Protocol C4491011

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

Statistical Analysis Plan (SAP)

Version: 2

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APPENDICES

1. VERSION HISTORY

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
2 (26 Jun 2020)	Original protocol (*03 Jun 2020*)	QC review was conducted by following the DMB02-GSOP-RF21 *Statistical Analysis Plan Quality Control Checklist*	No changes were made to the SAP. ***QMS05-GSOP-RF06 Quality Control Review Record*** was filled by Jeffrey Zhang after DMB02-GSOP-RF21 *Statistical Analysis Plan Quality Control Checklist* was reviewed.
1 (08 Jun 2020)	Original protocol (*03 Jun 2020*)	N/A	N/A

2. INTRODUCTION

Note text directly taken from protocol is ***italicized***.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4491011. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on non-HDL-C.	• Percent change from baseline in non-HDL-C at Week 24.
Secondary:	**Secondary:**
• To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on lipid parameters including TG, ApoB, and LDL-C. • To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on ANGPTL3.	• Percent change from baseline in TG, ApoB, and LDL-C at Week 16 and Week 24. • Percent change from baseline in non-HDL-C at Week 16. • Percent change from baseline in ANGPTL3 at Week 16 and Week 24.
Safety:	**Safety:**
• To evaluate the safety, tolerability, and immunogenicity of multiple dose levels and regimens of vupanorsen. • To evaluate the effect of multiple dose levels and regimens of vupanorsen on HFF.	• Incidence of treatment-emergent SAEs and AEs throughout the study. • Incidence of AESI. • Categorical summaries of clinical laboratory abnormalities. • UACR. • ADA. • Change from baseline in AST, ALT, platelet counts, and eGFR. • Change and percent change from baseline in HFF (assessed by MRI-PDFF) at Week 24.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on total cholesterol, HDL-C, VLDL-C, Lp(a), FFA, ApoB-48, ApoB-100, ApoC-III, and ApoA-I. • To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on hsCRP. • To evaluate the PK of vupanorsen.	• Percent change from baseline at Week 24 in total cholesterol, HDL-C, VLDL-C, Lp(a), FFA, ApoB-48, ApoB-100, ApoC-III, and ApoA-I. • Percent change from baseline in hsCRP at Week 24. • Plasma concentrations of vupanorsen at Weeks 12, 16, and 24.

2.1.1. Primary Estimand(s)

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

- *Population: Patients with dyslipidemia taking a statin who meet the inclusion/exclusion criteria.*
- *Variable: The percent change from baseline in non-HDL-C at Week 24.*

- *Intercurrent event: All off-treatment data (ie, occurring at least 1 dosing interval after discontinuation of treatment), or data collected post treatment of severe hypertriglyceridemia (ie, change in statin dose or addition of TG lowering therapy; Section 8.2.7), if collected, will be excluded from analysis.*

- *Population-level summary: Difference of variable means between PF-07285557 and placebo.*

2.1.2. Secondary Estimand(s)

The primary estimand of secondary endpoints will follow the hypothetical estimand approach to estimate the effect of treatment under the hypothetical condition that all participants maintained their randomized treatment through Week 16 or 24 (as indicated below in Variable). This estimand is meant to estimate the pharmacological effect of the drug when taken as directed. It includes the following 4 attributes:

- Population: Patients with dyslipidemia taking a statin who meet the inclusion/exclusion criteria.

- Variable:

  - Percent change from baseline in TG, ApoB, LDL-C, non-HDL-C, ANGPTL3 at Week 16;

  - Percent change from baseline in TG, ApoB, LDL-C, ANGPTL3 at Week 24.

- Intercurrent event: All off-treatment data (ie, occurring at least 1 dosing interval after discontinuation of treatment), or data collected post treatment of severe hypertriglyceridemia (ie, change in statin dose or addition of TG lowering therapy; Section 8.2.7 of the protocol), if collected, will be excluded from analysis.

- Population-level summary: Difference of variable means between PF-07285557 and placebo.

2.1.3. Additional Estimand(s)

Estimands of supplementary analyses

In many settings due to intolerance or inadherence, such as discontinuation of treatment or initiation of an add-on therapy when pre-specified criteria are met, including all data collected in the analysis will violate the assumption of the hypothetical estimand.

Following the estimand theory, as detailed in [1], the following two additional estimands will be used for supplemental analyses of primary and key secondary endpoints (ie, at Week 24). The treatment policy estimand estimates the between-group difference of treatment effect without regard to tolerance or adherence to the randomized treatment (eg, receipt of treatment for severe hypertriglyceridemia). The principal stratum

estimand estimates the between-group difference of treatment effect, restricted to the stratum that subjects who adhere to their randomized vupanorsen groups, but regardless of adherence to the placebo group (ie, S_{*+} in [2]).

2.1.3.1. Treatment Policy

- Population: Patients with dyslipidemia taking a statin who meet the inclusion/exclusion criteria.
- Variable:
  - Percent change from baseline in non-HDL-C, TG, ApoB, LDL-C, ANGPTL3 at Week 24 at Week 24.
- Intercurrent event: All off-treatment data (ie, occurring at least 1 dosing interval after discontinuation of treatment), or data collected post treatment of severe hypertriglyceridemia (ie, change in statin dose or addition of TG lowering therapy; Section 8.2.7 of the protocol), if collected, will be included in the analysis.
- Population-level summary: Difference of variable means between PF-07285557 and placebo.

2.1.3.2. Principal Stratum Estimand

- Population: Patients with dyslipidemia taking a statin who meet the inclusion/exclusion criteria.
- Variable:
  - Percent change from baseline in non-HDL-C at Week 24;
  - Percent change from baseline in TG, ApoB, LDL-C, ANGPTL3 at Week 24.
- Intercurrent event: Subjects with off-treatment data (ie, occurring at least 1 dosing interval after discontinuation of treatment), or with data collected post treatment of severe hypertriglyceridemia (ie, change in statin dose or addition of TG lowering therapy; Section 8.2.7) in the vupanorsen groups, will be excluded from analysis. However, data of such subjects in the placebo group, will be included in the analysis.
- Population-level summary: Difference of variable means between vupanorsen and placebo.

<u>Estimands of sensitivity analyses</u>

Hypothetical estimand.

2.2. Study Design

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

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

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

Table 1. Dosing Plan

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

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- *Percent change from baseline in non-HDL-C at Week 24.*

3.2. Secondary Endpoint(s)

- *Percent change from baseline in TG, ApoB, and LDL-C at Week 16 and Week 24;*

- *Percent change from baseline in non-HDL-C at Week 16;*
- *Percent change from baseline in ANGPTL3 at Week 16 and Week 24.*

3.3. Other Endpoint(s)

The following safety endpoints and tertiary/exploratory endpoints will also be analyzed and reported.

Safety endpoints:

- Change from baseline in AST, ALT, platelet counts, and eGFR;
- Change and percent change from baseline in liver fat (assessed by MRI-PDFF) at Week 24;
- Percent change from baseline in UACR.

Tertiary/Exploratory:

- Percent change from baseline at Week 24 in total cholesterol, HDL-C, VLDL-C, Lp(a), FFA, ApoB-48, ApoB-100, ApoC-III, and ApoA-I;
- Percent change from baseline in hsCRP at Week 24.

3.4. Baseline Variables

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

3.5. Safety Endpoints

- *Incidence of treatment-emergent SAEs and AEs throughout the study;*
- *Incidence of AESI;*
- *Categorical summaries of clinical laboratory abnormalities;*
- *UACR;*
- *ADA;*
- *Change from baseline in AST, ALT, platelet counts, and eGFR;*
- *Change and percent change from baseline in liver fat (assessed by MRI-PDFF) at Week 24.*

3.5.1. Adverse Events

Treatment-emergent AE is defined as any adverse event with an onset date no earlier than the first dose of study medication.

A 3-tier approach will be used to summarize AEs. Different analyses will be performed for different tiers (see Section 6.6.1).

Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's Safety Review Plan.

The full list is not restricted to the following. As the study is ongoing, the study team will monitor all adverse events on a blinded basis and hence the list might be updated accordingly in the safety review plan.

- Injection site reactions.

Tier 2 events: These are events that are not tier 1 but are "common." A Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) is defined as a Tier 2 event if there are at least 10% in one or more treatment groups.

Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events. For this study, tier 3 events won't be reported separately, but will be included in the overall AE summary tables.

3.5.2. Laboratory Data

The following laboratory tests will be reported:

Table 2. Clinical Laboratory Tests

Clinical Chemistry Panel	Hematology Panel	Urinalysis	Lipid Panel
• Sodium • Potassium • Chloride • Bicarbonate • Total protein • Albumin • Calcium • Magnesium • Glucose • BUN • Creatinine • eGFR based on CKD-Epi • Uric acid • Total bilirubin • Direct (conjugated) bilirubin • Indirect (unconjugated) bilirubin • AST • ALT • Alkaline phosphatase	• Red blood cells • Hemoglobin • Hematocrit • MCV, MCH, MCHC • Platelets • WBC differential (% and absolute) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	• Routine urinalysis - Color - Appearance - Specific gravity - pH - Protein - RBC - Glucose - Ketones - Bilirubin - Urobilinogen - Leukocyte esterase - Nitrate • Microscopic examination (reflex testing based on urinalysis results) • A/C ratio (UACR)	• Total cholesterol • LDL cholesterol – direct measurement • HDL cholesterol • Non-HDL cholesterol • Triglycerides • VLDL cholesterol – direct measurement
Extended Lipoprotein Panel, FFA	**Coagulation**	**Pharmacokinetics**	**Immunogenicity**
• Lp(a) • ApoB • ApoB-48 • ApoB-100 • ApoC-III • ApoA-I • FFA	• aPTT (sec) • PT (sec) • INR	• PF-07285557 concentration in plasma	• Anti-PF-07285557 antibodies
PD	**Inflammatory**	**Other**	
• ANGPTL3	• hsCRP	• FSH[a] • Pregnancy test (β-hCG), urine and serum[b] • HbA1c	

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

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention (All Subjects Randomized)	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the randomized intervention.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the treatment group they are randomized to unless the wrong study intervention is received throughout the study.

4.1. Full Analysis Set

The Full Analysis set (FAS) is defined as subjects in the "Evaluable" population who have a baseline measurement and at least one post-baseline measurement. Furthermore, FAS_primary is defined as FAS with all observations that occur after discontinuation of treatment or after initiation of severe hypertriglyceridemia (Section 8.2.7. of protocol) excluded. FAS_primary will be the primary analysis set for the analysis of primary, secondary endpoints and tertiary/exploratory endpoints. FAS serves as the analysis set for supplementary analyses corresponding to the TP estimand.

4.2. Safety Analysis Set

The safety analysis set is defined as subjects in the "Safety" population, ie, randomized subjects who have taken at least one dose of study intervention. They will be analyzed according to their randomized treatment, unless the incorrect treatment is received throughout the study, in which case they will be analyzed according to the treatment received.

4.3. PK/PD Analysis Set

The PK/PD analysis set includes all randomized subjects with at least one PK or PD sample.

4.4. Other Analysis Sets

FAS_ps will be the analysis set for supplementary analyses using the principal stratum estimand (Section 2.1.3.2). The set is defined differently in vupanorsen groups vs placebo group. For vupanorsen groups, this set consists of FAS subjects who adhere to the randomized treatment group with no occurrence of intercurrent events. In other words, subjects who prematurely discontinue treatment or are assigned additional medication for treatment of severe hypertriglyceridemia prior to Week 24 will be excluded from this set. However, for the placebo group, the set is simply the FAS restricted to the placebo group, regardless of treatment adherence.

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary analysis will be performed when all subjects have finished the visit of Week 24 or have prematurely discontinued the study prior to Week 24. Although this study has an additional 12-week safety follow-up period, the data collected until Week 24 constitutes the efficacy part of this study. Therefore, the sponsor will be unblinded and efficacy and safety results will be reported after this milestone is reached. Additional observations that occur after Week 24 will be reported after the 12-week safety follow-up is completed.

5.1. Hypotheses and Decision Rules

The null hypothesis for the primary endpoint is:

H_0: There is no difference in mean percent change from baseline in non-HDL-C at Week 24 between vupanorsen and placebo.

The study objective is treatment effect estimation and dose selection and therefore no formal decision rules for inferential purposes are planned. Each vupanorsen treatment group will be compared to the pooled placebo group, ie, placebo-adjusted LS-mean treatment effect for each dose will be reported along with 95% CI and p-value without adjustment for multiple comparisons to placebo.

The Mixed Model Repeated Measurements (MMRM) will be used as the primary statistical method to estimate the difference of treatment effect between each dose of vupanorsen versus placebo at Week 24. Statistical inference including effect size, p-value, 95% CI will be presented for primary and secondary endpoints respectively, with no adjustment for multiplicity.

Although an interim analysis will occur at Week 16, no formal hypothesis testing nor statistical inference will be conducted.

5.2. General Methods

5.2.1. Analyses for Continuous Endpoints

Continuous endpoints will be summarized using the following descriptive statistics: number of subjects, arithmetic mean, standard deviation, median, minimum, maximum. Other descriptive statistics such as standard error, 1st quartile, 3rd quartile, IQR, etc. will

be added where appropriate. They will be summarized and tabulated by treatment groups and visits (including the 12-week safety follow-up visits when available), for the observed data and (percent) change from baseline.

For graphical summaries, mean +/- standard error, LS-Mean +/- standard error will be plotted for the observed data, (percent) change from baseline over time by treatment groups.

For statistical efficacy analyses, an MMRM model featuring the hypothetical estimand will be applied to primary and secondary endpoints, as primary analyses. All eligible post-baseline visits up to and including the analysis visit will be included in the MMRM model, in which baseline value, treatment (categorical), visit (categorical) and interaction term of treatment (categorical) by visit (categorical) will be treated as fixed effects and an unstructured covariance matrix will be used to account for the correlation among visits. If a model convergence issue is encountered with unstructured covariance matrix, then a simpler covariance structure, such as Toeplitz or compound symmetry will be considered. The restricted maximum likelihood (REML) method along with Kenward-Roger adjustment for degrees of freedom will be used for parameter estimation.

In addition to the primary analysis, the following three supplementary analyses will be conducted for additional evaluation of the primary and key secondary endpoints (ie, evaluated at Week 24). The first two, one using the MMRM model and the other using the multiple imputation using retrieved dropouts (MI-RD) approach, based on the TP estimand will be applied to the FAS (ie, including data collected post occurrence of intercurrent events as defined in Section 2.1.3.1). The last one, will be conducted in the framework of the principal stratum estimand, with details to be described in Section 5.2.1.1. One sensitivity missing data analysis (Section 5.3) under the assumption of missing not at random (MNAR) will be implemented to evaluate the robustness of the primary results, for primary and key secondary endpoints. As in the primary analysis, both supplementary and sensitivity analyses will report the estimates for treatment arms.

Apart from the above statistical efficacy analyses, a Bayesian dose-response model will be constructed to model the relationship between percent change from baseline at Week 24 and doses listed in Table 3, along with estimated 95% CI, for each of the primary and selected key secondary endpoints (Appendix 1) respectively. The parameter estimates from the phase 2a study will inform the model estimation, ie, used as prior distribution of the 3 parameters (E0, Emax, ED50) and the standard deviation of the residual term.

Table 3. Dose Groups for Dose-response Model

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

5.2.1.1. Principal Stratum Estimand Approach

A principal stratum estimand approach will be applied to primary and key secondary endpoints as a supplementary analysis. The estimator based on method A and stratum S_{*+} of [2] will be used to estimate the difference of treatment effect between each dose of vupanorsen and placebo. It aims to compare the average endpoint response in those who adhere to vupanorsen, with their virtual twin endpoint response that would have been observed on placebo [2]. More specifically, for subjects who are able to adhere to their randomized vupanorsen group (reference FAS_ps), their "hypothetical" expected percent change from baseline at Week 24 in the placebo group will be derived using a 2-step regression approach. In terms of treatment adherence, subjects adhere to the treatment if they are on-treatment until Week 24 with no initiation of treatment of hypertriglyceridemia. This two-step approach has an underlying assumption that the endpoint is normally distributed conditional on baseline value and all intermediate post-baseline measurements (ie, post-baseline visits prior to Week 24) and is implemented as follows. First a linear regression will be constructed by regressing the endpoint of interest on baseline value and intermediate post-baseline measurements, restricted to all FAS subjects in the placebo group (ie, regardless of treatment adherence, reference FAS_ps). Next, linear regressions characterizing linear relationships between each of the intermediate post-baseline measurements and baseline value will be estimated, still using the same placebo dataset. By combining these two steps of linear regressions and use of subjects' baseline values as input, their "hypothetical" value in the placebo group can be estimated. Then the average difference between subjects' actual value of percent change from baseline at Week 24 and their corresponding "hypothetical" expected value in the placebo group will be calculated as the estimate of difference of treatment effect for each dose of vupanorsen groups. Bootstrap, a non-parametric statistical method will be used to estimate the variance of the difference of treatment effect, and at least 5000 bootstrap samples will be generated for the estimation of variance, 95% CI and empirical p-value (ie, proportion of bootstrap samples with estimates as extreme as or more extreme than the observed).

5.2.2. Analyses for Categorical Endpoints

Categorical endpoints will be summarized using total number of subjects, number of subjects in each response category and percentage, by treatment groups and visits.

Selected binary endpoints, such as post-hoc or pre-specified exploratory lipid or pharmacodynamic endpoints will be analyzed using logistic regression based on MMRM multiple imputation. The missing data at the analysis time point will be first imputed using a normal distribution with the predicted value and variance estimated from the MMRM as the mean, and the variance. A total of 100 imputations will be performed, with each dataset analyzed using a logistic regression adjusting for treatment (categorical) and baseline value (continuous). All 100 results will then be combined into a single estimate using Rubin's rules [3].

5.3. Methods to Manage Missing Data

The missing data of the primary hypothetical estimand are defined as all visits post occurrence of intercurrent events (Section 2.1.1). In the primary analysis, due to its inherent assumption of missing at random (MAR), no explicit imputation is needed. The following return to baseline (RTB) sensitivity analysis will be conducted to further evaluate the robustness of the primary results, by using a specific MNAR assumption to impute the missing data of Week 24. Then we will introduce the MI-RD supplementary analysis, as it's the only approach that explicitly imputes missing data, out of all three supplementary analyses.

The RTB missing data sensitivity analysis will be implemented on the same analysis set and hypothetical estimand as the primary analysis, but with a varied assumption, to assess how robust the primary results are. The RTB approach assumes for subjects with missing values at Week 24, their values at Week 24 should eventually return to around their baseline level, ie, their values at Week 24 will be imputed using a normal distribution with the baseline level as the mean and the mean squared error (MSE) from ANCOVA model excluding subjects with missing Week 24 values as the variance. A total of 100 imputations will be performed and each dataset will be analyzed using ANCOVA adjusting for baseline value and treatment group (categorical), then all 100 results will be combined into a single estimate following Rubin's rules [3].

The MI-RD approach serves as additional evaluation of the primary results, along with the other two supplementary analyses. It defines missing data differently, due to the TP estimand it represents. More specifically, it includes data collected post occurrence of intercurrent events in the analysis, and therefore its missing data scope is smaller than the hypothetical estimand. This approach assumes subjects who discontinue the study are expected to have similar values of endpoints, compared to those in the same treatment group that agree to stay in the study for safety follow-up after treatment discontinuation ("retrieved dropouts"), after adjusting for values of baseline visit and last on-treatment visits. The imputation is implemented within groups defined by treatment groups. The missing values at Week 24 are imputed with baseline, last on-treatment visit as predictors, using a regression-based MI approach. The imputation dataset only contains

subjects with missing values of Week 24, together with retrieved dropouts. After a total of 100 datasets are imputed, each completed dataset consisting of all subjects will be analyzed using ANCOVA adjusting for baseline, treatment group. Then all 100 results will be combined into a single estimate [3]. Note if this method is not fully applicable, eg, no sufficient RDs to impute the missing values in one treatment group, then this supplementary analysis might not be produced.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Percent Change From Baseline in Non-HDL-C at Week 24

6.1.1.1. Main Analysis

- Estimand strategy: Hypothetical (Section 2.1.1).
- Analysis set: FAS_primary (Section 4.1).
- Analysis methodology: MMRM (Section 5.2.1).
- Intercurrent events and missing data: All off-treatment data (ie, occurring at least 1 dosing interval after discontinuation of treatment), or data collected post treatment of severe hypertriglyceridemia (Section 2.1.1), if collected, will be excluded from analysis.
- The sample size, mean, standard deviation, median, minimum, and maximum at the baseline and post-baseline visits for observed non-HDL-C values and percent change from baseline will be presented for each treatment arm.
- The least-squares (LS) means, the 95% confidence interval for the LS means, the difference in the LS means between each dose group of the vupanorsen and the placebo, its corresponding 95% confidence interval and p-value will be presented.

6.1.1.2. Sensitivity/Supplementary Analyses

Supplementary Analysis

Three supplementary analyses, with two using the treatment policy estimand strategy, and one using the principal stratum estimand strategy (Section 2.1.3) will be conducted to provide additional support and context for the primary analysis. The first two will be MMRM model and the MI-RD approach applied to the analysis set of FAS respectively. While the last one will be a two-step regression approach (Section 5.2.1.1) applied to the set of FAS_ps (Section 4.4).

Sensitivity Analyses

To assess the robustness of the primary analysis, the RTB analysis based on the primary estimand but an assumption of MNAR will be conducted (Section 5.3), using the FAS analysis set.

For each supplementary/sensitivity analysis, the least-squares (LS) means, the 95% confidence interval for the LS means, the difference in the LS means between each dose of vupanorsen and placebo, its corresponding 95% confidence interval and p-value will be presented.

6.2. Secondary Endpoint(s)

6.2.1. Percent Change From Baseline in TG, ApoB, LDL-C, ANGPTL3 at Week 24

6.2.1.1. Main Analysis

Same as primary endpoint (Section 6.1.1.1).

6.2.1.2. Sensitivity/Supplementary Analysis

Same as primary endpoint (Section 6.1.1.2).

6.2.2. Percent Change From Baseline in Non-HDL-C, TG, ApoB, LDL-C, ANGPTL3 at Week 16

Only summary statistics and mean plot (Mean +/- SE) over time will be produced.

6.3. Other Endpoint(s)

6.3.1. Safety Endpoints

The following will be summarized according to Section 5.2, using the safety analysis set defined in Section 4.2.

- Incidence of treatment-emergent SAEs and AEs throughout the study.
- Incidence of AESI.
- Categorical summaries of clinical laboratory abnormalities:
  - ALT/AST abnormalities:
    - Value >=3 x ULN;
    - Value >=5 x ULN;
    - Value >=8 x ULN.
  - Percent reduction from baseline in eGFR>=40%.
  - Platelet abnormality:
    - Confirmed platelet counts<100,000;

- Confirmed platelet counts<75,000;
- Confirmed platelet counts<50,000.

- Platelet count changes:
  - Percent reduction from baseline in platelet counts >=30%;
  - Percent reduction from baseline in platelet counts >=50%.

- UACR;
- ADA.

Immunogenicity of vupanorsen will be assessed before, during, and after treatment. A listing of individual plasma ADA results (including ADA positive, negative, and unknown status samples and titers) sorted by treatment group, participant ID, planned visit, and the visit date/time will be reported. The incidence (number) and incidence rate (percent) of ADA positive, negative and unknown participants will be summarized by treatment group and planned visit and for the overall study. The ADA positive (ADA+) participants will be further subcategorized into TEADA if the baseline ADA is negative. The incidence and incidence rate of TEADA will be summarized by treatment group and planned visit and for the overall study.

- ECG (Section 9.4.5.1. of the protocol);
- Vital signs (BP and pulse rate).

The following will be summarized and (percent) change from baseline will be analyzed according to Section 5.2, using the safety analysis set:

- AST;
- ALT;
- Platelet counts;
- eGFR;
- Hepatic fat fraction;
- UACR.

6.3.2. Tertiary/Exploratory Endpoints

The following will be summarized, along with percent change from baseline at Week 24 analyzed according to Section 5.2, using the FAS_primary defined in Section 4.1:

- Total cholesterol;
- HDL-C;

- VLDL-C;
- Lp(a);
- FFA;
- ApoB-48;
- ApoB-100;
- ApoC-III;
- ApoA-I;
- HsCRP.

Plasma concentrations of PF-07285557 at planned visit will be listed using the set of PK/PD analysis set (Section 4.3) respectively. Summary tables of vupanorsen concentration by treatment and planned visit with and without stratification by ADA status will also be provided. Population PK and PK/PD analyses may be explored using the combined data from this study and other clinical studies of vupanorsen and reported in a separate population analysis report.

6.4. Subset Analyses

Subgroup analyses of primary and key secondary endpoints (ie, at Week 24) will be performed, to check the consistency of conclusion of treatment effect within each category of the subgroup. The following subgroups will be analyzed:

- Baseline statin use (2 categories: high, low/moderate);
- Baseline TG level (< median, >=median);
- Baseline non-HDL-C level (<median, >=median);
- ADA status (positive, negative);
- BMI (<median, >=median).

FAS_primary will be the analysis set of subgroup analyses. An ANCOVA model adjusting for baseline value, treatment (categorical), subgroup (categorical) and interaction term of treatment (categorical) by subgroup (categorical) will be applied. The p-value of the interaction term will also be reported.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic information including age (years), categorical age, sex, race, ethnicity, weight (kg), BMI (kg/m^2) will be summarized by treatment group.

Baseline characteristics including baseline statin products, statin level (high, low/moderate), ezetimibe products, LDL-C (mg/dL), TG (mg/dL), non-HDL-C (mg/dL), ANGPTL3 (ug/L), ApoB (mg/dL), total cholesterol (mg/dL), VLDL-C (mg/dL), HDL-C (mg/dL), HbA1c (%) will be summarized by treatment group.

Medical history on T2DM, atherosclerosis including prior MI, stroke, revascularization, peripheral artery disease (PAD), etc. will be summarized by treatment group.

6.5.2. Study Conduct and Participant Disposition

Number of subjects screened, randomized, discontinuing treatment and study will be tabulated by treatment group.

6.5.3. Study Treatment Exposure

Extent of exposure by treatment group will be summarized at Week 24 and end of study.

6.5.4. Concomitant Medications and Nondrug Treatments

Subjects with specific concomitant medications will be summarized at baseline, Week 24 and end of study, using the WHO-Drug dictionary.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

A 3-tier approach will be used to summarize AEs. Risk difference of each dose group (Table 1) vs placebo will be reported.

Tier 1 AEs are clinically important events that come from a Targeted Medical Event (TME) list or any other important clinical consideration (Section 3.5.1). Point estimates, 95% confidence intervals for the risk difference, and p-values will be reported. P-values and confidence intervals are not adjusted for multiplicity and are used for descriptive purpose only.

Tier 2 AEs are those that are not tier 1 AEs, but are more common adverse events of interest and that occur in a pre-specified minimum number /percentage of subjects in one or more treatment groups. For this study, the pre-specified minimum number is 10%. Only point estimates and 95% confidence intervals for the risk difference will be reported. The 95% confidence intervals are provided to help gauge the precision of the estimates for risk difference.

Tier 3 AEs are those that are neither tier 1 nor tier 2 AEs. They won't be identified and reported separately but will be reported as part of the overall AE summary.

AEs will be displayed in alphabetical order of SOC and PT.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such,

safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

6.6.2. Laboratory Data

Laboratory test values for individual subjects will be listed. The observed laboratory values and change from baseline over time, shifts in clinical laboratory tests and subjects with laboratory test abnormalities will be summarized by treatment group.

6.6.3. Vital Signs

Descriptive statistics will be used to summarize seated blood pressure (systolic and diastolic) and seated pulse rate (bpm).

6.6.4. Electrocardiograms

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

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

Safety QTc Assessment

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

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

6.6.5. Body Weight

Baseline body weight and change from baseline in body weight at Week 24 will be summarized.

7. INTERIM ANALYSES

7.1. Introduction

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

7.2. Interim Analyses and Summaries

In addition to DMC safety tables, the demographic and baseline characteristics tables described in 6.5.1. will be provided.

The following endpoints will be summarized by treatment group at the interim analyses:

- Percent change from baseline in non-HDL-C at Week 16;
- Percent change from baseline in TG at Week 16;
- Percent change from baseline in ApoB at Week 16;
- Percent change from baseline in LDL-C at Week 16;
- Percent change from baseline in ANGPTL3 at Week 16.

Since no decision rules of futility or early stopping for success is planned for the IA, no hypothesis testing will be conducted. Bayesian probabilities of having at least one vupanorsen group achieve the following targets will be calculated respectively.

- >=35% reduction in non-HDL-C;
- >=75% reduction in ANGPTL3.

8. REFERENCES

1. National Research Council (2010). The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press.

2. Yongming Qu, Haoda Fu, Junxiang Luo & Stephen J. Ruberg (2020) A General Framework for Treatment Effect Estimators Considering Patient Adherence, Statistics in Biopharmaceutical Research, 12:1, 1-18, DOI: 10.1080/19466315.2019.1700157.

3. Rubin DB. Multiple Imputation for Nonresponse in Surveys. 1987; Wiley, New York.

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Estimand	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model	Explicit Imputation
Percent change from baseline in non-HDL-C at Week 24	Main analysis	Hypothetical	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	MMRM	N
Percent change from baseline in non-HDL-C at Week 24	Supplementary analysis	Principal Stratum	FAS_ps	All data collected in the placebo group will be included regardless of intercurrent events; Subjects who experience intercurrent events in the vupanorsen groups will be excluded from analysis.	The principal stratum estimand approach	N
Percent change from baseline in non-HDL-C at Week 24	Supplementary analysis	TP	FAS	All data collected will be included regardless of intercurrent events	MMRM	N
Percent change from baseline in non-HDL-C at Week 24	Supplementary analysis	TP	FAS	All data collected will be included regardless of intercurrent events	MI-RD	Y
Percent change from baseline in non-HDL-C at Week 24	Sensitivity analysis	Hypothetical	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	RTB	Y
Percent change from baseline in non-HDL-C at Week 24	Dose-response analysis	NA	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	Bayesian Emax	N
Percent change from baseline in TG at Week 24	Main analysis	Hypothetical	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	MMRM	N
Percent change from baseline in TG at Week 24	Supplementary analysis	Principal Stratum	FAS_ps	All data collected in the placebo group will be included regardless of intercurrent events; Subjects who experience intercurrent events	The principal stratum estimand approach	N

Endpoint	Analysis Type	Estimand	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model	Explicit Imputation
				in the vupanorsen groups will be excluded from analysis.		
Percent change from baseline in TG at Week 24	Supplementary analysis	TP	FAS	All data collected will be included regardless of intercurrent events	MMRM	N
Percent change from baseline in TG at Week 24	Supplementary analysis	TP	FAS	All data collected will be included regardless of intercurrent events	MI-RD	Y
Percent change from baseline in TG at Week 24	Sensitivity analysis	Hypothetical	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	RTB	Y
Percent change from baseline in TG at Week 24	Dose-response analysis	NA	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	Bayesian Emax	N
Percent change from baseline in ApoB at Week 24	Main analysis	Hypothetical	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	MMRM	N
Percent change from baseline in ApoB at Week 24	Supplementary analysis	Principal Stratum	FAS_ps	All data collected in the placebo group will be included regardless of intercurrent events; Subjects who experience intercurrent events in the vupanorsen groups will be excluded from analysis.	The principal stratum estimand approach	N
Percent change from baseline in ApoB at Week 24	Supplementary analysis	TP	FAS	All data collected will be included regardless of intercurrent events	MMRM	N
Percent change from baseline in ApoB at Week 24	Supplementary analysis	TP	FAS	All data collected will be included regardless of intercurrent events	MI-RD	Y
Percent change from baseline in ApoB at Week 24	Sensitivity analysis	Hypothetical	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	RTB	Y

Endpoint	Analysis Type	Estimand	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model	Explicit Imputation
Percent change from baseline in LDL-C at Week 24	Main analysis	Hypothetical	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	MMRM	N
Percent change from baseline in LDL-C at Week 24	Supplementary analysis	Principal Stratum	FAS_ps	All data collected in the placebo group will be included regardless of intercurrent events; Subjects who experience intercurrent events in the vupanorsen groups will be excluded from analysis.	The principal stratum estimand approach	N
Percent change from baseline in LDL-C at Week 24	Supplementary analysis	TP	FAS	All data collected will be included regardless of intercurrent events	MMRM	N
Percent change from baseline in LDL-C at Week 24	Supplementary analysis	TP	FAS	All data collected will be included regardless of intercurrent events	MI-RD	Y
Percent change from baseline in LDL-C at Week 24	Sensitivity analysis	Hypothetical	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	RTB	Y
Percent change from baseline in ANGPTL3 at Week 24	Main analysis	Hypothetical	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	MMRM	N
Percent change from baseline in ANGPTL3 at Week 24	Supplementary analysis	Principal Stratum	FAS_ps	All data collected in the placebo group will be included regardless of intercurrent events; Subjects who experience intercurrent events in the vupanorsen groups will be excluded from analysis.	The principal stratum estimand approach	N
Percent change from baseline in ANGPTL3 at Week 24	Supplementary analysis	TP	FAS	All data collected will be included regardless of intercurrent events	MMRM	N

Endpoint	Analysis Type	Estimand	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model	Explicit Imputation
Percent change from baseline in ANGPTL3 at Week 24	Supplementary analysis	TP	FAS	All data collected will be included regardless of intercurrent events	MI-RD	Y
Percent change from baseline in ANGPTL3 at Week 24	Sensitivity analysis	Hypothetical	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	RTB	Y
Percent change from baseline in ANGPTL3 at Week 24	Dose-response analysis	NA	FAS_primary	Data collected post occurrence of intercurrent events will be excluded from analysis.	Bayesian Emax	N

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

Visit	Target Day	Visit Window
Baseline	1	Screening to Day 1
Week 4	29	Day 15 to Day 42
Week 8	57	Day 43 to Day 70
Week 12	85	Day 71 to Day 98
Week 16	113	Day 99 to Day 126
Week 20	141	Day 127 to Day 154
Week 24	169	Day 155 to Day 182
12-week follow-up	Week 32 for Q4W: 225	Day 211 to Day 238
	Week 34 for Q2W: 239	Day 225 to Day 252

Appendix 3. List of Abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
BA	bioavailability
BE	bioequivalence
BLQ	below the limit of quantitation
BOCF	baseline observation carried forward
BP	blood pressure
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CI	confidence interval
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
EAC	event adjudication committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
FAS	full analysis set
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GLIMMIX	generalized linear mixed-effects model with repeated measures

Abbreviation	Term
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
ICH	International Council for Harmonisation
IRC	internal review committee
IST	independent statistical team
ITT	intent-to-treat
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOD	limit of detection
LS	least-squares
LSM	least-squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MI-RD	Multiple imputation based on retrieved dropouts
MMRM	mixed-effects model with repeated measures
MNAR	missing not at random
N/A	not applicable
NNB	number needed to benefit
NNH	number needed to harm
NNT	number needed to treat
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol
PPAS	per-protocol analysis set
PRO	patient-reported outcome
PT	preferred term
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RCDC	reverse cumulative distribution curve
RR	relative risk
RTB	Return to baseline
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGS	Statistical Guidance Standards
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Term
TA	therapeutic area
ULN	upper limit of normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

Appendix 4. Example SAS code

MMRM:

```
proc mixed data=adeff method=reml;
class subjid avisitn trt01pn;
model chg=base trt01pn avisitn trt01pn*avisitn/ddfm=kr s;
repeated avisitn/sub=subjid type=un;
run;
```

Bayesian dose-response model:

```
proc mcmc data=adeff nbi=10000 nmc=5000000 thin=50 seed=12345
monitor=(e0 ed50 emax sigma dose_80 dose_120 dose_160 dose_240 dose_320
);
/*x1-x4 are starting values for precision and parameters of Emax dose-
response model*/
parms precision x1;
parms e0 x2;
parms ed50 x3;
parms emax x4;
prior precision~normal(xx, xx, lower=0);
prior e0~normal(xx, xx);
prior ed50 ~normal(xx, xx);
prior emax ~normal (xx, xx);
BEGINNODATA ;
dose_80=e0+emax*80/(80+ed50);
dose_120=e0+emax*120/(120+ed50);
dose_160=e0+emax*160/(160+ed50);
dose_240=e0+emax*240/(240+ed50);
dose_320=e0+emax*320/(320+ed50);
sigma=1/sqrt(precision);
ENDNODATA ;

mu=e0+emax*dose/(dose+ed50);
model y~normal(mu, sigma);
run;
```