Title Page

A Phase 2b Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Ranging Study to Assess the Efficacy, Safety, and Tolerability of Vupanorsen (PF-07285557) in Statin-Treated Participants with Dyslipidemia

Compound: Vupanorsen (PF-07285557)

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[redacted]

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	18 September 2020	• Section 10.13 (Appendix 13): New appendix was added describing alternative measures that may be allowed during a public emergency, such as COVID-19. • The Protocol Summary was revised as appropriate for consistency with changes in the body of the document. Title page, Schedule of Activities, Section 2.1, Section 9.2, Section 10.14 (Appendix 14): Administrative changes were made for clarification.
Original protocol	03 June 2020	Not applicable

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2b Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Ranging Study to Assess the Efficacy, Safety, and Tolerability of Vupanorsen (PF-07285557) in Statin-Treated Participants with Dyslipidemia

Short Title: A Phase 2b Dose-Ranging Study with Vupanorsen (PF-07285557) (TRANSLATE-TIMI 70)

Rationale:
This multicenter, Phase 2b, double-blind, placebo-controlled, parallel group study is being conducted internationally to provide data on efficacy, safety, tolerability, and pharmacokinetics (PK) of PF-07285557 (hereafter, vupanorsen) administered subcutaneously (SC) at various doses and regimens in participants with dyslipidemia, defined in this study as participants with elevated non-HDL-C and TG who are receiving a stable dose of a statin. This study is intended to enable selection of a dose(s) for future development of vupanorsen for cardiovascular (CV) risk reduction and hypertriglyceridemia.

This study is also known as TaRgeting ANGPTL3 with an aNtiSense oLigonucleotide in AdulTs with dyslipidEmia (TRANSLATE-TIMI 70).

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on non-HDL-C.	• Percent change from baseline in non-HDL-C at Week 24
Secondary:	**Secondary:**
• To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on lipid parameters including TG, ApoB, and LDL-C. • To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on ANGPTL3.	• Percent change from baseline in TG, ApoB, and LDL-C at Week 16 and Week 24 • Percent change from baseline in non-HDL-C at Week 16 • Percent change from baseline in ANGPTL3 at Week 16 and Week 24
Safety:	**Safety:**
• To evaluate the safety, tolerability, and immunogenicity of multiple dose levels and regimens of vupanorsen. • To evaluate the effect of multiple dose levels and regimens of vupanorsen on HFF.	• Incidence of treatment-emergent SAEs and AEs throughout the study • Incidence of AESI • Categorical summaries of clinical laboratory abnormalities • UACR • ADA • Change from baseline in AST, ALT, platelet counts, and eGFR • Change and percent change from baseline in HFF (assessed by MRI-PDFF) at Week 24

Objectives	Endpoints
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on total cholesterol, HDL-C, VLDL-C, Lp(a), FFA, ApoB-48, ApoB-100, ApoC-III, and ApoA-I. • To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on hsCRP. • To evaluate the PK of vupanorsen.	• Percent change from baseline at Week 24 in total cholesterol, HDL-C, VLDL-C, Lp(a), FFA, ApoB-48, ApoB-100, ApoC-III, and ApoA-I • Percent change from baseline in hsCRP at Week 24 • Plasma concentrations of vupanorsen at Weeks 12, 16 and 24

Estimands: The primary estimand of this study will follow the hypothetical estimand approach to estimate the effect of treatment under the hypothetical condition that all participants maintained their randomized treatment through Week 24. This estimand is meant to estimate the pharmacological effect of the drug when taken as directed. It includes the following 4 attributes:

- Population: Participants with dyslipidemia taking a statin who meet the inclusion/exclusion criteria.
- Variable: The percent change from baseline in non-HDL-C at Week 24.
- Intercurrent event: All off-treatment data (ie, occurring at least 1 dosing interval after discontinuation of treatment) or data collected post treatment of severe hypertriglyceridemia (ie, change in statin dose or addition of TG lowering therapy), if collected, will be excluded from analysis.
- Population-level summary: Difference of variable means between vupanorsen and placebo.

Overall Design
This is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging, 8-arm parallel-group study in adults ≥40 years of age with dyslipidemia who are on a stable dose of a statin (with or without ezetimibe). Following the Screening Period to confirm eligibility, a total of approximately 260 participants will be randomized in the study to receive SC doses of vupanorsen or placebo administered Q2W or Q4W for the purpose of assessing efficacy, safety, and tolerability of vupanorsen. The total duration of treatment in the study is 24 weeks with an additional 12-week safety follow-up period.

The sponsor, along with academic leadership of the study (TIMI Study Group), will monitor the proportion of participants enrolled according to statin intensity to ensure that an adequate number of participants on high intensity statin are enrolled. High intensity statin use is defined as atorvastatin (40 mg or 80 mg per day) or rosuvastatin (20 mg or 40 mg per day). All other statin regimens are considered low or moderate intensity. Approximately 40% or more of participants enrolled should be on high intensity statin therapy, and enrollment of participants using low/moderate intensity statin may be capped.

Vupanorsen dosing will be accomplished by administration of 1 or 2 prefilled syringes of either 60 mg or 80 mg strength according to required total dose. Placebo will be provided as a prefilled syringe and will be administered as either 1 or 2 syringes. See Table S1 for the dosing plan.

Table S1. Dosing Plan

Treatment Arm	Total Monthly Dose	Injection Regimen	Number of Participants
Placebo	0 mg	Single or double injection Q2W or Q4W	40
80 mg Q4W	80 mg	Single injection Q4W	20
60 mg Q2W	120 mg	Single injection Q2W	20
120 mg Q4W	120 mg	Double injection Q4W	20
80 mg Q2W	160 mg	Single injection Q2W	40
160 mg Q4W	160 mg	Double injection Q4W	40
120 mg Q2W	240 mg	Double injection Q2W	40
160 mg Q2W*	320 mg	Double injection Q2W	40

*Treatment arm will be capped at 10 participants until E-DMC performs unblinded data review and recommends whether enrollment should be re-opened for this dose group for the remaining 30 participants.

During the Screening Period, sites will instruct participants or caregivers how to perform the SC injection, and participants (or caregivers) willing to perform the injection will be assessed for ability to inject correctly. Sites will determine whether a participant or caregiver is willing and able to correctly perform the SC injection. Participants receiving monthly injections will self-administer study intervention (or be injected by their caregiver) on-site. Participants receiving Q2W injections will self-administer study intervention (or be injected by their caregiver) on-site when study visits coincide with the dosing interval (Weeks 2 and 6, and at designated monthly visits). The study site will dispense study intervention for the participant or caregiver to inject at home for the doses that do not coincide with a study visit (Weeks 10, 14, 18, and 22).

Safety clinical laboratory parameters and AEs, including injection site reactions, will be monitored throughout the study. HFF will be assessed at Screening and Week 24 using MRI-PDFF, and blood samples will be collected for lipids, lipoproteins, PK, PD, hsCRP, and anti-vupanorsen antibodies at various time points during the study according to the SoA. MRI-PDFF will be read by a central reviewer, blinded to treatment group, lipid levels, and other clinical variables, such as concentrations of hepatic enzymes.

This study will include an E-DMC who will be responsible for ongoing, unblinded monitoring of efficacy and the safety of participants in the study according to the E-DMC charter.

Since administration of 160 mg Q2W (total monthly dose of 320 mg) has not been studied previously, enrollment in this arm will be capped after 10 participants. Following unblinded data review by the E-DMC as described in the E-DMC charter, enrollment in this treatment arm may be re-opened for the remaining 30 participants or be stopped based on recommendation by the E-DMC. Separately, an interim analysis is planned and will also be reviewed by the E-DMC. The interim analysis will take place approximately 16 weeks after

50% of the planned participants (ie, approximately 110 participants), with the exception of the 160 mg Q2W group, are randomized.

Efficacy and safety analyses will occur when all participants either complete 24 weeks of study participation or discontinue study participation. Additional summarizing of follow-up safety data will occur after the 12-week post-dose follow-up visit.

Number of Participants:
Approximately 260 participants will be randomly assigned/enrolled to study intervention.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

Intervention Groups and Duration:
Participants will be randomized to receive blinded placebo or 1 of 7 blinded vupanorsen treatment regimens for 24 weeks.

Data Monitoring Committee: Yes

Statistical Methods:
Assuming a common standard deviation of 17.5% (observed in the Month 6 data of the Phase 2a proof-of-concept and dose-ranging study) for the percent change from baseline in non-HDL-C at Week 24 and a treatment discontinuation rate of 15%, 20 participants per arm will correspond to a 95% CI of point estimate ±11.76% for the difference of treatment effect (versus placebo). These parameters correspond to a power of 91.5% using a 2-sided alpha of 0.05, to detect a difference of -20%, without adjustment for multiple comparison to placebo.

A permutation block schedule will be used in enrollment within each arm, including vupanorsen and matching placebo. If enrollment is stopped for the 160 mg Q2W arm, the corresponding matching placebo enrollment will also be stopped.

The primary statistical method of Mixed Model Repeated Measurements (MMRM) will apply to continuous endpoints.

Statistical efficacy comparison will be made between each dose of vupanorsen and placebo for primary and secondary endpoints, respectively. Placebo-adjusted LS mean difference, 95% CI, and p-value will be presented. Since this study is exploratory in nature, no multiplicity adjustment of endpoints nor adjustment of multiple comparison to placebo will be made. Sensitivity analyses/supplementary analyses are defined in the SAP. Since the visit after Week 24 is considered safety follow-up, the statistical analyses at those visits will be presented but the p-value will be treated only as nominal.

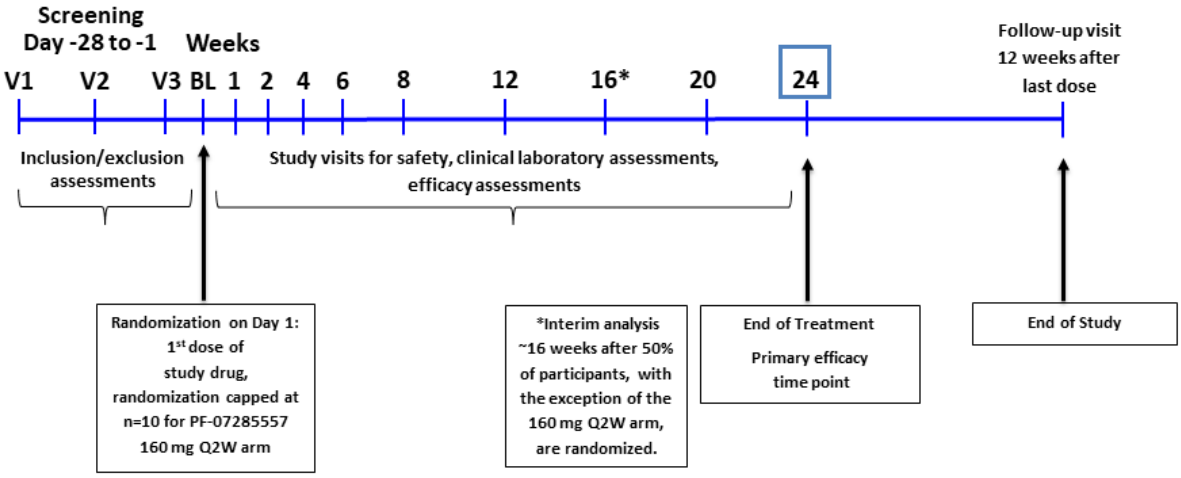
In addition, a Bayesian E_{max} dose-response model will be estimated to illustrate the expected relationship between doses and their corresponding (percent) change from baseline at

Week 24 for primary and key secondary endpoints, respectively. For each endpoint, 95% CI at each studied dose level will also be constructed.

In addition to analyses, summary statistics, listings, and figures will be provided.

1.2. Schema

Figure 1. Study Schematic



1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant. In the event of a health care crisis, pandemic, or other emergency, some of the assessments may be performed via home health visits or other ways after discussion with the sponsor. See Appendix 13 for alternative measures that may be allowed during a public emergency, such as COVID-19.

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 14.	**Screening**[b] **(Days -28 to -1)**			**Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 85**	**Day 113 Interim Analysis Time Point**	**Day 141**	**Day 169**	**Follow-up (+12 weeks after last dose)**[e,f]	**Early Termination/ Discontinuation**[g]
	Visit 1[c,d]	**Visit 2**	**Visit 3**												
Week	**-4 to -1**			**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**32 or 34**	
Month	**-1**						**1**		**2**	**3**	**4**	**5**	**6**	**8**	
Visit Window (Days)					**±1**	**±1**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±7**	
Informed consent	X														
Medical history	X														
Inclusion/Exclusion Criteria	X			X											
Physical examination	X														
Vital signs (seated blood pressure and pulse rate)	X			X							X		X		X
Weight	X			X									X		X
Height	X														
Provide contact card to participant	X														
Dispense diary and instruct participant on use				X[h]											
Laboratory															
Hematology	X			X	X[i]	X	X	X	X	X	X	X	X	X	X
Blood chemistry	X			X	X[i]	X	X	X	X	X	X	X	X	X	X
Lipid panel and ApoB[j]	X			X			X		X	X	X	X	X	X	X
Extended lipoprotein panel and FFA[k]				X									X		X
ANGPTL3[l]				X			X		X	X	X	X	X		X
HbA1c	X			X									X	X	X

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 14.	**Screening**[b] **(Days -28 to -1)**			**Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 85**	**Day 113 Interim Analysis Time Point**	**Day 141**	**Day 169**	**Follow-up (+12 weeks after last dose)**[e,f]	**Early Termination/ Discontinuation**[g]
	Visit 1[c,d]	**Visit 2**	**Visit 3**												
Week	**-4 to -1**			**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**32 or 34**	
Month	**-1**						**1**		**2**	**3**	**4**	**5**	**6**	**8**	
Visit Window (Days)					**±1**	**±1**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±7**	
Urinalysis	X			X	X[i]	X	X	X	X	X	X	X	X	X	X
Urine albumin to creatinine ratio	X			X	X[i]	X	X	X	X	X	X	X	X	X	X
FSH (women, if applicable)	X														
Pregnancy test[m]	X			X		X	X	X	X	X	X	X	X	X	X
Plasma PK										X[n]	X[n]		X[o]		X
hsCRP				X									X		X
PT, aPTT, INR				X	X[i]	X	X	X	X	X	X	X	X	X	X
Anti-vupanorsen antibodies (ADA)				X[p]						X[p]	X[p]	X[p]	X[p]	X	X
Banked Biospecimen Samples Prep B1.5 (plasma), B2.5 (serum), M4 (urine)[q]				X									X[o]		X
Pfizer Prep D1 Banked Biospecimen(s)[q]				X											
Contraception check				X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X												X[o]		X
MRI-PDFF[r]			X										X[o,s]		X
Randomization				X											
IRT interaction	X	X		X		X[t]	X	X[t]	X	X	X	X			X
Study intervention															
Placebo-injection instruction and training		X													
Q2W[u,v]				X		X[i]	X	X	X	X	X	X			
Q4W[u]				X			X[i]		X	X	X	X			
Review diary to assess treatment compliance										X	X	X	X		X

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 14.	**Screening**[b] **(Days -28 to -1)**			**Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 85**	**Day 113 Interim Analysis Time Point**	**Day 141**	**Day 169**	**Follow-up (+12 weeks after last dose)**[e,f]	**Early Termination/ Discontinuation**[g]
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Month	**-1**						**1**		**2**	**3**	**4**	**5**	**6**	**8**	
Visit Window (Days)					**±1**	**±1**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±7**	
Prior and concomitant treatment(s)	X			X	X	X	X	X	X	X	X	X	X	X	X
Serious and nonserious adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 14.	Screening[b] (Days -28 to -1)			Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113 Interim Analysis Time Point	Day 141	Day 169	Follow-up (+12 weeks after last dose)[e,f]	Early Termination/ Discontinuation[g]
	Visit 1[c,d]	Visit 2	Visit 3												
Week	-4 to -1			0	1	2	4	6	8	12	16	20	24	32 or 34	
Month	-1						1		2	3	4	5	6	8	
Visit Window (Days)					±1	±1	±2	±2	±2	±3	±3	±3	±3	±7	

a. Day relative to start of study intervention (Day 1).
b. Screening Period is a maximum of 28 days. Complete all inclusion/exclusion procedures and assessments denoted at Screening Visit 1; placebo injection training may be performed at Screening Visit 1 or Screening Visit 2. After participant has otherwise qualified for the study, including review of lipid and clinical laboratory results and completion of successful placebo training injections, perform MRI-PDFF at Screening Visit 3 or any time prior to randomization.
c. If participants are not fasted for lipid panel and ApoB collection, perform other Screening activities and have participants return fasted for these tests.
d. Screening Visit 1 activities should be completed within 7 days.
e. Occurs 12 weeks after last dose: Week 32 for participants assigned to Q4W regimen or Week 34 for participants assigned to Q2W regimen.
f. For participants who discontinue the study after Week 24, perform Follow-up procedures; do not perform Early Termination/Discontinuation procedures.
g. For participants who discontinue study intervention or discontinue the study prior to Week 24, the procedures should be performed. Early Termination/Discontinuation procedures to be performed *as soon as practically possible* after decision to stop study intervention but participants should stay in study with continuation of scheduled visits unless participant withdraws consent from further study participation.
h. Diary to be dispensed only to participants assigned to Q2W regimen.
i. Laboratory results from Week 1 visit should be reviewed by the investigator prior to Week 2 dosing for participants dosing Q2W and prior to Week 4 dosing for participants dosing Q4W.
j. Lipid panel and ApoB should be obtained with participants in a fasted state (Section 5.3.2). Lipid panel includes non-HDL-C, TG, direct LDL-C, total cholesterol, HDL-C, direct VLDL-C.
k. Extended lipoprotein panel and FFA should be obtained with participants in a fasted state (Section 5.3.2). Extended lipoprotein panel includes Lp(a), ApoB-48, ApoB-100, ApoC-III, ApoA-I.
l. ANGPTL3 should be obtained with participants in a fasted state (Section 5.3.2 and Section 8.6).
m. For WOCBP. Perform serum pregnancy test at Screening. Perform urine pregnancy test prior to dosing at visits on Week 0, Week 2 through Week 24, Follow-up, and Early Termination/Discontinuation (if applicable).
n. PK sample collected with participants in a fasted state (Section 5.3.2) at trough (prior to dosing with study intervention) and 2 to 4 hours after administration.
o. Do not perform assessment/procedure at Day 169 for participants who continued scheduled visits after stopping study intervention and completed Early Termination/Discontinuation assessments/procedures.
p. ADA samples to be collected prior to dosing with study intervention.
q. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
r. Assessment to be performed, following ≥4-hour fast, at site (as part of site visit) or separate visit(s) to Imaging facility (see Section 5.3.2).
s. Attempts to be made to stay within ±2-hour window of the time when MRI-PDFF was performed at Screening.
t. Dispense study intervention only to participants assigned to Q2W regimen for home dosing.
u. For each site visit, perform all indicated procedures and assessments prior to participant self-injection (or caregiver administering injection).
v. Dosing at home for participants in the Q2W regimens will occur on Weeks 10, 14, 18, and 22; the window for each scheduled dosing day is ±2 days. Study intervention will be dispensed at the prior visit for these doses.

2. INTRODUCTION

ANGPTL3 is a protein primarily synthesized and secreted by the liver and is a member of the angiopoietin-like family of proteins. ANGPTL3 is a genetically-validated target of lipid metabolism and CV disease.[1]

PF-07285557 (hereafter, vupanorsen) is a second-generation 2'-MOE ASO targeting hepatic ANGPTL3 mRNA. Vupanorsen is planned to be developed for CV risk reduction and for TG lowering in patients with severe hypertriglyceridemia.

Vupanorsen is a synthetic oligomer of 20 nucleotides that are connected sequentially by phosphorothioate and phosphodiester linkages (mixed backbone design) and covalently bound to GalNAc, which binds with high affinity to the ASGPR on hepatocytes, increasing hepatocyte delivery and potency. The mixed backbone design reduces the total number of phosphorothioate linkages in the MOE-modified regions, which reduces non-specific interactions with proteins and further enhances potency of GalNAc-conjugated ASOs.

Phase 1 and Phase 2a studies with vupanorsen administered SC have demonstrated marked reductions in ANGPTL3 protein and reductions in TG, VLDL-C, and non-HDL-C. The favorable lipid changes along with human genetic data indicate that inhibition of ANGPTL3 with vupanorsen could represent a novel approach to decrease CV disease risk and reduce TG in participants with hypertriglyceridemia.

2.1. Study Rationale

This multicenter, Phase 2b, double-blind, placebo-controlled, parallel group study is being conducted internationally to provide data on efficacy, safety, tolerability, and PK of vupanorsen administered SC at various doses and regimens in participants with dyslipidemia, defined in this study as participants with elevated non-HDL-C and TG who are receiving a stable dose of a statin. This study is intended to enable selection of a dose(s) for future development of vupanorsen for CV risk reduction and hypertriglyceridemia.

This study is also known as TaRgeting ANGPTL3 with an aNtiSense oLigonucleotide in AdulTs with dyslipidEmia (TRANSLATE-TIMI 70).

2.2. Background

2.2.1. Atherosclerotic Cardiovascular Disease

Individuals with established ASCVD, a prior history of ischemic events, or multiple risk factors for atherothrombosis are at high risk for future ischemic events and CV death.[2] Both epidemiological and pharmacological intervention trials have demonstrated a strong and linear relationship between levels of LDL-C and CV events. Early intensive statin therapy to lower LDL-C has become a foundation of treatment for patients with ASCVD.[3] However, even with guideline-based optimal LDL-C lowering treatment, patients with ASCVD remain at high risk for CV death and recurrent ischemic events.[4]

A growing body of clinical and epidemiological data indicate that non-HDL-C is a better predictor of CV risk than LDL-C alone.[5,6] Non-HDL-C encompasses the cholesterol content

of all the atherogenic ApoB-containing lipoproteins including LDL, VLDL, IDL, Lp(a), chylomicrons, and chylomicron remnants. Thus, non-HDL-C provides a simple way to assess the total amount of atherogenic lipoproteins containing ApoB. Collectively, IDL, VLDL, and chylomicron remnants are termed TG-rich lipoproteins. Elevated plasma TG is a marker for elevated TG-rich lipoproteins. Several lines of evidence have established a likely causal role for TG-rich lipoproteins in atherogenesis, mediated by their cholesterol content rather than the TG content.[7] TG-rich lipoproteins are strong independent predictors of ASCVD and all-cause mortality in epidemiological studies and genetic studies using Mendelian randomization.[7] Genetic studies of various factors influencing the function of lipoprotein lipase, a key enzyme that degrades TG-rich lipoproteins in plasma and regulates the delivery of fatty acids to adipose tissue and muscle, provide evidence that TG-rich lipoproteins are a causal factor in ASCVD.[5]

In randomized controlled trials, reduction in TG (a surrogate of TG-rich lipoproteins) is associated with a lower risk of major vascular events, even after adjustment for LDL-C lowering, although the effect on vascular events is less than that for LDL-C or non-HDL-C reduction.[8] Most previous non-statin trials of existing therapies to lower TG (fibrates, niacin, omega-3 fatty acids) have had modest reductions in non-HDL-C and TG and have been underpowered to detect reductions in CV events.[6]

Therapies that primarily reduce LDL-C such as statins, ezetimibe, and PCSK9 inhibitors have modest effects on TG (5% to 15%). Other therapies that reduce TG such as fenofibrate and niacin can result in larger reductions in TG but have not been shown to reduce CV risk. High doses of icosapent ethyl also has modest effects on TG (median reduction of approximately 20%) but reduced CV risk by 25%, suggesting effects on CV outcomes beyond lowering TG.[9]

Therapies that increase lipoprotein lipase activity through inhibition of ANGPTL3 have the potential for large reductions in non-HDL-C and TG-rich lipoproteins resulting in additional reduction in CV risk.

2.2.2. Hypertriglyceridemia

Two categories of hypertriglyceridemia have been defined: moderate hypertriglyceridemia (TG 150-499 mg/dL) and severe hypertriglyceridemia (TG ≥500 mg/dL). Moderate hypertriglyceridemia is commonly associated with obesity, T2DM, and insulin resistance, and the excess TG are primarily carried in VLDL.[3] Patients with severe hypertriglyceridemia have an excess of chylomicrons (chylomicronemia) in addition to an excess of TG-rich lipoproteins.

In addition to increased ASCVD risk, hypertriglyceridemia is a well-established cause of acute pancreatitis. The pancreatitis risk is highest in familial chylomicronemia syndrome, but there is evidence to indicate that pancreatitis risk is increased even in mild or moderate hypertriglyceridemia and the risk increases in a dose-dependent manner as TG levels increase.[10]

Treatment of severe hypertriglyceridemia has 2 aspects: lowering lipid levels to decrease ASCVD risk and the more acute goal of reducing elevated TG to reduce risk of acute pancreatitis. LDL-C lowering treatments have only moderate effects on TG, but lower ASCVD risk in patients with hypertriglyceridemia or mixed dyslipidemia. There is a need for therapies that decrease TG and reduce CV risk for individuals whose TG levels remain elevated despite treatment.

2.2.3. Rationale for ANGPTL3 Inhibition

ANGPTL3 is a protein primarily synthesized and secreted by the liver and is a member of the angiopoietin-like family of proteins. ANGPTL3 inhibits lipoprotein lipase, which is the primary mechanism by which TG-rich lipoproteins are cleared from the circulation.[11] ANGPTL3 also inhibits endothelial lipase, which is involved in HDL metabolism. Genome sequencing studies of individuals with very low plasma lipids have identified loss-of-function mutations in ANGPTL3 which result in a distinct hypolipidemia phenotype.[12] Individuals with complete ANGPTL3 loss-of-function mutations present with low levels of multiple atherogenic plasma lipids, including ApoB-100-containing lipoproteins, VLDL-C, and LDL-C, without an increase in prevalence of fatty liver or other adverse clinical effects and have lower glucose and less insulin resistance.[13] Inhibition of ANGPTL3 lowers LDL-C through a mechanism that is independent of LDL receptor-mediated clearance.[14] Epidemiological studies have shown that ANGPTL3 deficiency is associated with a reduced risk of coronary artery disease.[15]

2.2.4. Clinical Overview

One Phase 1 single- and multiple-ascending dose study (CS1) (hereafter, Phase 1) in healthy volunteers, 1 Phase 2a proof-of-concept and dose-ranging study (CS2) (hereafter, Phase 2a), and 2 small, open-label, single-arm, proof-of-concept studies (in participants with Familial Chylomicronemia Syndrome and Familial Partial Lipodystrophy) have been conducted. Refer to the IB for more details on these studies, including clinical efficacy and safety results for the Phase 2a study.

Clinical PK results for the Phase 2a study are presented in Section 2.2.4.1.

2.2.4.1. Clinical Pharmacokinetics

Concentrations of total full-length oligonucleotide in plasma, including the parent compound vupanorsen, its full-length oligonucleotide metabolites with 1, 2, and/or 3 GalNAc sugar deletions and unconjugated vupanorsen, were quantitated as they are all potentially pharmacologically active. For simplicity, vupanorsen concentration refers to all full length oligonucleotides in the context of PK.

In the Phase 1 study, following single-dose or multiple-dose SC administration, vupanorsen was absorbed rapidly into the systemic circulation, with median T_{max} ranging from 1 to 8 hours. After reaching C_{max}, plasma concentrations of vupanorsen declined in a multi-phasic fashion with a rapid disposition phase, followed by a slower elimination phase with mean terminal elimination half-life of 3 to 5 weeks. C_{max} and AUC increased approximately dose proportionally from 20 mg to 120 mg after a single SC dose, and from 10 mg to 60 mg after

single and multiple weekly SC doses. No accumulation was observed based on C_{max} and AUC after weekly doses. Plasma trough concentrations indicated that steady-state was not reached after 6 weeks of weekly dosing, consistent with the observed long half-life of the drug.

Vupanorsen PK profiles were evaluated in a subset of participants in the Phase 2a study. Following 20 mg QW, 40 mg and 80 mg Q4W SC dosing, the observed preliminary vupanorsen PK in the Phase 2a study were consistent with those in the Phase 1 study. Plasma trough concentrations appeared to reach steady-state after 21 weeks of dosing. The presence of ADA showed no apparent impact on C_{max} and AUC, but increased plasma trough concentrations based on preliminary analysis.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of vupanorsen may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) [vupanorsen]		
Decreased platelet counts, elevated transaminases, and decreased renal function are potential risks associated with vupanorsen.	The potential risks are based on reports of thrombocytopenia, elevated liver enzymes, and decreases in renal function in clinical and non-clinical studies of other non-GalNAc conjugated ASOs.[16,17] Thrombocytopenia has not been observed in non-clinical and clinical studies of vupanorsen (see IB for non-clinical and clinical study results). No vupanorsen-associated severe decline in platelet counts were reported in the Phase 1 or 2a study (see IB). The potential risk of elevated transaminases is based on the results of the Phase 2a study where increases in mean ALT that appeared dose dependent were observed in all vupanorsen treatment groups, and mild isolated transaminase increases that exceeded the 3 times the upper limit of normal occurred in 2 participants at the 20 mg QW dose; the transaminase increases were not associated with an	Eligibility criteria will ensure the appropriate participants enter the study (see Exclusion Criterion 4). AEs and clinical laboratories will be obtained and monitored throughout the study (see SoA). Also, the protocol includes monitoring and stopping criteria for abnormal platelet counts, elevated transaminases, and decrease in eGFR (see Section 7.1). Instructions for managing potential liver injury are provided (see Appendix 6).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	increase in bilirubin or liver-related symptoms (see IB).	
Injection site reactions are a potential risk of vupanorsen.	Injection site AEs were the most common side effects observed following SC administration of unconjugated 2'-MOE ASOs and were dose dependent.[18] Injection site AEs have been observed in the Phase 1 and Phase 2a (see IB) studies of vupanorsen and have generally been mild.	Injection site instructions to minimize injection site AEs will be provided to the participant or caregiver (if applicable). AEs will be monitored on an ongoing basis throughout the study (see SoA). Also, the protocol requires discontinuation of dosing if a severe injection site reaction occurs (see Section 7.1.2).
Study Procedures		
MRI-PDFF will be used to assess liver fat.	MRI-PDFF can cause claustrophobia and also is contra-indicated in individuals with certain medical devices or other internal metallic objects.	Eligibility criteria will ensure the appropriate participants enter the study (see Exclusion Criterion 19).
Participants will self-inject (or caregivers will inject) study intervention.	Participants or caregivers may perform the injection incorrectly. Participants may be uncomfortable self-injecting.	Sites will train participants or caregivers to perform the injection. During Screening, participants or caregivers will inject placebo in order to determine whether study intervention can be correctly administered.

2.3.2. Benefit Assessment

Treatment with vupanorsen may lower non-HDL-C, TG, and other lipids/lipoproteins associated with ASCVD and ischemic events. Participants will be followed closely by a physician for approximately 32 weeks (Q4W regimen) or 34 weeks (Q2W regimen) and will have measurements of lipids, blood pressure, and other clinical laboratories throughout the study. Measurements of liver fat using MRI-PDFF may, after unblinding of the study, identify elevated liver fat in some participants who were unaware that they had this condition and inform their post-study management by their primary health care provider. Finally, participants will be contributing to the development of a potential therapy to reduce risk of CV events and to treat individuals with elevated TG.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with vupanorsen and study procedures are justified by the anticipated benefits that may be afforded to participants with ASCVD or severe hypertriglyceridemia.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on non-HDL-C.	• Percent change from baseline in non-HDL-C at Week 24
Secondary:	**Secondary:**
• To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on lipid parameters including TG, ApoB, and LDL-C. • To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on ANGPTL3.	• Percent change from baseline in TG, ApoB, and LDL-C at Week 16 and Week 24 • Percent change from baseline in non-HDL-C at Week 16 • Percent change from baseline in ANGPTL3 at Week 16 and Week 24
Safety:	**Safety:**
• To evaluate the safety, tolerability, and immunogenicity of multiple dose levels and regimens of vupanorsen. • To evaluate the effect of multiple dose levels and regimens of vupanorsen on HFF.	• Incidence of treatment-emergent SAEs and AEs throughout the study • Incidence of AESI • Categorical summaries of clinical laboratory abnormalities • UACR • ADA • Change from baseline in AST, ALT, platelet counts, and eGFR • Change and percent change from baseline in HFF (assessed by MRI-PDFF) at Week 24

Objectives	Endpoints
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on total cholesterol, HDL-C, VLDL-C, Lp(a), FFA, ApoB-48, ApoB-100, ApoC-III, and ApoA-I. • To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on hsCRP. • To evaluate the PK of vupanorsen.	• Percent change from baseline at Week 24 in total cholesterol, HDL-C, VLDL-C, Lp(a), FFA, ApoB-48, ApoB-100, ApoC-III, and ApoA-I • Percent change from baseline in hsCRP at Week 24 • Plasma concentrations of vupanorsen at Weeks 12, 16, and 24

The primary estimand of this study will follow the hypothetical estimand approach as described in Section 9.1.1.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging, 8-arm parallel-group study in adults ≥40 years of age with dyslipidemia who are on a stable dose of a statin (with or without ezetimibe). Following the Screening Period to confirm eligibility, a total of approximately 260 participants will be randomized in the study to receive SC doses of vupanorsen or placebo administered Q2W or Q4W for the purpose of assessing efficacy, safety, and tolerability of vupanorsen. The total duration of treatment in the study is 24 weeks with an additional 12-week safety follow-up period.

The sponsor, along with academic leadership of the study (TIMI Study Group), will monitor the proportion of participants enrolled according to statin intensity to ensure that an adequate number of participants on high intensity statin are enrolled. High intensity statin use is defined as atorvastatin (40 mg or 80 mg per day) or rosuvastatin (20 mg or 40 mg per day). All other statin regimens are considered low or moderate intensity. Approximately 40% or more of participants enrolled should be on high intensity statin therapy, and enrollment of participants using low/moderate intensity statin may be capped.

Vupanorsen dosing will be accomplished by administration of 1 or 2 prefilled syringes of either 60 mg or 80 mg strength according to required total dose. Placebo will be provided as a prefilled syringe and will be administered as either 1 or 2 syringes. See Table 1 for the dosing plan.

Table 1. Dosing Plan

Treatment Arm	Total Monthly Dose	Injection Regimen	Number of Participants
Placebo	0 mg	Single or double injection Q2W or Q4W	40
80 mg Q4W	80 mg	Single injection Q4W	20
60 mg Q2W	120 mg	Single injection Q2W	20
120 mg Q4W	120 mg	Double injection Q4W	20
80 mg Q2W	160 mg	Single injection Q2W	40
160 mg Q4W	160 mg	Double injection Q4W	40

Table 1. Dosing Plan

Treatment Arm	Total Monthly Dose	Injection Regimen	Number of Participants
120 mg Q2W	240 mg	Double injection Q2W	40
160 mg Q2W∗	320 mg	Double injection Q2W	40

∗Treatment arm will be capped at 10 participants until E-DMC performs unblinded data review and recommends whether enrollment should be re-opened for this dose group for the remaining 30 participants.

During the Screening Period, sites will instruct participants or caregivers how to perform the SC injection, and participants (or caregivers) willing to perform the injection will be assessed for ability to inject correctly. Sites will determine whether a participant or caregiver is willing and able to correctly perform the SC injection. Participants receiving monthly injections will self-administer study intervention (or be injected by their caregiver) on-site. Participants receiving Q2W injections will self-administer study intervention (or be injected by their caregiver) on-site when study visits coincide with the dosing interval (Weeks 2 and 6, and at designated monthly visits). The study site will dispense study intervention for the participant or caregiver to inject at home for the doses that do not coincide with a study visit (Weeks 10, 14, 18, and 22).

Safety clinical laboratory parameters and AEs, including injection site reactions, will be monitored throughout the study. HFF will be assessed at Screening and Week 24 using MRI-PDFF, and blood samples will be collected for lipids, lipoproteins, PK, PD, hsCRP, and anti-vupanorsen antibodies at various time points during the study according to the SoA. MRI-PDFF will be read by a central reviewer, blinded to treatment group, lipid levels, and other clinical variables, such as concentrations of hepatic enzymes.

This study will include an E-DMC who will be responsible for ongoing, unblinded monitoring of efficacy and the safety of participants in the study according to the E-DMC charter (Section 9.6).

Since administration of 160 mg Q2W (total monthly dose of 320 mg) has not been studied previously, enrollment in this arm will be capped after 10 participants. Following unblinded data review by the E-DMC as described in the E-DMC charter, enrollment in this treatment arm may be re-opened for the remaining 30 participants or be stopped based on recommendation by the E-DMC. Separately, an interim analysis is planned and will also be reviewed by the E-DMC. The interim analysis will take place approximately 16 weeks after 50% of the planned participants (ie, approximately 110 participants), with exception of the 160 mg Q2W group, are randomized.

Efficacy and safety analyses will occur when all participants either complete 24 weeks of study participation or discontinue study participation. Additional summarizing of follow-up safety data will occur after the 12-week post-dose follow-up visit.

4.2. Scientific Rationale for Study Design

As reviewed in the IB, vupanorsen demonstrated significant reductions in TG and multiple lipid endpoints in the Phase 2a study in participants with hypertriglyceridemia, NAFLD, and diabetes; however, the maximal reduction in ANGPTL3 achieved with the highest dose of 80 mg Q4W in the study was below the magnitude needed to observe maximal lipid lowering with this mechanism (ie, ≥75% ANGPTL3 reduction). From a safety perspective, the numerical increases in liver fat at 20 mg QW and 40 mg Q4W, along with the larger increase noted at 80 mg Q4W need to be further evaluated.

In the current study, the participant population is focused on those with elevated non-HDL-C and TG and are on a stable dose of a statin to determine the optimum dose for future development for hypertriglyceridemia and CV risk reduction. To further evaluate potential changes in liver fat accumulation, participants will complete MRI-PDFF at Screening and end of treatment (Week 24). In addition, banked biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of vupanorsen.

Vupanorsen has an unlikely risk of human teratogenicity/fetotoxicity. However, participants who are WOCBP must use an acceptable contraceptive method (see Appendix 4). The risk of vupanorsen causing damage to the DNA of sperm is considered low, and the risk of exposure to vupanorsen in a sexual partner of a male participant in this study via ejaculate is low; therefore, no contraception (condom) use in male participants is required (see Appendix 4). The highest dose of vupanorsen planned for this study would result in maternal systemic exposures via seminal transfer well below (>5000-fold) the exposure at the NOAEL for developmental toxicity in nonclinical studies, including the conservative assumptions that an ASO ejaculate:serum ratio would be 1 and there is 100% uptake by the partner.

4.3. Justification for Dose

A dose range of 80 mg Q4W to 160 mg Q2W will be evaluated for safety and efficacy in this study. Based on simulation results using a preliminary population PK/PD model developed from the combined data in the Phase 1 and Phase 2a studies, vupanorsen 80 mg Q4W is expected to be a minimal efficacious dose in non-HDL-C reduction (<8% probability of achieving 35% mean reduction) and is included to bridge the data from previous studies. Vupanorsen 160 mg Q2W is expected to achieve >90% probability of ≥35% mean reduction in non-HDL-C, which translates to a potential ≥20% CV relative risk reduction in CV events assuming non-HDL-C baseline of 125 mg/dL, in addition to maximizing ANGPTL3 and TG reductions.

Both Q2W and Q4W dosing regimens are included for the total monthly doses of 120 mg and 160 mg in order to discern if there is any effect of dosing frequency or any effect of maximum single dose administered at one time on the frequency of AEs.

Single doses of vupanorsen up to 120 mg SC and multiple doses up to 60 mg SC QW for 6 doses (total exposure of 360 mg) were safe and well-tolerated in healthy volunteers in the Phase 1 study. There was no evidence of treatment-associated AEs or negative effects on platelets or renal function. At the highest multiple dose administered (60 mg QW), 2 out of

6 participants had elevations in liver enzymes, with 1 participant exceeding >3 × ULN and without elevation in bilirubin. Both participants with ALT elevations in Phase 1 completed the study.

Doses of vupanorsen up to 80 mg Q4W were well tolerated in the Phase 2a study. There were observations in the vupanorsen-treated participants that were not considered safety issues but warrant additional study in a larger sample size to understand if they are related to vupanorsen administration or could reflect a stochastic finding. These observations included increase in HFF and small increases in mean ALT. Injection-site reactions will also be assessed in a larger sample size relative to earlier studies. This Phase 2b study includes measures to mitigate these identified risks (Section 2.3.1) and provide close oversight of participants.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including follow-up visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants aged ≥40 years at Screening.

    - Refer to Appendix 4 for male and female reproductive inclusion criteria (Section 10.4.1, Section 10.4.2, and Section 10.4.3) and for contraceptive requirements for female participants (Section 10.4.4).

Type of Participant and Disease Characteristics:

2. Fasting non-HDL-C at Screening ≥100 mg/dL.

3. Fasting TG at Screening of 150 to 500 mg/dL, inclusive, which may be repeated once if deemed necessary.

4. Participants must be on a stable dose of a statin for at least 1 month before Screening and plan to remain on the same medication and dose for the duration of the study.

Weight:

5. Body weight ≥50 kg and ≤136 kg at Screening.

Informed Consent:

6. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Participant has active liver disease (other than NAFLD or NASH, which are permitted), including chronic active hepatitis B or C or primary biliary cirrhosis.

2. Uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg). Note: participants who are on an anti-hypertensive medication to treat hypertension should be on a stable dose at least 1 month prior to Screening. The investigator should ensure participant took anti-hypertensive medication as prescribed prior to evaluation of blood pressure.

3. Participant with a known bleeding diathesis or coagulation disorder.

4. Participants with ANY of the following abnormalities in clinical laboratory tests at Screening, as assessed by the central laboratory and confirmed by a single repeat test, if deemed necessary:

    - HbA1c ≥9.5%
    - eGFR <30 mL/min/1.73 m^2 (as determined by the CKD-Epi equation)
    - ALT or AST >2 × ULN
    - Total bilirubin ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ULN
    - Platelet count <LLN

5. History of clinically significant acute cardiac event within 3 months before Screening (includes ischemic stroke, transient ischemic attack, myocardial infarction, revascularization procedures, hospitalization for heart failure).

6. Presence of New York Heart Association Functional Classification IV heart failure symptoms at Screening.

7. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.

8. Current history of alcoholism or drug addiction according to Diagnostic and Statistical Manual of Mental Disorders IV criteria within 12 months prior to Screening. Use of any recreational drugs within 12 months prior to Screening.

9. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

10. Prior treatment at any time with vupanorsen.

11. Prior treatment with any oligonucleotide (including small interfering ribonucleic acid) within 6 months of Screening or prior treatment with inclisiran within 12 months of Screening.

12. Use of TG lowering medication (eg, Vascepa [icosapent ethyl]), non-prescription dietary supplements (eg, fish oil) or other cholesterol lowering medication (eg, fibric acid derivatives, niacin, PCSK9 inhibitors, bile acid sequestrants, bempedoic acid) 30 days prior to Screening, other than statins and ezetimibe.

13. Use of warfarin or other coumarins, direct thrombin inhibitors, Factor Xa inhibitors, heparins or heparinoids 30 days prior to Screening.

Prior/Concurrent Clinical Study Experience:

14. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

15. Participant has a clinically significant ECG abnormality during the Screening Period that requires further diagnostic evaluation or intervention (eg, new, clinically significant arrhythmia or a conduction disturbance).

Other Exclusions

16. Unstable weight (>5% shift in past month) or plan to start a diet for the purpose of significant weight loss.

17. Hypersensitivity to the active substance or to any of the excipients or GalNAc.

18. Any major surgery, including bariatric surgery, within 3 months of Screening.

19. Participants with conditions contraindicated for MRI procedures including pacemakers or aneurysm clips; the presence of MRI incompatible implanted devices; metallic foreign bodies; metal tattoos (including permanent make-up); or severe claustrophobia impacting the ability to perform MRI. Participants who may require mild sedative or anxiolytic in order to complete the MRI may be enrolled.

20. Participants unwilling or unable to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator.

21. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

Contraception is required only for female participants of childbearing potential (see Appendix 4 Section 10.4.3). The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.2. Dietary Restrictions and Fasting

Participants should maintain their usual diet and exercise regimen throughout the study.

Participants should abstain from all food and drink (except water) for ≥10 hours prior to Screening Visit 1 and visits at Weeks 0, 4, 8, 12, 16, 20, 24, follow-up, and Early Termination/Discontinuation visit (if applicable) for testing of lipids, extended lipoprotein panel, FFA, ANGPTL3, hsCRP, or PK. Prior to the visit, the study site should contact the participant to remind him/her of the fasting requirement and specify the time the participant should stop eating relative to the time of the visit. Participants are permitted to take concomitant medications (provided that they can be taken in the fasting state), taken as prescribed with water, on the morning of a study visit.

Participants must abstain from all food and drink (except water) for ≥4 hours prior to MRI-PDFF assessment.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the 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 failure) may be rescreened if they failed for a documented treatable condition. Individuals may not be rescreened if they did not meet inclusion requirements for TG and non-HDL-C.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

Not applicable.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to vupanorsen or placebo administered SC.

6.1. Study Intervention(s) Administered

Study Intervention	Vupanorsen							Placebo
ARM Name	80 mg Q4W	60 mg Q2W	120 mg Q4W	80 mg Q2W	160 mg Q4W	120 mg Q2W	160 mg Q2W	Placebo
Type	Drug							Placebo
Dose Formulation	100 mg/mL							0 mg/mL
Unit Dose Strength(s)	60 mg/syringe or 80 mg/syringe							0 mg/ syringe
Dosage Level(s)	80 mg Q4W	60 mg Q2W	120 mg Q4W	80 mg Q2W	160 mg Q4W	120 mg Q2W	160 mg Q2W	0 mg Q2W or Q4W
Route of Administration	SC							SC
Use	Experimental							Placebo
IMP or NIMP	IMP							IMP
Sourcing	Prefilled syringes will be provided centrally by the sponsor. See IP manual.							
Packaging and Labeling	Study intervention will be provided in masked, prefilled syringes. Each prefilled syringe will be labeled as required per country requirement.							
Current/Former Name or Alias	PF-07285557 ISIS 703802							

6.1.1. Administration

During the Screening Period, sites will instruct participants (or caregivers) how to perform the SC injection and proper sterile technique. Participants (or caregivers) will be dispensed a prefilled syringe of open-label placebo to inject, and sites will determine if a participant or caregiver is willing and able to correctly perform the SC injection.

On Day 1, the initial dose of study intervention administered by the participant or caregiver must be observed by study site personnel to ensure the participant or caregiver is using proper technique.

Vupanorsen or placebo will be administered as a single or double SC injection at 2-week or 4-week intervals depending on the treatment arm. At the study site or at home, SC injections should be administered by the participant or caregiver according to dosing instructions in any of the following locations: upper arm, thigh, or abdomen quadrant, as preferred by the participant. Participants receiving 2 injections should consecutively administer each injection in a different location. To minimize injection site reactions, the SC injection should not be administered in areas where the skin is burned, reddened, inflamed, swollen, or scarred. If a participant receiving study intervention Q2W or Q4W misses or delays their dose outside the dosing window and is within 7 or 14 days, respectively, of the next dose, the dose should be skipped altogether and recorded on the CRF.

Participants receiving study intervention Q2W will receive a diary to record home dosing. Study intervention administration details will be recorded on the CRF.

6.1.2. Medical Devices

1. The sponsor manufactured medical devices provided for use in this study are vupanorsen 100 mg/mL (60 mg/syringe), vupanorsen 100 mg/mL (80 mg/syringe), or placebo (0 mg/syringe) for Solution for Injection.
2. Instructions for medical device use are provided in the IP manual.
3. All medical device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.8) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations

must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. Only study intervention administered Q2W will be taken home by the participant; cooler bags will be provided for transporting study intervention from the site to the participant's home. A biohazard sharps container will be provided to the participant for disposal of used syringes. When the biohazard sharps container is full or at end of study or early discontinuation visit, the participant will return the biohazard sharps container to the study site for destruction. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

Vupanorsen and placebo will be provided as prefilled syringes packaged and dispensed in cartons with tamper-evident seals. Only single-use syringes will be used. Study intervention should be dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. The qualified staff member will dispense the study intervention using an IRT drug management system via unique container numbers in the cartons provided and in quantities appropriate to the SoA. A second staff member will verify the dispensing. The participant or caregiver should be instructed to maintain the product in the cartons provided, and the cartons should not be opened until the study intervention is to be administered. See the IP manual for detailed instructions.

The following procedures should be followed to help protect the blind:

- Used syringes should be placed immediately after use, whenever or wherever dosing occurs, in a biohazard sharps container, and the container will be returned to the study site, as needed, eg, when the biohazard sharps container is full or at end of study/early discontinuation visits.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Study intervention will be dispensed at the study visits listed in the SoA.

Returned study intervention must not be redispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor or TIMI Hotline prior to unblinding a participant's treatment assignment unless this could delay further management

of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

At site visits, study intervention will be dispensed by the investigator or designee, and participants will self-administer (or caregivers will administer) study intervention under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study site staff other than the person dispensing the study intervention.

Participants receiving study intervention Q2W will receive a diary to record home dosing. When participants self-administer (or caregivers administer) study intervention at home, compliance with study intervention will be assessed at each on-site visit. Compliance will be assessed by reviewing the participant's diary (Q2W only), direct questioning, and checking empty cartons during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of vupanorsen and placebo syringes dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

6.5. Concomitant Therapy

All concomitant medications taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. Attempts must be made to not alter the doses and regimens of background lipid lowering therapy (statin and ezetimibe [if applicable]) after randomization and for the duration of participation in this study. All participants must be questioned about concomitant medication at each visit to the clinical site.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

6.5.1. Prohibited Therapy During the Study

- Use of TG lowering or cholesterol lowering medication (eg, fibric acid derivatives, niacin, PCSK9 inhibitors, bile acid sequestrants, bempedoic acid).
- Use of TG lowering dietary supplements (eg, fish oil) and prescription products containing omega-3 fatty acids (eg, Vascepa [icosapent ethyl]).

- Use of warfarin or other coumarins, direct thrombin inhibitors, Factor Xa inhibitors, heparins or heparinoids is prohibited during the study.

6.5.2. Prohibited Prior Treatments

- Use of any therapy listed in Section 6.5.1 30 days prior to Screening.
- Prior treatment at any time with vupanorsen is prohibited.
- Prior treatment with any oligonucleotide (including small interfering ribonucleic acid) within 6 months of Screening or prior treatment with inclisiran within 12 months of Screening is prohibited.
- Prior administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer) is prohibited.

6.5.3. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with vupanorsen; standard medical supportive care must be provided to manage any AEs.

6.6. Dose Modification

Dose modifications will not be performed during this study.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Due to unforeseen circumstances, all participants may not complete the study as planned. Regardless of study intervention status, participants should continue in the study if willing. Possible discontinuations may include:

1. Discontinuation of study intervention: Participants will discontinue study intervention but continue in the study.

    a. Temporary discontinuation: If a participant temporarily discontinues study intervention for any reason other than safety, they should resume study intervention at the next scheduled dosing, if possible.

    b. Definitive discontinuation: If study intervention is permanently discontinued (as requested by the investigator or the participant), the participant will remain in the study to be evaluated during the regular visit schedule (see Section 7.1.2 and Section 7.2.1). At the time of discontinuing from the study intervention, if possible, an Early Termination/Discontinuation visit should be conducted. See the SoA for

assessments to be collected at the time of discontinuation of study intervention and for any further evaluations that need to be completed.

Whenever possible, restart of study intervention should be encouraged. Even if an Early Termination/Discontinuation visit was completed due to the discontinuation of study intervention, this should not prevent complete study follow-up procedures including restart of randomized treatment. All efforts must be taken to assure that the participant will be seen and assessed by an investigator. Participants fulfilling a study-specific discontinuation criteria should never be restarted on study intervention.

2. Participant discontinuation/withdrawal from the study: Participants will not continue in the study (see Section 7.2).

   a. Withdrawal of consent (see Section 7.2.1).

   b. Lost to follow-up (see Section 7.3).

7.1. Discontinuation of Study Intervention

7.1.1. Monitoring Criteria

In general, all laboratory assessments to monitor participant safety or to determine whether a participant may continue or resume dosing with study intervention should be done by the central laboratory, if possible. Local laboratory testing may be acceptable in some situations and should be discussed by contacting the TIMI Hotline on a case-by-case basis.

The following laboratory abnormalities require prompt retesting within 7 days of receipt of results:

- Any platelet count <100,000 /mm^3. The participant should be managed according to Appendix 10 flow chart for managing decreased platelet counts.

- Any decrease in eGFR of ≥50% from baseline or eGFR <15 mL/min/1.73 m^2. The participant should be managed according to Appendix 11 flow chart for managing eGFR decreases.

- Either of the following AST or ALT abnormalities (Note: Participants meeting either of the following retesting criteria should be managed according to Appendix 12 for management of elevated AST or ALT. This should also prompt review of Appendix 6 [liver safety] to determine if additional investigations must be conducted):

  - Any single AST and/or ALT elevation >3 × ULN for participants with baseline AST and ALT within normal limits, regardless of accompanying symptoms or total bilirubin.

  - Baseline AST or ALT values above the reference range: AST or ALT values >2 times the baseline values AND >3 × ULN, regardless of accompanying symptoms or total bilirubin.

7.1.2. Discontinuation Criteria

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following:

- Platelet count is <75,000 /mm^3 on a re-test (ie, initial platelet count is <100,000 /mm^3 and the repeat platelet count is <75,000 /mm^3 or both the initial and re-test are <75,000 /mm^3). Refer to Appendix 10 for management of participants who discontinue due to decreased platelets as additional investigations must be conducted.
- The participant's eGFR falls to <15 mL/min/1.73 m^2 and confirmed by a repeat laboratory measurement.
- Participant meets criteria for DILI (Hy's Law) as defined in Appendix 6.
- AST or ALT elevations are >8 × ULN, confirmed on a repeat laboratory measurement, regardless of total bilirubin or accompanying symptoms.
- A severe hypersensitivity reaction or severe injection site reaction occurs following a SC study intervention dose. Severe hypersensitivity reactions are defined as those causing anaphylaxis. Severe injection site reactions are defined as those in which ulceration or severe necrosis occurs.
- Participant becomes pregnant.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated during the regular visit schedule. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for stopping study participation include the following:

- Refused further follow-up
- Lost to follow-up
- Death

- Study terminated by sponsor

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Participants should be questioned regarding their reason for withdrawal.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified procedures. The only exception to this is when a participant specifically withdraws consent for any further assessments or contact with his or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator of the decision to withdraw consent from future follow-up. Participants should be questioned regarding their reason for withdrawal. The investigator must inform the TIMI Hotline of the withdrawal of consent. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the participant is only stopping further receipt of study intervention or withdrawing from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. At the time of withdrawal from the study, if possible, an Early Termination/Discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study withdrawal.

If a participant withdraws consent from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Publicly available information should be used to determine vital status (whether the participant is alive or dead) only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

To prevent participants being lost to follow-up, their contact details, including next of kin contacts, should be collected initially and updated regularly by the site staff or representative. The investigator should educate the participant on the importance of contact with the investigator throughout the study.

Repeated attempts will be made to locate and obtain pertinent medical information for participants who are initially lost to follow-up. A participant will be classified as lost to follow-up only if he/she has failed to return for the required study visits and his/her vital

status remains unknown at the end of the study despite multiple attempts to contact him/her via telephone, fax, email, certified letter, or through patient locator agencies (if allowed by national regulation). Where permissible by local law, the ICD will include language to grant the option to employ outside companies to assist in obtaining updated contact information or ascertainment of vital status of lost participants using publicly available source.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 250 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

8.1.1. Lipids

Blood samples for measurement of TC, direct LDL-C, HDL-C, TG, and direct VLDL-C should be collected from participants in a fasted state (see Section 5.3.2) as indicated in the SoA; non-HDL-C will be calculated as TC – HDL-C.

Lipid results from Day 1 onward will not be reported to study sites or other blinded personnel until the study has been unblinded (see Section 8.2.7 for potential exception).

8.1.2. Lipoproteins and FFA

Blood samples for measurement of Lp(a), ApoB, ApoB-48, ApoB-100, ApoC-III, ApoA-I, and FFA should be collected from participants in a fasted state (see Section 5.3.2) as indicated in the SoA.

Lipoprotein and FFA results from Day 1 onward will not be reported to study sites or other blinded personnel until the study has been unblinded.

8.1.3. hsCRP

Blood samples for measurement of hsCRP should be collected from participants in a fasted state (see Section 5.3.2) as indicated in the SoA.

hsCRP results will not be reported to study sites or other blinded personnel until the study has been unblinded.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. MRI-PDFF Assessments

At scheduled visits (refer to the SoA), liver fat will be assessed via MRI using the PDFF acquisition method. Each assessment will require the participants to be in a supine position in the confined space of the MRI scanner for approximately 25 minutes with the image acquisition undertaken following a fast (except water) of ≥4 hours, and as much as practically possible, at the same time (±2 hours) of the day relative to assessment at Screening.

Across the study sites selected for this study, the sponsor-identified central imaging vendor will train the imaging facility staff on the MRI-PDFF acquisition protocol, on just-in-time review of the acquired images for assessment of images being deemed evaluable, and on transfer (preferably electronically) of the images to the sponsor-identified central imaging vendor for analysis and quantification of liver fat. **Only the staff members at the imaging facility who are trained by the sponsor-identified central imaging vendor are permitted to acquire images**; however in rare/limited situations, exceptions may be granted with

written approval of the sponsor. Complete details on the MRI-PDFF acquisition protocol, determination of quality of images, and transmission of data to sponsor-identified central imaging vendor will be provided in an Imaging Manual provided to the sites prior to the start of the study.

As much as practically possible, analysis of the MRI-PDFF images acquired at baseline and Week 24 will be undertaken by a single reviewer at the sponsor-identified central imaging vendor who will be blinded to individual participant's clinical data, as well as randomization assignment. MRI-PDFF images will be blinded to study sites, blinded personnel, participants, and sponsor until the study has been unblinded.

8.2.1.1. Management of Incidental Findings

An incidental finding is one unknown to the participant that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study but is unrelated to the purpose and beyond the aims of the study. The images will be reviewed by a sponsor-identified central review facility. The purpose of this review is to evaluate images for the amount of fat in the liver. Central image review is not a complete medical review of the participant. If, during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study sponsor for disclosure to the PI. All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician-participant relationship. The PI will be responsible for reporting any AEs identified from incidental findings as described in the AE reporting section. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all images as per site protocols.

8.2.2. Physical Examinations

Physical examination will be performed at Screening.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

Height will be measured and recorded at Screening, and weight will be measured and recorded at Screening, Day 1, Day 169, and Early Termination/Discontinuation, if applicable (see SoA).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.3. Vital Signs

Single seated blood pressure and pulse rate will be assessed at times specified in the SoA with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.4. Electrocardiograms

Standard 12-lead ECG utilizing limb leads (with 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be done given the potential risk of discrepancies with ECGs acquired using standard limb lead placement.

- All *scheduled* 12-lead ECGs should be performed with the participant in a supine position;
- ECG values of potential clinical concern are listed in Appendix 7.
    - If a machine-read QTc value is prolonged, as defined in Appendix 7, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range;
        - Assessment of whether prolonged QTc interval meets criteria as defined in Appendix 7, must assess QTc interval using ***only*** the Fridericia's correction (ie, QTcF) ***either*** as reported by the 12-lead ECG machine *or* QTcF derived using sponsor-provided tool and reported QT and RR intervals.
- In some cases, it may be appropriate to repeat abnormal 12-lead ECG to rule out improper lead placement as contributing to the ECG abnormality; ***as much as practically possible,*** it is important that leads be placed in the same positions each time in order to achieve precise ECG recordings.

8.2.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. Safety assessments include blood chemistry, hematology, urinalysis, UACR, PT, aPTT, INR, HbA1c, and pregnancy test. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. *Note: safety laboratory results from Week 1 visit should be reviewed by the investigator prior to Week 2 dosing for participants dosing Q2W and prior to Week 4 dosing for participants dosing Q4W*. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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 CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease under study, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 12 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or TIMI Hotline.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified as much as possible and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at Screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded and discontinued from study intervention if the serum pregnancy result is positive.

8.2.7. Potential Severe Cases of Hypertriglyceridemia

In certain circumstances, unblinding of TG results may occur during the study. In the event a participant's fasting (see Section 5.3.2) TG is >1000 mg/dL, as reported by the sponsor-identified central laboratory, the investigator and sponsor will receive an alert from the laboratory along with the unblinded TG level. The investigator is to repeat the TG test via the central laboratory, ideally within 7 days of receipt. The investigator should counsel the participant on diet and lifestyle factors to improve the TG level prior to the repeat measurement. For participants with a confirmed TG value of >1000 mg/dL, the investigator will again counsel the participant on diet and lifestyle, and the investigator can titrate the statin dose (if applicable) or can add a medication to lower TG at the investigator's discretion. In only these circumstances (confirmed TG value of >1000 mg/dL), the prohibited TG lowering medications in Section 6.5.1 are not applicable.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 8. Device deficiencies are covered in Section 8.3.8.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant'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 to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE (see Appendix 3) or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 12 weeks, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in

Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

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.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant 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 participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member of healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 21 weeks after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving study intervention or for a minimum of 21 weeks after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The

information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Cardiovascular and death events will be reported according to Adverse Event reporting procedures.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Disease-related events are not applicable to this study.

8.3.8. Adverse Events of Special Interest

Injection site reactions are AESI. In case of acute injection site reactions, the Investigator should institute treatment measures deemed medically appropriate such as topical therapy at the injection site. Such events and treatments are to be captured and reported on the appropriate CRF. If an injection site reaction occurs at more than 1 injection site location, each location should be captured as a separate injection site AE. For each injection site AE, an injection site assessment should be conducted and captured on the CRF. A separate injection site assessment should be conducted for each injection location where an injection site reaction occurs. The site should also complete the injection site reaction assessment and all concomitant treatments should be recorded and captured in the CRF, together with the Adverse Event of injection site reactions. AEs should be reported as serious per the criteria in Section 10.3.2.

Additional AESI include increases in ALT/AST, decreases in platelet count, or decreases in eGFR (as described in Section 7.1.1) that result in a missed dose due to temporary dose interruption or permanent discontinuation.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer only if associated with an SAE (see Section 10.3.1).

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study as the study intervention is supplied in prefilled syringes. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 8.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Sections 8.3.1 through 8.3.4 and Appendix 3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 8.

8.3.9.2. Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the investigator determines that the event meets the protocol definition of a medical device deficiency.

Information will be provided to the sponsor as described in the IP manual. The Medical Device Complaint CRF will also be completed.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in Sections 8.3.1.1 and 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- Injection administered via any route (ie, intramuscular, intravenous) other than SC.
- Injection administered in a location other than upper arm, thigh, or abdomen quadrant.
- For dose regimens requiring 2 injections, both injections administered at the same injection site.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of vupanorsen greater than 320 mg (more than four 80 mg/placebo syringes or more than five 60 mg/placebo syringes) given within a 21-day period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the TIMI Hotline within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until vupanorsen can no longer be detected systemically (at least 5 half-lives [ie, 150 days]).

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the TIMI Hotline based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

For all participants, trough and post-treatment concentrations of vupanorsen in plasma (as total full-length oligonucleotides, including fully conjugated, partially conjugated, and unconjugated vupanorsen) will be determined as specified in the SoA. A listing of individual vupanorsen concentration sorted by treatment group, participant ID, planned visit, visit date and time, and time post the most recent dose will be reported and summarized by treatment with and without stratification by individual immunogenicity status using descriptive statistics. Population PK and PK/PD analyses may be explored using the combined data from this study and other clinical studies of vupanorsen and reported in a separate population analysis report.

Blood samples of approximately 4 mL will be collected in K2 EDTA tubes, to provide a minimum of 2 mL plasma for measurement of plasma concentrations of vupanorsen from participants in a fasted state (see Section 5.3.2). Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of vupanorsen. Each plasma sample will be divided into 2 aliquots. Samples collected for analyses of vupanorsen plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Samples collected for measurement of plasma PK concentrations of vupanorsen will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Drug concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned PK study assessments must be documented and then archived in the sponsor and site study files, but will not constitute a protocol deviation.

8.6. Pharmacodynamics

Serum ANGPTL3 will be measured as the target PD endpoint in this study.

Blood samples of approximately 4 mL, to provide a minimum of 2 mL serum, will be collected for measurement of ANGPTL3 from participants in a fasted state (see Section 5.3.2) as specified in the SoA.

As part of understanding the PD of the study intervention, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PD samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping

conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

ANGPTL3 results will not be reported to investigator sites during the study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

A 4-mL blood sample optimized for DNA isolation (Prep D1) will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and dyslipidemia or CV disease. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Central Laboratory Manual.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.8.1. Banked Biospecimens for Biomarkers

Additional Banked Biospecimens in this study are:

- 6-mL whole blood (Prep B1.5) will be collected and isolate plasma retained.
- 6-mL whole blood (Prep B2.5) will be collected and isolate serum retained.
- 5-mL urine (Prep M4) will be collected and retained.

Banked Biospecimens will be collected as local regulations and IRB/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and dyslipidemia. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in central laboratory manual.

8.9. Immunogenicity Assessments

Immunogenicity of vupanorsen will be assessed before, during, and after treatment. A listing of individual plasma ADA results (including ADA positive, negative, and unknown status

samples and titers) sorted by treatment group, participant ID, planned visit, and the visit date/time will be reported. The incidence (number) and incidence rate (percent) of ADA positive, negative and unknown participants will be summarized by treatment group and planned visit and for the overall study. The ADA positive participants will be further subcategorized into TEADA if the baseline ADA is negative. The incidence and incidence rate of TEADA will be summarized by treatment group and planned visit and for the overall study.

Potential relationships of immunogenicity with selected efficacy, safety, and PK concentrations may be evaluated.

Blood samples of approximately 6 mL will be collected in K2 EDTA tubes, to provide a minimum of 3 mL plasma for determination of ADA as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for determination of ADA may also be used for additional characterization of the immune response or for other internal exploratory purposes. These data will be used for internal exploratory purposes.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

No immunogenicity data will be provided to study sites, blinded personnel, or the study team until the study has been unblinded.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The primary estimand of this study will follow the hypothetical estimand approach to estimate the effect of treatment under the hypothetical condition that all participants maintained their randomized treatment through Week 24. This estimand is meant to estimate the pharmacological effect of the drug when taken as directed. It includes the following 4 attributes:

- Population: Participants with dyslipidemia taking a statin who meet the inclusion/exclusion criteria.
- Variable: The percent change from baseline in non-HDL-C at Week 24.
- Intercurrent event: All off-treatment data (ie, occurring at least 1 dosing interval after discontinuation of treatment), or data collected post treatment of severe hypertriglyceridemia (ie, change in statin dose or addition of TG lowering therapy; Section 8.2.7), if collected, will be excluded from analysis.
- Population-level summary: Difference of variable means between vupanorsen and placebo.

9.2. Sample Size Determination

Assuming a common standard deviation of 17.5% (observed in the Month 6 data of the Phase 2a proof-of-concept and dose-ranging study) for the percent change from baseline in non-HDL-C at Week 24 and a treatment discontinuation rate of 15%, 20 participants per arm will correspond to a 95% CI of point estimate ±11.76% for the difference of treatment effect (versus placebo). These parameters correspond to a power of 91.5% using a 2-sided alpha of 0.05, to detect a difference of -20%, without adjustment for multiple comparison to placebo.

A permutation block schedule will be used in enrollment within each arm, including vupanorsen and matching placebo. If enrollment is stopped for the 160 mg Q2W arm (see Section 4.1), the corresponding matching placebo enrollment will also be stopped.

9.3. Analysis Set

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

Evaluable	All participants who are randomized, take at least 1 dose of study intervention and have baseline measurements and at least 1 post-baseline measurement.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the treatment group they are randomized to unless the wrong study intervention is received throughout the study.

Defined Analysis Set	Description
FAS_Primary	In the evaluable analysis set, for participants who discontinue treatment, all post-discontinuation observations will be censored to missing.
FAS	In the evaluable analysis set, for participants who discontinue treatment, all observations post-discontinuation will be included in the analysis set.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

The primary statistical method of MMRM will apply to continuous endpoints.

Statistical efficacy comparison will be made between each dose of vupanorsen and placebo for primary and secondary endpoints, respectively. Placebo-adjusted LS mean difference, 95% CI, and p-value will be presented. Since this study is exploratory in nature, no multiplicity adjustment of endpoints nor adjustment of multiple comparison to placebo will be made. Sensitivity analyses/supplementary analyses are defined in the SAP. Since the visit after Week 24 is considered safety follow-up, the statistical analyses at those visits will be presented but the p-value will be treated only as nominal.

In addition, a Bayesian E_{max} dose-response model will be estimated to illustrate the expected relationship between doses and their corresponding (percent) change from baseline at Week 24 for primary and key secondary endpoints, respectively. For each endpoint, 95% CI at each studied dose level will also be constructed.

If the baseline value is not available, the last measurement prior to the randomization visit will be used. However, for non-HDL-C and other lipid parameters, the baseline value will be calculated using the average of all values obtained at Screening and on Day 1 prior to dosing, except that for TG, when the initial value is exclusionary, the repeat value after the initial value and Day 1 value will be used to derive the baseline value.

In addition to analyses, summary statistics, listings, and figures will be provided.

9.4.2. Primary Endpoint(s)

The treatment effect of vupanorsen relative to placebo on the mean percent change/reduction from baseline in non-HDL-C at Week 24 will be estimated from the MMRM using the FAS_Primary analysis set, ie, assuming all participants in the analysis maintain their randomized treatments. The LS-mean percent change from baseline at Week 24 along with 95% CI for each treatment group and placebo-adjusted LS-mean at Week 24 along with 95% CI and p-value for each vupanorsen treatment group will be presented.

A Bayesian E_{max} dose-response model will be also be estimated using the FAS_Primary analysis set, incorporating with the prior distribution of the E_{max} model parameters estimated from the Phase 2a study. Sensitivity analyses will also be performed to evaluate the robustness of the primary analysis results (details are covered in the SAP).

9.4.3. Secondary Endpoint(s)

No multiplicity adjustments will be applied to secondary endpoints. All secondary endpoints will be primarily analyzed using the FAS_Primary analysis set.

For continuous secondary endpoints, MMRM analyses will be implemented, with both LS-mean and placebo-adjusted LS-mean along with 95% CI, p-value at Weeks 4, 8, 12, 16, 20, and 24 estimated. The same type of Bayesian E_{max} dose-response model will be estimated using the FAS_Primary analysis set for each of the key secondary endpoints respectively. Sensitivity analyses will also only be performed on key secondary endpoints (details are covered in the SAP).

9.4.4. Tertiary/Exploratory Endpoint(s)

No multiplicity adjustments will be applied. All tertiary/exploratory endpoints will be analyzed using the FAS_Primary analysis set.

For continuous tertiary/exploratory endpoints except for PK, MMRM analyses will be implemented, with both LS-mean and placebo-adjusted LS-mean along with 95% CI, p-value at Weeks 4, 8, 12, 16, and 24 estimated.

Listings of individual vupanorsen PK concentration values will be provided.

9.4.5. Other Safety Analyse(s)

All safety analyses will be performed on the safety population.

From the safety perspective, the following key laboratory endpoints will be explored:

- Change and percent change from baseline in HFF at Week 24
- Change from baseline in eGFR
- Change from baseline in ALT/AST
- Percent change from baseline in UACR
- Percent change from baseline in platelet counts
- Summary of ALT/AST abnormalities
- Summary of confirmed thrombocytopenia

TEAEs, SAEs, death, injection site reactions, ADA, ECGs, vital signs, immunogenicity, and other safety laboratory data, including categorical abnormalities in laboratory data, will be summarized/analyzed, listed, or presented in figures by treatment group or by treatment group and by visit where appropriate. All safety data, including data collected post the occurrence of intercurrent events, will be reported.

9.4.5.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and visit.

The number (%) of participants with maximum post-dose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc Assessment			
Degree of Prolongation	**Mild (msec)**	**Moderate (msec)**	**Severe (msec)**
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

9.4.6. Other Analyses

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

The population PK analysis will be performed using vupanorsen concentration data pooled from this study and previous studies and may be reported separately from the main CSR. Exploratory PK/PD analyses may also be performed for further characterization of biomarker and efficacy effects, eg, ANGPTL3, non-HDL-C, and TG levels.

9.5. Interim Analyses

An interim analysis will be performed to assess efficacy and safety. The interim analysis will take place approximately 16 weeks after 50% of the planned participants (ie, approximately 110 participants), with the exception of the 160 mg Q2W group, are randomized. Interim analysis results, which will include all available data from enrolled participants at the time of data cutoff, may be used for internal business decisions regarding future study planning or adapting the study after the interim analysis. Before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in a DMC charter. In addition, the analysis details must be documented and approved in an interim analysis SAP or the finalized SAP.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an E-DMC. The E-DMC is independent of the study team and includes only external members. The E-DMC charter describes the role of the E-DMC in more detail.

The E-DMC will be responsible for ongoing, unblinded monitoring of the efficacy and safety of participants in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

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 CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor 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/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks

associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for

determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring),

methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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 ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are 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.

Definition of what constitutes source data can be found in the Study Monitoring Plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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 upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/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 participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor and academic leadership 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any

study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, the coordinating investigator will be TIMI Study Group.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation/study portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following clinical laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Clinical Chemistry Panel	Hematology Panel	Urinalysis	Lipid Panel
• Sodium • Potassium • Chloride • Bicarbonate • Total protein • Albumin • Calcium • Magnesium • Glucose • BUN • Creatinine • eGFR based on CKD-Epi • Uric acid • Total bilirubin • Direct (conjugated) bilirubin • Indirect (unconjugated) bilirubin • AST • ALT • Alkaline phosphatase	• Red blood cells • Hemoglobin • Hematocrit • MCV, MCH, MCHC • Platelets • WBC differential (% and absolute) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	• Routine urinalysis - Color - Appearance - Specific gravity - pH - Protein - RBC - Glucose - Ketones - Bilirubin - Urobilinogen - Leukocyte esterase - Nitrate • Microscopic examination (reflex testing based on urinalysis results) • A/C ratio (UACR)	• Total cholesterol • LDL cholesterol – direct measurement • HDL cholesterol • Non-HDL cholesterol • Triglycerides • VLDL cholesterol – direct measurement
Extended Lipoprotein Panel, FFA	**Coagulation**	**Pharmacokinetics**	**Immunogenicity**
• Lp(a) • ApoB • ApoB-48 • ApoB-100 • ApoC-III • ApoA-I • FFA	• aPTT (sec) • PT (sec) • INR	• Vupanorsen concentration in plasma	• Anti-vupanorsen antibodies in plasma
PD	**Inflammatory**	**Other**	
• ANGPTL3	• hsCRP	• FSH[a] • Pregnancy test (β-hCG), urine and serum[b] • HbA1c	

a. For confirmation of postmenopausal status only.
b. For female participants of childbearing potential.

Investigators must document their review of each laboratory safety report.

Lipid panel results, extended lipoprotein panel results, and inflammatory results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

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 patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • 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 study intervention.

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  • Is associated with accompanying symptoms.
  • Requires additional diagnostic testing or medical/surgical intervention.
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
• New conditions detected or diagnosed after study intervention 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 study intervention 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.
• The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per Section 8.3.8.1. Also, “lack of efficacy” or “failure of expected pharmacological action” does not constitute an AE or SAE.

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 participant'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 participant's condition. • Medical or surgical procedure (eg, 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, 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:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant 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 preexisting condition that did not worsen from baseline is not considered an AE.
d. 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. 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 participant or may require medical or surgical intervention to prevent one 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.

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- 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 investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention 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 study intervention 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 sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- 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 one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an

assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

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 sponsor 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 healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

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

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the highest dose of vupanorsen planned for this study would result in maternal systemic exposures via seminal transfer well below (>5000-fold) the exposure at the NOAEL for developmental toxicity in nonclinical studies, including the conservative assumptions that an ASO ejaculate:sperm ratio would be 1 and there is 100% uptake by the partner.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3)

  OR

- Is a WOCBP and using an acceptable contraceptive method as described in Section 10.4.4 during the intervention period (for a minimum of 21 weeks after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

1. 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, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a

     - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

     - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen 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.

10.4.4. Contraception Methods

Contraceptive use by women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials. Women participants considered of childbearing potential must use at least one of the following acceptable contraception methods:

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;
    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to vupanorsen or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for banking will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator for study participants, users, and other persons. This definition also includes events considered related to procedures for study participants only. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect

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

An SAE is an AE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time

of the event. It does not refer to an event, that hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization, planned hospitalization for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
SADE Definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.8.4. Recording/Reporting and Follow-up of AEs and/or SAEs and Device Deficiencies

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the IP manual and completing the Medical Device Complaint CRF.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- 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.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- 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 study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.

- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency 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 sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- 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 one of the criteria used when determining regulatory reporting requirements

Follow-up of AE/SAE/Device Deficiency

- 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 sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.8.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.8.6. Reporting of SADEs

SADE Reporting to Pfizer Safety

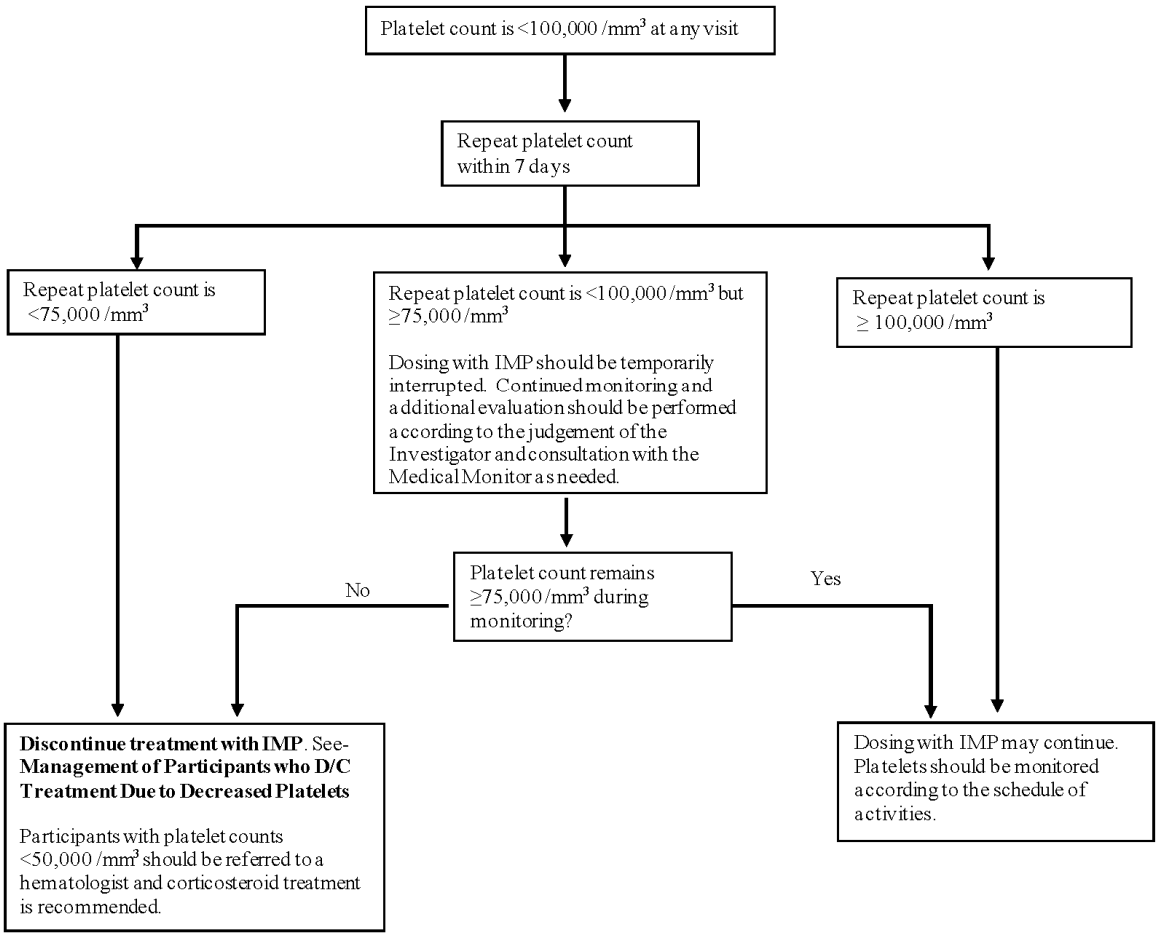
NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.9. Appendix 9: Country-specific Requirements

Not applicable.

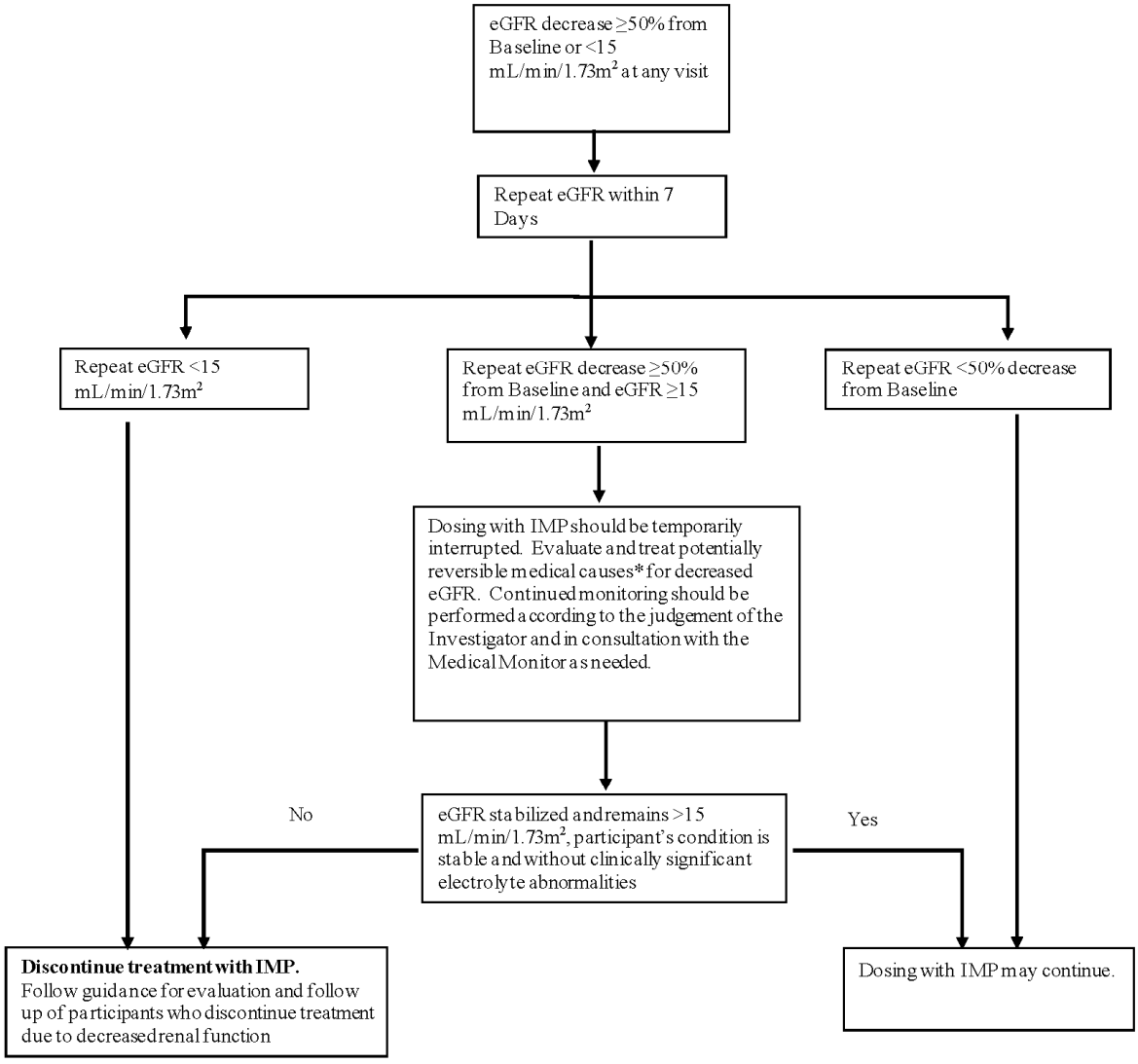
10.10. Appendix 10: Evaluation of Participants with Decreased Platelet Count



Management of Participants who D/C Dosing Due to Decreased Platelets: The PI should obtain a history and physical to evaluate for potential causes of thrombocytopenia such as concomitant medications (eg heparin), intercurrent illnesses, and evidence of bleeding.

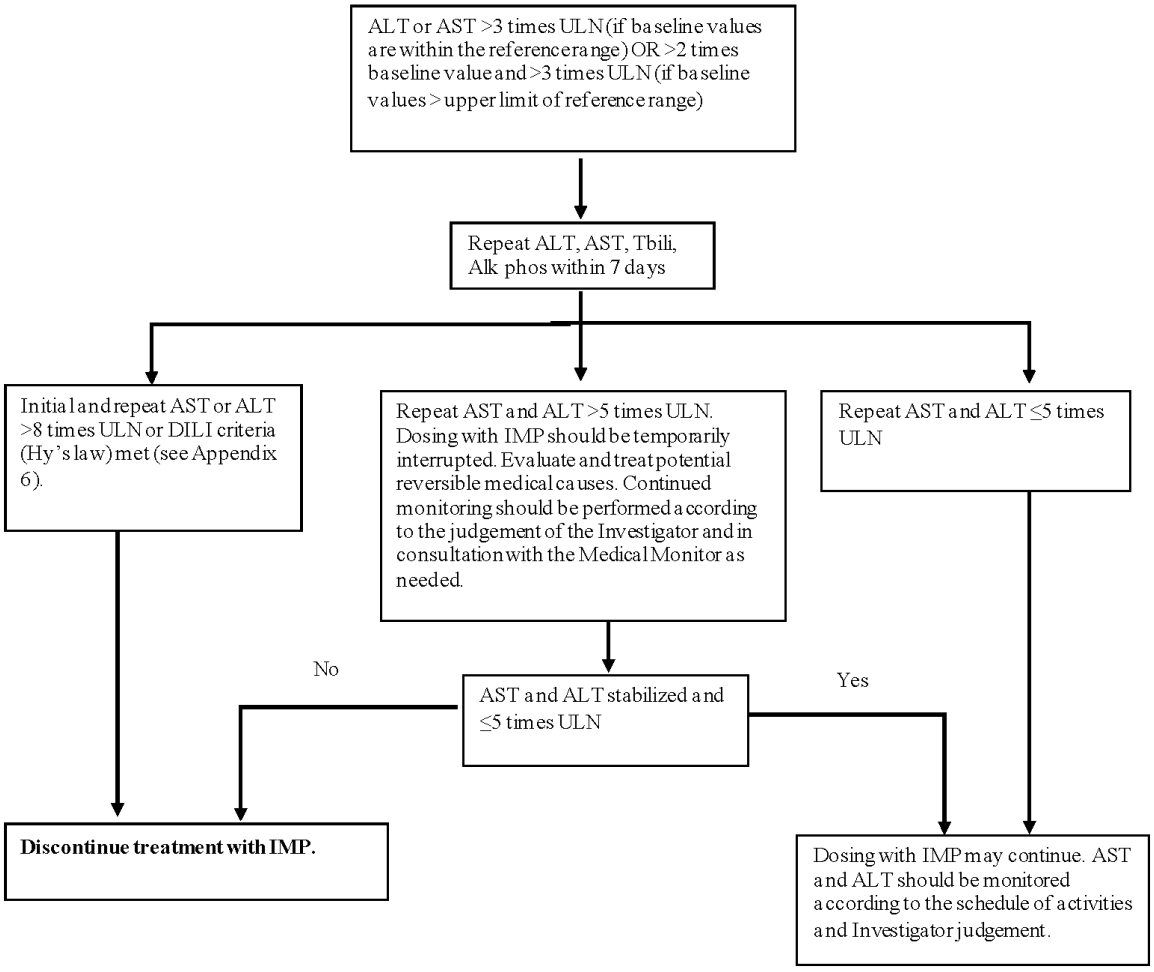
The PI should obtain CBC with platelets, blood smear, electrolytes, renal and liver function, fibrinogen degradation products, PT, aPTT. Consider obtaining viral serologies for EBV, HIV, hepatitis A, B, C, CMV, mumps, varicella, or rubella in susceptible or symptomatic individuals. Other evaluations may be obtained as indicated. Samples for PK and ADA should be obtained. Platelet counts should be monitored according to the judgment of the Investigator and in consultation of the Medical Monitor until platelet counts stabilize.

10.11. Appendix 11: Evaluation of Participants with Worsening Renal Function



*Potential causes to consider (not inclusive): concurrent use of NSAIDS, antibiotics, or other medications known to effect eGFR; volume depletion; urinary tract infection or obstructive uropathy.

10.12. Appendix 12: Management of Elevated AST or ALT



10.13. Appendix 13: Alternative Measures During Public Emergencies

The alternative study measures described in this section may be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer. This appendix is not intended for use during screening.

Consult with the site monitor prior to utilizing this appendix.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.13.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. Participants with active infections are excluded from study participation as per Exclusion Criterion 9 (other medical condition or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study). When the infection resolves, the participant may be considered for re-screening if the participant has not been randomized.

10.13.2. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. **If the participant does not allow blood draws for laboratory assessments, the participant will be discontinued from study intervention.** The following may be performed during a home health visit:

- Obtain vital signs (seated blood pressure and pulse rate).
- Obtain weight.
- Draw blood for laboratory assessments. (See Section 10.13.4.1 and Section 10.13.7).
- Collect urine specimen for laboratory assessments. (See Section 10.13.4.1).
- Perform 12-lead ECG.
- Review and record study intervention, including compliance (review dosing diary, if available) and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing, if applicable. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 regarding pregnancy tests.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.13.3. Telehealth Visits

In the event that in-clinic study visits or home health visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. **If the participant does not allow blood draws for laboratory assessments, the participant will be discontinued from study intervention.** Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing, if applicable. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.13.4. Alternative Facilities for Safety Assessments

10.13.4.1. Laboratory Testing

All specimen collections under this appendix will be performed by home health care and will be processed in the central laboratory. It is preferred that participants utilize home health care for safety and efficacy laboratory evaluations. Use of local laboratories will be allowed only if on site or home health care measures cannot be used. If a study participant is unable to visit the site or have home health utilized for protocol-specified laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and

certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing or engage in home health care, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.13.4.2. Imaging

If the participant is unable to visit the study site for MRI-PDFF assessment, the participant may visit an alternative facility to have the MRI-PDFF assessment performed. Qualified study site personnel must order, receive, and review results.

10.13.4.3. Electrocardiograms

All 12-lead ECG assessments under this appendix will be performed by home health care. Qualified study site personnel must order, receive, and review results.

10.13.5. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Study intervention may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments and the chain of custody of study intervention must be kept in the participant's source documents/medical records.

If in-home dosing is instituted, a dosing diary will be provided to the participant for documenting compliance. The dosing diary should be returned to the site for review as soon as possible.

The following is recommended for the administration of study intervention for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection:

- For symptomatic participants with active SARS-CoV2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.

- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered for a minimum of 72 hours. Notify the study team when treatment is restarted.

- Continue to record any concomitant medication administered for treatment of SARS-CoV2 infection.

10.13.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided per standard process. If a participant has positive COVID-19 (SARS-CoV2) test, even if asymptomatic, this should be recorded as an AE (see Section 8.3).

Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.13.7. Efficacy Assessments

There will be no alternative measures for efficacy assessments other than what is in the protocol, Section 8.1. It is preferred that participants utilize home health care for efficacy laboratory evaluations. Use of local laboratories will be allowed only if on site or home health care measures cannot be used. If a study participant is unable to visit the site or have home health utilized for protocol-specified laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations.

10.13.8. Independent Oversight Committees

The External Data Monitoring Committee will be informed when this appendix has been utilized.

10.14. Appendix 14: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
A/C	albumin/creatinine
ADA	anti-drug antibodies
ADE	adverse device effect
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANGPTL3	angiopoietin-like protein 3
ApoA	apolipoprotein A
ApoB	apolipoprotein B
ApoC	apolipoprotein C
aPTT	activated partial thromboplastin time
ASCVD	atherosclerotic cardiovascular disease
ASGPR	asialoglycoprotein receptor
ASO	anti-sense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
bpm	beats per minute
BL	baseline
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-Epi	Chronic Kidney Disease-Epidemiology Collaboration
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	corona virus disease 19
CRF	case report form
CRO	contract research organization
CS1	clinical study 1
CS2	clinical study 2
CSR	clinical study report
CT	clinical trial
CV	cardiovascular
DILI	drug-induced liver injury
DMC	data monitoring committee
DU	dispensable unit
E-DMC	external data monitoring committee

Abbreviation	Term
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
E_{max}	maximal effect
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FFA	free fatty acids
FSH	follicle-stimulating hormone
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HFF	hepatic fat fraction
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IDL	intermediate density lipoproteins
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology
ISO	International Organization for Standardization
IWR	interactive web-based response
K2	dipotassium
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
LLN	lower limit of normal
Lp(a)	lipoprotein(a)

Abbreviation	Term
LS	least squares
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMRM	Mixed Model Repeated Measurements
MOE	methoxyethyl
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
msec	millisecond
n	number
N/A	not applicable
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
Non-HDL-C	non-high-density lipoprotein cholesterol
PDFF	proton density fat fraction
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PVC	premature ventricular contraction/complex
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
QW	every week
Q2W	every 2 weeks
Q4W	every 4 weeks
RBC	red blood cells
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TE	treatment-emergent
TEADA	treatment-emergent anti-drug antibodies
TEAE	treatment-emergent adverse event
TG	triglyceride(s)

Abbreviation	Term
TIMI	Thrombolysis in Myocardial Infarction
T2DM	type 2 diabetes
T_{max}	time to reach C_{max}
UACR	urine albumin: creatinine ratio
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
VLDL	very low-density lipoproteins
VLDL-C	Very low-density lipoprotein cholesterol
WBC	white blood cell
WOCBP	woman of childbearing potential

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