A PHASE 1, RANDOMIZED, OPEN-LABEL, SINGLE DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND TOLERABILITY OF VUPANORSEN ADMINISTERED SUBCUTANEOUSLY TO HEALTHY CHINESE ADULTS

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Short Title: A Phase 1 Study To Investigate The Pharmacokinetics, Pharmacodynamics, Safety And Tolerability Of Single Dose Vupanorsen In Healthy Chinese Adults

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	28 August 2020	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 Study To Investigate The Pharmacokinetics, Pharmacodynamics, Safety And Tolerability Of Single Dose Vupanorsen In Healthy Chinese Adults.

Rationale

The purpose of the study is to investigate the pharmacokinetics, pharmacodynamics, safety and tolerability of vupanorsen following 80 and 160 mg single subcutaneous dose in healthy Chinese adults. Results from this study will be used to inform clinical development of vupanorsen in China and to support China registration of vupanorsen.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the PK of vupanorsen following 80 and 160 mg single subcutaneous dose in healthy Chinese adults.	• Vupanorsen plasma PK parameters: AUC_{24h}, AUC_{48h}, AUC_{last}, C_{max}, AUC_{inf}, T_{max}, $t_{½}$, CL/F and Vz/F, as data permit.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of vupanorsen following 80 and 160 mg single subcutaneous dose in healthy Chinese adults. • To characterize the PD effects of vupanorsen following 80 and 160 mg single subcutaneous dose in healthy Chinese adults.	• AEs, clinical safety laboratory tests (serum chemistry, hematology, urinalysis, coagulation), vital signs (BP, PR), physical examination findings, 12-lead ECGs. • Percentage change from baseline in ANGPTL3 on Day 2, Day 3, Day 8, Day 15, Day 30, Day 60 and Day 90. • Percentage changes from baseline in Lipid Panel on Day 2, Day 3, Day 8, Day 15, Day 30, Day 60 and Day 90, including fasting TG, LDL-C, HDL-C, VLDL-C, non-HDL-C, and TC. • Percentage changes from baseline in ApoA-I, ApoB total (including

	ApoB-48, ApoB-100), and ApoC-III on Day 15, Day 60, and Day 90.

Overall Design

This is a Phase 1, randomized, parallel-cohort, open-label study to characterize the PK, PD, safety and tolerability of vupanorsen following 80 mg and 160 mg single subcutaneous dose in healthy Chinese adults with fasting triglyceride ≥90 mg/dL.

Number of Participants

Approximately 18 participants will be enrolled in this study (N=9 for each cohort) with the goal of attaining approximately 8 evaluable participants in each cohort for a total of 16 evaluable participants.

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, unless otherwise specified by the protocol.

Intervention Groups and Duration

The total duration of participation in this study is approximately 118 days, including a screening period of up to 28 days to confirm eligibility and a follow-up period of approximately 90 days. Eligible participants will progress to admission to the clinical research unit on Day -1 for a 4-day (3-night) inpatient stay. Participants enrolled will receive a single 80 mg (cohort 1) or 160 mg (cohort 2) subcutaneous dose of vupanorsen on Day 1. Following discharge on Day 3, participants will return for an on-site post-treatment evaluation on Days 8, 15, 30, 60 and 90.

Participants who discontinue prior to completion of the study for non-safety related reasons may be replaced, at the discretion of the principal investigator and sponsor study team.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

There is no statistical hypothesis for this study, therefore, the study sample size is not based on statistical decision rule. The sample size has been chosen based on the need to minimize exposure to humans of a new chemical entity and to fulfill the NMPA requirement for a PK study to support the registration in China. Considering the possibility of participant dropouts/withdrawals, approximately 18 participants (N=9 per each cohort) will be enrolled to ensure approximately 16 participants (N=8 per each cohort) will be evaluable for the primary endpoint.

Plasma PK parameters and plasma concentrations of vupanorsen will be listed and summarized descriptively. Percentage changes from baseline in PD assessments will be summarized using descriptive statistics. Safety and tolerability data will be presented in tabular and/or graphical format and summarized descriptively.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

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.

Visit Identifier Abbreviations used in this table may be found in Appendix 7.	**Screening**	**Single Dose and Post-Treatment Evaluation/Early Termination**								
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 15**	**Day 30**	**Day 60**	**Day 90/ET**
Visit Window (days)	**-**	**0**	**0**	**0**	**0**	**±1**	**±2**	**±2**	**±2**	**±5**
Hours After Dose	-	-	0	24	48					
Informed consent	X									
CRU confinement		X	→	→	X					
Inclusion/exclusion criteria	X	X								
Medical/medication history (update)	X	X								
Physical exam (including height and body weight at Screening only)[b]	X	X								
Safety laboratory (≥10-hour fasting) (hematology, chemistry, urinalysis, coagulation)	X	X		X[c]	X	X	X	X	X	X
Lipid panel[d]	X		X[f]	X[c]	X	X	X	X	X	X
Extended lipoprotein panel[e]			X[f]				X		X	X
Demography	X									
Pregnancy test (WOCBP only)	X	X						X	X	X
Contraception check	X	X				X	X	X	X	X
FSH[g]	X									
Urine drug testing	X	X								
12-Lead ECG	X		X[h]	X[c]			X			X
Blood pressure and pulse rate	X		X[h]	X[c]	X	X	X			X
HIV, HBsAg, HCVAb, syphilis test	X									
Study intervention administration			X[i]							
Pharmacokinetic blood sampling[j]			X	X	X	X	X	X	X	X
Pharmacodynamic blood sampling (ANGPTL3)			X[f]	X[c]	X	X	X	X	X	X

Visit Identifier Abbreviations used in this table may be found in Appendix 7.	**Screening**	**Single Dose and Post-Treatment Evaluation/Early Termination**								
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 15**	**Day 30**	**Day 60**	**Day 90/ET**
Visit Window (days)	**-**	**0**	**0**	**0**	**0**	**±1**	**±2**	**±2**	**±2**	**±5**
Hours After Dose	-	-	0	24	48					
CRU discharge					X					
Serious and nonserious adverse event monitoring	X	→	→	→	→	X	X	X	X	X

a. Day relative to start of study intervention (Day 1).
b. A full physical examination may be done at screening or Day -1; otherwise brief physical exam envisioned for findings during previous PE or new/open AEs, at Investigator discretion.
c. 24 hours post-dose.
d. Lipid panel should be obtained with participants in a fasted state (≥10-hour fasting as mentioned in Section 5.3.1). Lipid panel includes TG, non-HDL-C, direct LDL-C, TC, HDL-C, direct VLDL-C.
e. Extended lipoprotein panel should be obtained with participants in a fasted state (≥10-hour fasting as mentioned Section 5.3.1). Extended lipoprotein panel includes ApoB, ApoB-48, ApoB-100, ApoC-III, and ApoA-I.
f. Pre-dose.
g. FSH in females amenorrhoeic ≥12 months, only.
h. Pre-dose and 4 hours post dose.
i. Participants should be monitored for a minimum of 2 hours after administration of vupanorsen to assess injection site reaction.
j. Refer to Pharmacokinetic Sampling Timepoints.

Pharmacokinetic Sampling Timepoints

Visit Identifier	**Single Dose and Post-Treatment Evaluation**																
Study Day	**1**										**2**	**3**	**8**	**15**	**30**	**60**	**90**
Hours Before/After Dose	**0**[a]	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**48**	**-**	**-**	**-**	**-**	**-**
Sampling Window	-	±10%	±10%	±10%	±10%	±10%	±10%	±10%	±10%	±1 hr	±1 hr	±1 hr	±1 day	±2 days	±2 days	±2 days	±5 days
Study intervention administration	X																
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Pre-dose sample collection.

2. INTRODUCTION

PF-07285557 (vupanorsen) is a second-generation 2'-MOE ASO drug targeted to human ANGPTL3 mRNA that has been covalently bonded to triantennary GalNAc. Vupanorsen is being developed for CV risk reduction and for TG lowering in patients with severe HTG.

2.1. Study Rationale

The purpose of the study is to investigate the pharmacokinetics, pharmacodynamics, safety and tolerability of vupanorsen following 80 and 160 mg single subcutaneous dose in healthy Chinese adults. Results from this study will be used to inform clinical development of vupanorsen in China and to support China registration of vupanorsen.

2.2. Background

Dysregulation of lipid metabolism is closely linked to a number of pathophysiological states including atherosclerosis, obesity, and insulin resistance. Despite effective LDL-C lowering therapies (eg, statins, ezetimibe and PCSK9 inhibitors), considerable residual risk for CVD remains. Emerging evidence suggests that TG and/or the cholesterol content within TG-rich lipoproteins may be important contributors to residual risk and may represent viable targets of therapy.

Vupanorsen is a second-generation 2'-MOE modified ASO drug targeted to ANGPTL3 that has been covalently bonded to triantennary GalNAc, a high affinity ligand for the hepatocyte-specific ASGPR. This GalNAc-conjugate approach results in enhanced ASO delivery to hepatocytes versus non-parenchymal cells and has increased ASO potency by approximately 10-fold in mice[1] compared to unconjugated ASOs. The ASO portion of vupanorsen binds to the ANGPTL3 mRNA by Watson-Crick base pairing and results in RNase H1-mediated degradation of the ANGPTL3 mRNA, thus preventing production of the ANGPTL3 protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues.[2,3] Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

ANGPTL3 is primarily synthesized and secreted by the liver and is a member of the angiopoietin-like family of proteins that binds reversibly to inhibit LPL and decrease the hydrolysis of TG in chylomicrons and VLDL.[4,5] Mice deficient in ANGPTL3 have very low plasma TG and cholesterol levels, while over-expression produces the opposite effects.[5,6,7] Human genetic studies have shown that carriers of ANGPTL3 LOF alleles have reduced concentrations of TG, LDL-C, HDL-C, VLDL-C, ApoB and ApoC-III.[4,8,9,10,11,12] Additionally, sequencing of large epidemiological cohorts revealed that heterozygous carriers of ANGPTL3 LOF mutations have a 30-40% reduced risk of coronary artery disease.[13,14] Taken together these data indicate that inhibiting ANGPTL3 by an ASO approach could represent a promising therapeutic strategy to improve CV outcomes.

2.2.1. Nonclinical Overview

Detailed information concerning the nonclinical studies conducted with ANGPTL3 ASOs can be found in the current IB.

2.2.2. Clinical Overview

As of 01 April 2020, 4 clinical studies have been completed where a total of 160 participants have received study treatment with vupanorsen or placebo; of these, 48 were healthy participants, 105 were participants with HTG, T2DM, and NAFLD, 3 were participants with FCS, and 4 were participants with FPL.

Detailed information concerning the clinical studies conducted with vupanorsen can be found in the IB.

A Phase 1 study (C4491006) to investigate the safety, tolerability, PK and PD of single doses of 80 mg and 160 mg of vupanorsen in Japanese healthy adult participants with elevated triglycerides has been planned, and the results are expected in 2021.

2.2.2.1. Clinical Pharmacokinetics

Concentrations of total full-length oligonucleotide (reported as vupanorsen equivalent) in human plasma were determined by a validated hybridization method with ECL detection. Total full-length oligonucleotides 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.

2.2.2.1.1. PK in Healthy Participants (Study CS1)

Plasma PK determined from intensive PK sampling following 20 to 120 mg of vupanorsen SC injection in the SAD (Day 1) and 10 to 60 mg QW MAD (Days 1 and 36) cohorts in healthy participants (Study CS1) are summarized in the current IB.

Following single-dose or multiple-dose SC administration, vupanorsen was absorbed 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 that dominated the plasma clearance, followed by a slower elimination phase with $t_{½}$ of 3 to 5 weeks in general. The geometric mean C_{max} and AUC increased approximately dose proportionally from 20 to 120 mg after a single dose, and from 10 to 60 mg after single and multiple QW dosing. No apparent accumulation of C_{max} or AUC was observed after 6 weeks of QW doses. Plasma trough concentrations in the MAD cohorts indicated that steady state had not been reached after 6 weeks, consistent with the observed long half-life of the drug. Urinary excretion of total full-length ASO within the first 24 hours was <1% of administered dose after single and multiple SC doses of vupanorsen.

2.2.2.1.2. PK in Participants with HTG, T2DM and NALFD (Study CS2)

Vupanorsen PK profiles were evaluated in a subset of CS2 study in participants with HTG, T2DM, and NAFLD. 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.

2.2.2.2. Clinical Pharmacodynamics

In the Phase 1 Study CS1, results from the SAD portion of the study showed dose dependent reductions in mean levels of serum ANGPTL3 protein at Day 15 (reductions of 5.5% to 80.2% for 20 to 120 mg). After 6 weeks of QW treatment, participants in the multiple-dose groups showed time- and dose-dependent reductions in mean levels of serum ANGPTL3 protein. The mean reductions of serum ANGPTL3 from baseline at Day 43 were 46.6% to 84.5% for 10 to 60 mg QW, ($P < 0.01$ for all doses versus placebo).

PD was evaluated in a Phase 2a study (Study CS2) in participants with HTG, T2DM, and NAFLD. The maximum lowering of the circulating ANGPTL3 protein was observed at vupanorsen 80 mg Q4W (reductions of 62% from baseline), with a similar effect at vupanorsen 20 mg QW (reductions of 59% from baseline) and smaller effect at vupanorsen 40 mg QW (reductions of 45% from baseline).

2.2.2.3. Clinical Safety

As of 01 April 2020, in completed studies, 121 participants have been treated with vupanorsen. Overall, vupanorsen was well tolerated as either single SC injections of 20, 40, 80 and 120 mg or multiple SC injections of 10, 20, 40 or 60 mg weekly (QW) for 6 weeks in the Phase 1 study, and in the Phase 2a study as 40 mg Q4W, and 80 Q4W, and 20 mg QW for 26 weeks.

2.2.2.3.1. Safety in Healthy Participants (Study CS1)

A total of 16 participants were randomized and treated in the single dose cohorts. There were no SAEs or discontinuations due to AEs. All AEs were mild in severity. There were no AEs reported related to platelets, transaminase increases, or injection site reactions. One participant in the vupanorsen 40 mg SC group had AEs of bilirubin increased and unconjugated bilirubin increased, considered possibly related to study drug by the investigator.

A total of 32 participants were randomized and treated in the multiple dose cohorts. No deaths or SAEs were reported and no AEs or TEAEs led to study treatment discontinuation. There were no severe TEAEs; the majority of reported TEAEs were mild in severity. There were no platelet related AEs (changes in platelet counts or thrombocytopenia) and no events involving inflammation (inflammatory markers or flu-like reactions). There were no clinically relevant changes in urinalysis and or urine protein. There were 2 participants with elevated ALT in the 60 mg QW dose cohort. These changes were reversible and both

participants completed study treatment and the increase in ALT was not associated with clinical symptoms or other laboratory abnormalities. Erythema and pruritus at the injection site were reported several times for a single participant. However, no local cutaneous reactions at the injection site were reported.

There were no platelet-related AEs and no events involving inflammation (inflammatory markers or flu-like reactions). There were no clinically relevant changes in hematology (no evidence of prothrombotic effects, or significant decreases in platelet count or thrombocytopenia), urinalysis, inflammatory markers, ECG, or vital signs and no bleeding episodes reported.

2.2.2.3.2. Safety in Participants with HTG, T2DM, and NAFLD-(Study CS2)

During the treatment period, a total of 65 (83.3%) participants in the vupanorsen treatment groups combined and 16 (59.3%) participants in the placebo treatment group experienced at least 1 AE. SAEs occurred in 4 (5.1%) participants in the pooled vupanorsen treatment groups and 1 (3.7%) participant in the placebo group. None of the SAEs were considered treatment related.

AEs resulting in permanent discontinuation from treatment occurred in 6 (7.7%) participants in the vupanorsen treatment groups. No AEs resulting in discontinuation occurred in the placebo group. The AEs resulting in treatment discontinuation were injection site reactions (4 participants - 1 participant each in the vupanorsen 40 mg Q4W and 80 mg Q4W treatment groups and 2 participants in the vupanorsen 20 mg QW treatment group), transaminases increased (1 participant in the vupanorsen 20 mg QW treatment group), and dehydration and acute prerenal failure (1 participant in the vupanorsen 80 mg Q4W treatment group reporting both AEs).

AEs occurring more frequently in the vupanorsen treatment groups were injection site pruritus, injection site erythema, pharyngitis, and hyperglycemia. There was 1 AE of thrombocytopenia (verbatim term: intermittent thrombocytopenia), mild in severity, reported in a participant in the vupanorsen 20 mg QW treatment group. No participant had a confirmed platelet count below 100,000 /mm^3. Two (7.7%) participants, both in the vupanorsen 20 mg QW group, had elevations in ALT >3 times but <5 times the ULN. These elevations were not associated with an increase in bilirubin or liver-related symptoms. Increases in mean AST and ALT from baseline to Week 25 were observed in all the vupanorsen treatment groups. The increases in AST and ALT were greatest in the vupanorsen 80 mg Q4W group. One (3.7%) participant in the placebo group, 1 (3.8%) participant in the vupanorsen 80 mg Q4W and 1 (3.8%) participant in the 20 mg QW group, had decline in eGFR by >25% from baseline. There were no notable differences between treatment groups in participants with new onset hematuria or proteinuria.

Safety and tolerability in Studies CS3 (participants with Familial Chylomicronemia Syndrome) and CS5 (participants with Familial Partial Lipodystrophy Syndrome) are summarized in the IB.

2.3. Benefit/Risk Assessment

A single dose of vupanorsen is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, pharmacokinetic and pharmacodynamic data for further clinical development.

Vupanorsen has been administered as single doses and repeated doses in healthy adults and patients with hypertriglyceridemia, T2DM, and NAFLD. It has been observed to be well-tolerated with an acceptable safety profile at single subcutanous doses as high as 120 mg and weekly repeated, subcutanous doses of up to 60 mg for a duration of up to 6 weeks.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of vupanorsen may be found in the investigator's brochure, which is the SRSD for this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the PK of vupanorsen following 80 and 160 mg single subcutaneous dose in healthy Chinese adults.	• Vupanorsen plasma PK parameters: AUC_{24h}, AUC_{48h}, AUC_{last}, C_{max}, AUC_{inf}, T_{max}, $t_{½}$, CL/F and Vz/F, as data permit.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of vupanorsen following 80 and 160 mg single subcutaneous dose in healthy Chinese adults. • To characterize the PD effects of vupanorsen following 80 and 160 mg single subcutaneous dose in healthy Chinese adults.	• AEs, clinical safety laboratory tests (serum chemistry, hematology, urinalysis, coagulation), vital signs (BP, PR), physical examination findings, 12-lead ECGs. • Percentage change from baseline in ANGPTL3 on Day 2, Day 3, Day 8, Day 15, Day 30, Day 60 and Day 90. • Percentage changes from baseline in Lipid Panel on Day 2, Day3, Day 8, Day 15, Day 30, Day 60 and Day 90, including fasting TG, LDL-C, HDL-C, VLDL-C, non-HDL-C, and TC. • Percentage changes from baseline in ApoA-I, ApoB total (including ApoB-48, ApoB-100), and ApoC-III on Day 15, Day 60 and Day 90.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, parallel-cohort, open-label study to characterize the PK, PD safety and tolerability of vupanorsen following 80 mg and 160 mg single subcutaneous dose in healthy Chinese adults with fasting triglyceride ≥ 90 mg/dL. Approximately 18 participants will be enrolled in this study (N=9 for each cohort) with the goal of attaining approximately 8 evaluable participants in each cohort for a total of 16 evaluable participants.

The total duration of participation in this study is approximately 118 days, including a screening period of up to 28 days to confirm eligibility and a follow-up period of approximately 90 days. Eligible participants will progress to admission to the clinical research unit on Day -1 for a 4-day (3-night) inpatient stay. Participants enrolled will receive a single 80 mg (cohort 1) or 160 mg (cohort 2) subcutaneous dose of vupanorsen on Day 1. Following discharge on Day 3, participants will return for an on-site post-treatment evaluation on Days 8, 15, 30, 60 and 90.

Participants who discontinue prior to completion of the study for non-safety related reasons may be replaced, at the discretion of the principal investigator and sponsor study team.

4.2. Scientific Rationale for Study Design

This study is the first clinical study with vupanorsen in the Chinese population. The purpose of the study is to characterize the PK, PD, safety and tolerability of vupanorsen following 80 mg and 160 mg subcutaneous dose in healthy male and female Chinese participants.

There is no expected significant PK difference between Chinese and Westerners because uptake/efflux-transporters, oxidative metabolism and conjugation, which may cause ethnic differences, are not involved in the disposition of ASOs. PK and PD parameters generated from this study will be compared with results from the global studies to further evaluate the impact of ethnicity/race on the PK/PD of vupanorsen.

Single-dose rather than repeated dosing is planned in the study as the steady-state PK and PD can be well predicted from single dose data, especially given that after QW multiple SC doses, the C_{max} and AUC increased approximately dose proportionally, and no apparent accumulation of C_{max} or AUC was observed. In terms of safety and tolerability, vupanorsen was well-tolerated with an acceptable safety profile at single doses up to 120 mg, and weekly repeated doses of up to 60 mg for 6 weeks in healthy participants in study CS1, and after repeated doses up to 80 mg per month (either 80 mg Q4W or 20 mg QW) for 6 months treatment duration in study CS2. The safety and tolerability of vupanorsen was consistent after single- and multiple-dose treatments except for the late onset of ADA (a median onset of 5.5 months) after multiple doses with no apparent impact on efficacy and safety, which is consistent with other ASOs in the same class. Moreover, considering the long terminal plasma half-life of vupanorsen in humans (3 to 5 weeks) and it will take approximately 21 weeks of vupanorsen dosing to reach steady-state, single-dose is planned to minimize the exposure duration of healthy participants to a new chemical entity.

The study duration and frequency of each assessment were decided based on information from previous studies. It was considered that 90 days are the necessary period to allow adequate characterization of terminal $t_{½}$ of vupanorsen to be eliminated. Sample collection points for PK were selected based on the results of PK profiles in Studies CS1 and CS2.

Serum ANGPTL3 and other lipid PD markers will be evaluated to confirm the target engagement of vupanorsen and the consistency with the results in Studies CS1 and CS2.

Vupanorsen has an unlikely risk of human teratogenicity/fetotoxicity. Participants who are WOCBP must use an acceptable contraceptive method (see Appendix 4). Also, the potential risk of exposure to vupanorsen in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is required (see Appendix 4). The calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[15]

4.3. Justification for Dose

The proposed single SC dose levels are 80 mg and 160 mg. These doses are selected based on the safety and tolerability in Studies CS1 and CS2, and the dosages for the Phase 2b study that is planned in patients with dyslipidemia (Study C4491011). In Study C4491011, the safety and efficacy of a dose range of 80 mg Q4W to 160 mg Q2W will be evaluated. Based on the simulation results using a preliminary population PK-PD model developed from the combined data in Studies CS1 and CS2, vupanorsen 80 mg Q4W is expected to be a minimal efficacious dose in non-HDL-C reduction, and to bridge the data from previous studies. Vupanorsen 160 mg Q2W is expected to achieve a >90% probability of a ≥35% mean reduction in non-HDL-C, in addition to maximizing ANGPTL3 and TG reductions. Thus, 80 mg and 160 mg are selected as the proposed dose level in the current study to cover the potential range of Phase 3 doses (lowest to highest) per dose.

As described in Section 2.2.2.3, vupanorsen single SC doses of up to 120 mg and multiple SC doses of up to 60 mg QW × 6 doses were generally safe and well-tolerated in healthy participants in Study CS1. Assuming dose-proportional exposure based on the observed mean PK values following a single 80 mg dose of vupanorsen (higher dose-normalized exposure than 120 mg), plasma AUC_{48h} and C_{max} after single SC administration at 160 mg dose are predicted to be 7.94 µg•h/mL and 0.676 µg/mL, respectively. The predicted safety margins on AUC_{48h} and C_{max} are 12-fold and 20-fold, respectively, relative to the AUC_{48h} of 95.6 µg•h/mL and C_{max} of 13.6 µg/mL at NOAEL (12 mg/kg/week) in monkeys. The PK, PD and safety data at these dose levels in the upcoming Japan Phase 1 study C4491006 will further support the dose selection in this study.

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 the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the trial.

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 and female Chinese participants must be 18 to 65 years of age, inclusive, at the time of signing the ICD.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

    - Chinese participant is defined as individuals currently residing in mainland China who were born in China and have both parents of Chinese descent.

Type of Participant and Disease Characteristics:

2. Male and female Chinese participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests (except for TG levels), and 12-lead ECG monitoring.

3. Fasting TG ≥ 90 mg/dL at Screening (up to 1 repeat allowed for TG and the second TG value will be used for the eligibility).

4. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

Weight:

5. BMI of 17.5 to 35.0 kg/m^2; and a total body weight >50 kg (110 lb).

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. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. History of human immunodeficiency virus (HIV) infection, syphilis, hepatitis B, or hepatitis C; positive testing for HIV, syphilis, HBsAg, or HCVAb. Prior Hepatitis B vaccination is allowed.

3. 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:

4. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.5 for additional details).

Prior/Concurrent Clinical Study Experience:

5. Previous administration with an investigational drug within 4 months or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

6. A positive urine drug test.

7. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

8. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTc interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision

making and reporting. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

9. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - AST **or** ALT level ≥1.25 × ULN;
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is≤ ULN.

Other Exclusions:

10. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).
11. Blood donation (excluding plasma donations) of approximately 400 mL or more within 60 days prior to dosing.
12. History of sensitivity to heparin or heparin-induced thrombocytopenia.
13. History of substance abuse within 12 months of the screening visit.
14. Pregnant females; breastfeeding females.
15. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
16. 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

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) for ≥10 hours prior to any safety laboratory evaluations.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing and during confinement in the CRU.

- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol during confinement in the CRU. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted;

5.3.4. Contraception

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 and his or her partner(s) 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 schedule of activities (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.

5.4. 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. Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

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.

6.1. Study Intervention(s) Administered

Participants will be randomized at Baseline to one of the following treatment cohorts, all participants will receive single SC dosing:

Treatment Cohort	Subcutaneous Treatment (SC)
1	Vupanorsen 80 mg single dose
2	Vupanorsen 160 mg single dose

Vupanorsen is presented as a sterile solution for subcutaneous administration, in a glass pre-filled syringe (PFS). Each PFS contains a sufficient amount of vupanorsen (80 mg/syringe) to provide the intended dose of drug at a concentration of 100 mg/mL.

All participants will be administered 1 or 2 PFS SC injections. The number of SC injections depends on the doses such that 1 SC injection for Cohort 1 (80 mg), and 2 SC injections for Cohort 2 (160 mg). Thus, the maximal number of SC injections will be 2.

Each prefilled syringe is packed in an individual carton.

6.1.1. Administration

The SC administration of vupanorsen must be performed by trained investigator site personnel. SC injections should be administered into a lower quadrant of the abdomin. To minimize injection site reactions, the SC injection should not be administered in areas where the skin is burned, reddened, inflamed, swollen, or scarred. The 2 SC injections for participants in Cohort 2 (160 mg) should not be administered in the same location.

Participants will receive investigational product at approximately 8 a.m. (plus or minus 2 hours). Study medication does not require fasting, but it should be noted that the lipid panel test and the extended lipid panel test at Day 1 prior to the study medication requires a fast of ≥10 hours.

Administer investigational product according to the investigational product (IP) manual.

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. 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.

7. 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

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider,

participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Vupanorsen 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. Each participant will receive a quantity of containers consistent with 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.3.2. Breaking the Blind

Not applicable since the study is open label.

6.4. Study Intervention Compliance

Participants will be dosed at the site. They will receive study intervention directly from the investigator or designee, 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 identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

6.6. Dose Modification

By design, this study only includes administration of single, SC dose of vupanorsen at 2 fixed dosage levels (80 mg and 160 mg) in parallel. As such, dose modifications will not be made during the 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

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

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 discontinuation from the study 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.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws 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 from the study and also withdraws consent (see Section 7.2.1) 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.

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 follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

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.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

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 350 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.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1. Efficacy Assessments

Not applicable.

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. Physical Examinations

A full physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

8.2.2. Vital Signs

Supine BP will be measured with the participant’s arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 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) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTc interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTc interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. 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. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. 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, 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 1 month 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 medical monitor.

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

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

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive study intervention.

8.2.5. 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.

8.3. Adverse Events and Serious Adverse Events

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

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 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 approximately 90 days after the last administration of the study intervention or until study completion or withdrawal, whichever is longer.

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 AE or SAE 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 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.

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 or 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

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.3.9. Medical Device Deficiencies

Not applicable.

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.

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 240 mg within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor 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 3 months).
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 medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples of approximately 4 mL, to provide a minimum of 2 mL K_2EDTA plasma, will be collected for measurement of plasma concentrations of vupanorsen 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.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of vupanorsen. Samples collected for measurement of plasma concentrations of vupanorsen will be analyzed using a validated analytical method in compliance with applicable SOPs.

An additional 6 mL of pre-dose blood sample will be collected from each patient for matrix effect evaluation of the bioanalytic method for vupanorsen concentration detection, PD assay and lipidprotein panel assays. These data will not be included in the CSR (clinical study report).

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

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.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Pharmacodynamics

Blood samples of approximately 4 mL, to provide a minimum of 2 mL serum, will be collected for measurement of ANGPTL3 as specified in the SoA.

Blood samples for measurement of TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, TG, ApoA-I, ApoB total (including ApoB-48, ApoB-100), and ApoC III will be collected from participants in a fasted state as specified in the SoA.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

As part of understanding the PD of the study intervention, samples may be used for evaluation of the bioanalytical method.

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.

8.7. Genetics

8.7.1. Specified Genetics

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

8.7.2. Banked Biospecimens for Genetics

Banked Biospecimens are not applicable in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments of vupanorsen are not included in this study due to the study duration of 90 days after single SC dose. In the non-clinical setting, following 9 months of treatment in Cynomolgus monkeys, the median onset time for ADA was Day 182 and the incidence rate appeared to increase with time. In the Phase 2a study (Study CS2), preliminary data showed that the median time of onset and the incidence of ADA were consistent with vupanorsen immunogenicity data in monkeys, and there was no evidence of altered safety profile or pharmacodynamics associated with the presence of ADA.

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 a 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. Statistical Hypotheses

There are no statistical hypotheses for this study. However, the number of 8 participants in each cohort is considered to be sufficient to provide a precise clearance estimate based on the previous PK data.

9.2. Sample Size Determination

There is no statistical hypothesis for this study, therefore, the study sample size is not based on statistical decision rule. The sample size has been chosen based on the need to minimize exposure to humans of a new chemical entity and to fulfill the NMPA requirement for a PK study to support the registration in China. Considering the possibility of participant dropouts/withdrawals, approximately 18 participants (N=9 per each cohort) will be enrolled to ensure approximately 16 participants (N=8 per each cohort) will be evaluable for the primary endpoint.

9.3. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	All participants who sign the ICD.
Pharmacokinetics (PK)	The PK concentration population is defined as all participants enrolled and treated who have at least 1 vupanorsen concentration. The PK parameter analysis population is defined as all participants enrolled and treated who have at least 1 of the vupanorsen PK parameters of interest.
Pharmacodynamics (PD)	The PD parameter analysis population is defined as all participants enrolled and treated who have at least 1 of the PD parameters of interest.
Safety	All participants enrolled and who take at least 1 dose of study intervention.

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

Plasma PK parameters and plasma concentrations of vupanorsen will be listed and summarized descriptively. Percentage changes from baseline in PD assessments will be summarized using descriptive statistics. Safety and tolerability data will be presented in tabular and/or graphical format and summarized descriptively.

9.4.2. Primary Endpoint(s)

PK parameters of vupanorsen following 80 mg and 160 mg single subcutaneous dose will be derived from the concentration-time profiles using standard noncompartmental methods as follows:

Table 1. Plasma Vupanorsen Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time at which C_{max} occurred	Observed directly from data as time of first occurrence
AUC_{24h}	Area under the concentration-time profile from time 0 to 24 hour post-dose	Linear/log trapezoidal method
AUC_{48h}	Area under the concentration-time profile from time 0 to 48 hour post-dose	Linear/log trapezoidal method
AUC_{last}	Area under the concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/log trapezoidal method
AUC_{inf} *	Area under the concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ was the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis
$t_{½}$*	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time profile
CL/F*	Apparent clearance	$Dose/AUC_{inf}$
V_z/F*	Apparent volume of distribution	$Dose/(AUC_{inf}*k_{el})$

* If data permitted.
Pharmacokinetic parameters were calculated using an internally validated software system, electronic non-compartmental analysis (eNCA, version 2.2.4).

Actual PK sampling times will be used in the derivation of PK parameters. The vupanorsen PK parameters will be listed and summarized descriptively in each vupanorsen dose group. For AUC and C_{max}, box whisker plots for individual participant parameters overlaid with geometric means will be plotted.

Plasma concentration of vupanorsen will be listed and summarized descriptively by treatment and PK sampling time. Mean and median concentration-time plots against nominal sampling time will be presented for each vupanorsen dose group respectively.

9.4.3. Secondary Endpoint(s)

9.4.3.1. Safety Endpoints

All safety analyses will be performed on the safety population.

AEs, ECGs, vital signs, and clinical safety laboratory tests data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG and vital signs abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and time. The number (%) of participants with maximum postdose 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

9.4.3.2. Pharmacodynamic Endpoints

Percentage changes from baseline in PD assessments will be summarized by treatment group and time using descriptive statistics.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a data monitoring committee.

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 subinvestigators 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.

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 identification. 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 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, a coordinating investigator will be designated by mutual agreement.

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.

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. For sites other than a Pfizer CRU, 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 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.

Table 2. Protocol Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	At screening only: • FSH[b] • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus • Syphilis. As per SoA: • Urine drug screening[c] • Pregnancy test (β-hCG)[d]
Lipid Panel	**Extended Lipoprotein Panel and PD Marker**	**Coagulation**	
• Total cholesterol • LDL cholesterol – direct measurement • HDL cholesterol • Non-HDL cholesterol • Triglycerides • VLDL cholesterol – direct measurement	• ANGPTL3 • ApoB • ApoB-48 • ApoB-100 • ApoC-III • ApoA-I	• aPTT (sec) • PT (sec) • INR	

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.

Investigators must document their review of each laboratory safety report.

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 <u>Meeting</u> 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.

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 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

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

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 below 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

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. Premenarchal.
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (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.

3. 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 old 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 men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

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: Liver Safety: Suggested Actions and Follow-up Assessments

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.”

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

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.

10.6. Appendix 6: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs

- 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 SAEs

- 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 participants 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 participants 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 (heart rate <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 SAEs

- 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 from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.7. Appendix 7: Abbreviations

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

Abbreviation	Term
ADA	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANGPTL3	angiopoietin-like protein 3
ApoA-I	apolipoprotein A-1
ApoB	apolipoprotein B
ApoC-III	apolipoprotein C-III
aPTT	activated partial thromboplastin time
ASGPR	asialoglycoprotein receptor
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24h}	AUC from time 0 to 24 hours post-dose
AUC_{48h}	AUC from time 0 to 48 hours post-dose
AUC_{inf}	AUC from time 0 extrapolated to infinite time
AUC_{last}	AUC from time 0 to T_{last}
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL/F	apparent clearance
C_{max}	maximum observed concentration
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CVD	cardiovascular disease
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
ECL	electrochemiluminescence
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency

Abbreviation	Term
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FPL	familial partial lipodystrophy
FSH	follicle-stimulating hormone
FCS	familial chylomicronemia syndrome
GalNAc	N-acetyl galactosamine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HbsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HDL-C	high density lipoprotein cholesterol
IPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
HTG	Hypertriglycemia
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonization
IND	Investigational New Drug
INR	international normalized ratio
IPAL	investigational product accountability log
IP manual	investigational product manual
IRB	institutional review board
IV	intravenous
LDL-C	low density lipoprotein cholesterol
LFT	liver function test
LOF	loss-of-function
MAD	multiple ascending doses
MCH	mean corpuscular hemoglobin
MAHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MOE	methoxyethyl
mRNA	messenger ribonucleic acid
msec	millisecond
N/A	not applicable
NAFLD	nonalcoholic fatty liver disease
NMPA	National Medical Products Administration
NOAEL	no-observed-adverse-effect level
non-HDL-C	non-high-density lipoprotein cholesterol

Abbreviation	Term
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	pulse rate
PT	prothrombin time
QW	weekly
Q2W	every 2 weeks
Q4W	every 4 weeks
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
RNA	ribonucleic acid
Rnase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSARs	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half life
Tbili	total bilirubin
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglyceride
THC	tetrahydrocannabinol
T_{max}	time at which C_{max} occurred
T2DM	type 2 diabetes mellitus
ULN	upper limit of normal
US	the United States
VLDL-C	very low density lipoprotein cholesterol
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential

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