponectin
- hsCRP
- [redacted]
- [redacted]
- [redacted]

Samples may be stored for a maximum of 15 years after the last subject's last visit for the study, at a facility selected by 89bio, to enable further analysis of biomarker responses to BIO89-100.

Residual blood samples will be stored for potential future analysis of biomarkers.

Additional information will be available in the study-specific laboratory manual.

Other parameters include:

- Imaging measures (Section 8.6.3)
  - MRI-PDFF
- Anthropomorphic measurements
  - Body weight
  - BMI
  - [redacted]
  - [redacted]

[redacted]

8.6.3. Magnetic Resonance Imaging – Whole Liver Proton Density Fat Fraction

MRI-PDFF is a non-invasive, quantitative, and accurate measure of liver fat content (imaging-based biomarker) to assess treatment response in clinical studies (Caussy, et al. 2018).

This technology enables post-processing of MRI data into a parametric map of Proton Density Fat Fraction (PDFF; Antaros Medical, Sweden) to provide accurate and quantitative measures of liver fat.

The PDFF is determined using a 6-echo gradient echo pulse sequence covering the liver in the axial plane. Analysis is performed by semi-automatic contouring of the liver in every slice avoiding major vessels and bile ducts. The method applies multi-peak lipid spectral models and simultaneous quantification and correction for T2 (refer to the Imaging Manual for more information). The liver fat value (PDFF) is the mean value of all voxels in the identified volume of interest.

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] (The study aims to enroll ~33% of subjects [~30 subjects total] in the main cohort with a baseline MRI-PDFF ≥6.0%.) 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.

[redacted]

8.6.4. Exploratory Analyses

[redacted]

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The study hypothesis is that BIO89-100 can significantly improve efficacy parameters and is well tolerated for subjects with SHTG.

The hypotheses for the primary endpoint are:

- Null hypothesis: treatment with BIO89-100 and placebo result in the same percentage change in serum TG from baseline to Week 8
- Alternative hypothesis: treatment with BIO89-100 and placebo result in significantly different percentage changes in serum TG from baseline to Week 8

The null hypotheses will be tested at significance level of 0.05 (2-sided) for each BIO89-100 treatment group versus placebo.

9.2. Sample Size Determination

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 TG lowering agents: [redacted]

Based on these results, it is estimated that the SD of the percent change in TG at Week 8 is ~40%. With 18 subjects in the placebo group and each BIO89-100 dose group, there would be at least 86% power to detect a 45% difference in TG between each BIO89-100 dose 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.

Fatty liver has been shown to be significantly associated with moderately severe or severe acute pancreatitis (Yoon, et al. 2017). Hence, another focus of this study is to assess the BIO89-100 effect on reducing liver fat as assessed by MRI-PDFF in the SHTG population, with or without concurrent stable fibrate therapy. In Study BIO89-100-002 (Part 1), BIO89-100 (27 mg QW) reduced liver fat as assessed by MRI-PDFF up to 60%. In the main cohort not on concomitant fibrate therapy, a sample size of ~30 subjects (e.g., ~33% of the main cohort total sample size, ~6 placebo vs ~24 pooled BIO89-100) is estimated to provide ~89% power to detect a difference of at least 50% mean percentage reduction in MRI-PDFF at Week 8 compared to placebo, using a significance level of 0.05 (2-sided). These calculations are based on an assumption that the percentage change from baseline in MRI-PDFF is normally distributed with a standard deviation of no greater than 30%, as estimated from data in Study BIO89-100-002. In the fibrate expansion cohort, assuming a difference of 50% mean percentage reduction in MRI-PDFF at Week 8

compared to placebo, a standard deviation of no greater than 30% under normal assumption, and a significance level of 0.05 (2-sided), the planned sample size of 18 subjects per group will have >99% power to detect such a mean difference.

This sample size assessment incorporates approximately 10% of subjects lost to follow-up.

9.3. Populations for Analyses

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

Population	Description
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 IP, have a baseline, and at least 1 post-baseline efficacy measurements.
Safety Analysis Set	All subjects who received at least 1 dose of IP.
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 MRI-PDFF at baseline and a post-baseline assessment.

9.4. Statistical Analyses

The analyses presented here represent an outline of the intended methodology. Changes, additions, and further details about the analyses will be described in the statistical analysis plan (SAP), as applicable. The SAP will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

Subjects with dose interruptions affected by the COVID-19 pandemic will be noted in the listings. The impact on COVID-19 related study interruption may be considered, as appropriate.

9.4.1. General Considerations

In general, summaries and analyses will be presented by dose/treatment group and by cohort. 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. Categorical variables will be summarized by number and percentage of subjects.

The analyses will be performed separately for the main cohort and the fibrate expansion cohort. All primary, secondary, and exploratory efficacy endpoints will be assessed in the Full Analysis Set. All safety assessments will be performed on the Safety Analysis Set. PK endpoints will be assessed in the Intensive PK Analysis Set as applicable. Endpoints of MRI-PDFF will be assessed in MRI-PDFF Analysis Set.

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.

9.4.2. Primary Endpoint(s)

The primary efficacy analysis of the primary endpoint, percentage change in serum TGs from baseline to Week 8, will be performed using the Full Analysis Set and observed data, and an analysis of covariance model with treatment and background therapy as factors and baseline TG as a covariate. Baseline TG will be defined as the average of [redacted] and the preceding lipid-qualifying visit [redacted]. For the TG at Week 8, it will be defined as the average of measurements at [redacted] and [redacted] If there are significant deviations from the normality assumption of the primary endpoint, the alternative non-parametric analysis will be performed using the median of the treatment differences and Hodges-Lehmann 2-tailed 95% confidence interval, with treatment comparison using the Wilcoxon rank-sum test.

Comparison of change from baseline to Week 8 in TG will be analyzed using the same analysis method for the primary endpoint.

The following sensitivity analysis will be conducted: the percentage change from baseline in TG at each post-baseline study visit be analyzed using a Mixed Effects Model with Repeated Measures (model) where the treatment group, time, treatment by time interaction, and the randomization stratification factor of background therapy will be included in the model as fixed effects; subjects will be a random effect; the baseline TG value will be included as a covariate. No imputation for missing data will be made for this sensitivity analysis. The unstructured covariance model will be used. The treatment contrast for the analysis at each study visit, including [redacted], will be estimated by the model.

9.4.3. Secondary Endpoint(s)

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 factors. To examine whether the response is consistent over a range of response thresholds, responder analysis with other response thresholds will be considered.

As sensitivity analyses of the responder of TG <500 mg/dL at Week 8, comparison between BIO89-100 and placebo groups of proportion of subjects with ≥50% reduction from baseline at Week 8 in TG will be analyzed using the CMH test stratified by the 2 stratification factors. To examine whether the response is consistent over a range of response thresholds, responder analysis with other response thresholds will be considered. 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.

The analysis methods for the primary endpoint will be used to analyze other similar secondary efficacy endpoints.

All serum concentrations of BIO89-100 will be listed. Pharmacokinetic parameters in the Intensive PK group will be determined where possible from the serum concentrations of BIO89-100. Further details on PK analysis will be provided in the SAP.

9.4.4. Exploratory Endpoints

[redacted]

9.4.5. Safety Analyses

Treatment duration and IP received will be summarized by treatment group.

Subject incidence of TEAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term, and treatment group. All TEAEs, all treatment-emergent related AEs, all TESAEs, and all treatment-emergent serious related AEs will be summarized. Laboratory tests, vital signs, and ECG measures will be summarized by visits and by treatment group.

[redacted]

9.5. Interim Analyses

No efficacy interim analysis will be performed.

9.6. Data Monitoring Committee

There is no data monitoring committee for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide 89bio with sufficient, accurate financial information as requested to allow 89bio to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his or her representative will explain the nature of the study to the subject or his or her legally authorized representative and answer all questions regarding the study.

- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

10.1.4. Data Protection

- Subjects will be assigned a unique identifier by 89bio. Any subject records or datasets that are transferred to 89bio will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his or her personal study-related data will be used by 89bio in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by 89bio, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

A clinical study report will be developed by 89bio at completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

89bio will register the study and post-study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

10.1.6. Data Quality Assurance

- All subject data relating to the study will be recorded on the eCRFs unless transmitted to 89bio or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy, methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- 89bio or designee is responsible for the data management of this study including quality checking of the data.
- 89bio assumes accountability for actions delegated to other individuals (e.g., CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator per ICH GCP and local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of 89bio. No records may be transferred to another location or party without written notification to 89bio, whether within the retention period or thereafter.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

10.1.8. Study and Site Start and Closure

89bio reserves the right to close a study site or terminate the study at any time for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given to 89bio in advance of the intended termination.

Reasons for the early closure of a study site by 89bio or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, 89bio's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further IP development
- Debarment

If the study is prematurely terminated or suspended, 89bio shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to 89bio before submission and only present or publish information after approval by 89bio. This allows 89bio to protect proprietary information and to provide comments.
- 89bio will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, 89bio will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The clinical laboratory tests detailed in Table 6 will be performed by a central laboratory at timing/frequency detailed in the SoA (Table 2). Laboratory tests will be performed under fasting conditions (for at least 12 hours; it is recommended that subjects fast no more than 14 hours). Subjects should be instructed to attempt to remain consistent in how long they fast prior to blood draws for the duration of the study.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 6: Protocol-Required Laboratory Assessments

Hematology	
WBC with differential (Total Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils – absolute and %)	RBC count RBC Indices: MCV, MCH, MCHC, RDW, Reticulocyte count
Hemoglobin	Hematocrit
Platelet count	Coagulation panel, including PT, INR, aPTT
Lipid Assessment	
[redacted]	non-HDL-C*
ApoB*	RLP-C*
[redacted]	[redacted]
HDL-C*	TG*
[redacted]	VLDL-C*
LDL-C*	VLDL-TG*
[redacted]	
Clinical Chemistries	
ALP	Fasting plasma glucose
ALT	GGT
AST	Lactate dehydrogenase
Albumin	Magnesium
Bicarbonate	Phosphorus
BUN	Potassium
Calcium	Sodium

Creatinine, eGFR	Total bilirubin, Indirect/direct bilirubin
CK	Total protein
Chloride	Uric acid
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 are abnormal or at the discretion of the PI or delegate.
Other Study-Specific Laboratory Assessments	
BIO89-100 (to be evaluated by bioanalytical laboratory) Thyroid function assessment (TSH, free T4, and free T3)	[redacted]
Serum hCG pregnancy test Urine hCG pregnancy test[#] FSH level	
Urine drug screen including amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, cannabinoids and phencyclidine Serology – HIV antibody, hepatitis B surface antigen (HBsAg, and HCV antibody). To determine current infection status, if HBsAg positive HBV DNA will be measured, if HCV antibody positive, HCV RNA will be measured, and if HIV antibody positive will be differentiated by HIV 1 or 2 and HIV RNA will be measured.	
24-hour urine for cortisol and creatinine [redacted] Insulin hsCRP [redacted] Serum adiponectin, total [redacted]	

* Post-baseline lipid panels to be blinded
# Tests can be performed locally with kits provided by the central laboratory
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; [redacted]; ApoB = apolipoprotein B100; [redacted]; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; [redacted]; BUN = blood urea nitrogen; CK = creatine kinase; [redacted]; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation; [redacted]; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HBsAg = Hepatitis B surface antigen; [redacted]; HBV = Hepatitis B virus; hCG = human chorionic gonadotropin; HCV = Hepatitis C Virus; HDL-C = high-density lipoprotein-cholesterol; HIV = human immunodeficiency virus; [redacted]; INR = international normalized ratio; LDL-C = lipoprotein-cholesterol; [redacted]; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; PT = prothrombin time; PINP = n-terminal propeptide of type I procollagen; MCV = Mean Corpuscular Volume; Non-HDL-C = non-high-density lipoprotein-cholesterol; RBC = red blood cell; RDW = Red Cell Distribution Width; RLP-C = remnant lipoprotein-cholesterol; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; [redacted]; TG = triglycerides; TSH = thyroid-stimulating hormone; VLDL-C = very low-density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides; WBC = white blood cell.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of IP, whether or not considered related to the IP. • NOTE: 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 IP.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline are considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after IP administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of Suspected and Unsuspected Adverse Reaction

Suspected adverse reactions are defined as:
• Any AE for which there is a reasonable possibility that the IP caused the AE. For the purposes of 89bio regulatory safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by an IP
Unexpected AEs are defined as:
• AE which is not listed in the IB of the IP or is not listed at the specificity or severity that has been observed

10.3.3. Definition of Events to Monitor

89bio-defined Events to Monitor for BIO89-100:
Events to Monitor include hypersensitivity reactions occurring after the first administration of study agent(s) in subjects participating in this clinical study. These events must be reported by the Investigator to 89bio within 24 hours and are to be considered serious (for regulatory reporting purposes) only if they meet the definition of an SAE. The events are to be reported on an SAE form

10.3.4. Definition of SAE

If an event is not an AE per definition in Section 10.3.1, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening

An SAE is defined as any untoward medical occurrence that, at any dose:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

3. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

4. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

6. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.5. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF/paper case report form (CRF) as appropriate.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Medical Monitor in lieu of completion of the AE/SAE eCRF page and paper CRF as appropriate.
- There may be instances when copies of medical records for certain cases are requested by the Medical Monitor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Medical Monitor.

AE and SAE Recording

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The severity of each AE will be assessed at onset by a nurse and/or physician. When recording the outcome of the AE the maximum severity of the AE experienced will also be recorded. The severity of the AE will be graded according to the CTCAE v5.0:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

ADL:

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

The Investigator is obligated to assess the relationship between IP and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IP administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Medical Monitor. However, **it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Medical Monitor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Assessment of Causality
Causality Categories: • UNRELATED – This relationship suggests that there is no association between the IP and the reported event. • UNLIKELY RELATED – The relationship suggests that the event is more likely due to other causes than IP, however the relationship to the IP cannot be ruled out. • POSSIBLY RELATED – This relationship is based on evidence suggesting a causal relationship between the IP and the AE, i.e., there is a reasonable possibility that the drug caused the event. The event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the IP but could also have been produced by other factors. • PROBABLY RELATED – This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with the IP seems likely. • DEFINITELY RELATED – This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Medical Monitor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Medical Monitor with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF and paper CRF as appropriate. • The Investigator will submit any updated SAE data to 89bio within 24 hours of receipt of the information.

10.3.6. Reporting of SAEs

Reporting of SAEs will be done using a paper CRF.

SAE Reporting to the Medical Monitor via Paper CRF
• Facsimile or email transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor. • In rare circumstances and in the absence of facsimile or email equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

SAE Reporting to the Medical Monitor via Paper CRF
• Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the relevant manual.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

WOCBP

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IP, additional evaluation should be considered.

Women in the Following Categories Are Not Considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.
    - Note: Documentation can come from the site personnel's review of the subject's medical records or medical examination. An ultrasound to document absence of a uterus is considered acceptable documentation of non-childbearing potential.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly-effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Subjects should use highly-effective, double contraception (with both male/female partners) during the study and for 30 days or 5 half-lives (whichever is longer) of IP.

Double contraception is defined as a condom with 1 of any of the following forms of birth control:

- Birth control pills (The Pill)
- Depot or injectable birth control
- IUD
- Birth Control Patch (e.g., Ortho Evra)
- NuvaRing®
- Documented evidence of tubal ligation prior to screening visit for women or history of vasectomy for men

Subjects must not donate sperm or oocytes during the study and for 30 days or 5 half-lives (whichever is longer) after last dose of IP.

Rhythm methods are not considered as highly-effective methods of birth control. Subject abstinence for the duration of the study and 30 days or 5 half-lives (whichever is longer) after last dose of IP is acceptable if it is the subject's regular practice.

Collection of Pregnancy Information

Male Subjects with Partners who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive IP.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to 89bio within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to 89bio. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who Become Pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to 89bio within 24 hours of learning of a subject's pregnancy. This applies only to female subjects who receive IP.

- The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to 89bio. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the IP by the Investigator will be reported to 89bio as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

10.5. Appendix 5: Abbreviations

Abbreviation Term	Description
~	Approximately
ABV	Alcohol By Volume
[redacted]	[redacted]
[redacted]	[redacted]
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (SGPT)
AP	Acute Pancreatitis
Apo	Apolipoprotein
[redacted]	[redacted]
ApoB	Apolipoprotein B100
[redacted]	[redacted]
[redacted]	[redacted]
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase (SGOT)
AUC	Area Under the Curve
$AUC_{0\text{-}tau}$	Area Under the Curve during the Dosing Interval
[redacted]	[redacted]
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum Concentration
CMH	Cochran Mantel Haenszel
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation Term	Description
[redacted]	[redacted]
CVD	Cardiovascular Disease
CYP3A	Cytochrome P450 3A
DHA	Docosahexaenoic acid
DILI	Drug-induced Liver Injury
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
EOT	End of Treatment
EPA	Eicosapentaenoic acid
FDA	Food and Drug Administration
[redacted]	[redacted]
FGF21	Fibroblast Growth Factor 21
FGFR	Fibroblast Growth Factor Receptor
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
[redacted]	[redacted]
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDL-C	High-Density Lipoprotein Cholesterol
HHP	Home health provider
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRT	Hormone replacement therapy
hsCRP	High-Sensitivity C-reactive Protein
IB	Investigator Brochure

Abbreviation Term	Description
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ICH	International Council for Harmonisation
[redacted]	[redacted]
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ISR	Injection Site Reaction
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein Cholesterol
[redacted]	[redacted]
MAD	Multiple Ascending Dose
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRI-PDFF	Magnetic Resonance Imaging – Whole Liver Proton Density Fat Fraction
NAb	Neutralizing Antibody
NAb-	Neutralizing Antibody Negative
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NOAEL	No Observed Adverse Effect Level
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PD	Pharmacodynamic
PDFF	Proton Density Fat Fraction
PEG	Polyethylene Glycol
PI	Principal Investigator
[redacted]	[redacted]

Abbreviation Term	Description
PK	Pharmacokinetic
PT	Prothrombin Time
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
SAD	Single Ascending Dose
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SHTG	Severe Hypertriglyceridemia
SoA	Schedule of Assessments
SUSAR	Suspected Unexpected Serious Adverse Reaction
t½	Half-life
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
T3	Triiodothyronine
T4	Thyroxine
[redacted]	[redacted]
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Events
TG	Triglycerides
t_{max}	Time to Maximum Concentration
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
V	Visit
VLDL-C	Very Low-Density Lipoprotein Cholesterol

Abbreviation Term	Description
VLDL-TG	Very Low-Density Lipoprotein Triglycerides
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

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