CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer Inc.

Investigational Product: Vupanorsen (PF-07285557)

Clinical Study Report Synopsis: Protocol C4491011

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

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Center(s): Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: Refer to Appendix 16.1.11 for a list of publications.

Study Initiation Date: 28 Sep 2020

Study Completion Date: 06 Dec 2021

Report Date: 28 Jun 2022

Previous Report Date(s): Not Applicable

Phase of Development: Phase 2b

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Primary and Secondary Study Objectives and Endpoints:

Table S1. Primary and Secondary Study Objectives and Endpoints

Objective	Endpoint
Primary	
• To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on non-high-density lipoprotein cholesterol (non-HDL-C).	• Percent change from baseline in non-HDL-C at Week 24
Secondary	
• To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on lipid parameters including triglyceride(s) (TG), apolipoprotein B (ApoB), and direct low-density lipoprotein cholesterol (LDL-C). • To estimate the effects of multiple dose levels and regimens of vupanorsen compared to placebo on angiopoietin-like protein 3 (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
• 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 Hepatic Fat Fraction (HFF).	• Incidence of treatment-emergent serious adverse events (SAEs) and adverse events (AEs) throughout the study • Incidence of adverse events of special interest (AESI) • Categorical summaries of clinical laboratory abnormalities • Urine albumin:creatinine ratio (UACR) • Anti-drug antibodies (ADA) • Change from baseline in aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet counts, and estimated glomerular filtration rate (eGFR) • Change and percent change from baseline in HFF [assessed by magnetic resonance imaging derived proton density fat fraction (MRI-PDFF)] at Week 24

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METHODS

Approximately 260 participants were to be randomized in this multicenter, double-blind, placebo-controlled, dose-ranging, 8-arm parallel-group study in adults ≥40 years of age with dyslipidemia who were on a stable dose of a statin (with or without ezetimibe) for the purpose of assessing efficacy, safety, and tolerability of subcutaneous (SC) doses of vupanorsen.

Approximately 40% or more of participants enrolled were to be on high intensity statin therapy defined as atorvastatin (40 mg or 80 mg per day) or rosuvastatin (20 mg or 40 mg per day). Enrollment of participants using low/moderate intensity statin (all other statin therapy) was capped at 50% on 01-Mar-2021.

Participants were randomized to self-administer (or injected by their caregiver) SC doses of vupanorsen or placebo every 2 weeks (Q2W) or every 4 weeks (Q4W) at a specified dosing regimen for 24 weeks. Study drug was supplied as prefilled syringes, with vupanorsen provided as either 60 mg or 80 mg strength according to the required total dose.

Diagnosis and Main Criteria for Inclusion: Adults ≥40 years of age with dyslipidemia who were on a stable dose of a statin were enrolled in this study.

Study Treatment: Vupanorsen was supplied in masked, single-use, prefilled syringes of either 60 mg or 80 mg strength according to required dose. Placebo was supplied in masked, single-use, prefilled syringes of 0 mg. The study drug description is presented in Table S2.

Table S2. Study Drug Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form Capsule
PF-07285557 Solution for Injection 100 mg/mL (60 mg/syringe)	DR1336	20-002135	60 mg	SOLUTION
PF-07285557 Solution for Injection 100 mg/mL (80 mg/syringe)	DP2607	20-002134	80 mg	SOLUTION
Placebo for PF-07285557 Solution for Injection 100 mg/mL (60 mg/syringe)	DX2875	20-002675	0 mg	SOLUTION
Placebo for PF-07285557 Solution for Injection 100 mg/mL (80 mg/syringe)	DN8045	20-002133	0 mg	SOLUTION

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Efficacy Evaluations:

Blood samples for measurement of total cholesterol (TC), direct LDL-C, HDL-C, TG, and direct very low-density lipoprotein cholesterol (VLDL-C) were collected from participants in a fasted state; non-HDL-C was calculated as TC – HDL-C. Blood samples for measurement of lipoprotein(a) (Lp[a]), ApoB, ApoB-48, ApoB-100, apolipoprotein C (ApoC)-III, apolipoprotein A (ApoA)-I, and free fatty acids (FFA) were collected from participants in a fasted state. Blood samples for measurement of high-sensitivity C-reactive protein (hsCRP) were also collected from participants in a fasted state.

Pharmacokinetic and Pharmacodynamic Evaluations:

For all participants, trough and post-treatment concentrations of vupanorsen in plasma were determined at specified times during the study. A listing of individual vupanorsen concentration was reported and summarized by treatment with and without stratification by individual immunogenicity status using descriptive statistics. Population pharmacokinetic (PK) and PK/ Pharmacodynamic (PD) analyses may have been explored using the combined data from this study and other clinical studies of vupanorsen are reported in a separate population analysis report.

Serum ANGPTL3 was measured as the target PD endpoint in this study. Blood samples were collected for measurement of ANGPTL3 from participants in a fasted state at specified times during the study.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (pulse rate, blood pressure), 12-lead electrocardiogram (ECG), adverse events (AEs) and safety laboratory tests.

Statistical Methods: Each vupanorsen treatment group was compared to the pooled placebo group, ie, placebo-adjusted Least Squares (LS)-mean treatment effect for each dose was reported along with 95% Confidence Interval (CI) and p-value without adjustment for multiple comparisons to placebo.

The Mixed Model Repeated Measurements (MMRM) was used as the primary statistical method to estimate the difference of treatment effect between each dose of vupanorsen versus placebo at Week 24 for the primary endpoint and secondary endpoints. For percent change from baseline in non-HDL-C, TG, ApoB, LDL-C, and ANGPTL3 at Week 16 only summary statistics and mean plot [Mean +/- Standard Error (SE)] over time were produced.

Three supplementary analyses were 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 treatment policy (TP) estimand was applied to the Full Analysis Set (FAS). The last one, was conducted in the framework of the principal stratum estimand.

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A Bayesian dose-response model was constructed to model the relationship between percent change from baseline at Week 24 and dose of vupanorsen, along with estimated 95% CI, for each of the primary and selected key secondary endpoints, respectively.

Safety endpoints were summarized using total number of participants, number of participants in each response category and percentage, by treatment groups and visits. PD endpoints were analyzed using logistic regression based on MMRM multiple imputation. A 3-tier approach was used to summarize AEs. Risk difference of each dose group versus placebo was reported.

RESULTS

Subject Disposition and Demography: A total of 286 participants were randomized into the study and received treatment (Table S5). The 160 mg Q2W dose group had the highest incidence (14 [38.9%] participants) of discontinuation from treatment due to AE followed by the 80 mg Q2W dose group (9 [20.0%] participants) and the 120 mg Q2W dose group (7 [15.2%] participants) (Table S3).

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Table S3. Disposition Events Summary - All Randomized Participants(Protocol C4491011_FCSR)

Number (%) of Participants	Placebo (N=44) n (%)	80 mg Q4W (N=23) n (%)	60 mg Q2W (N=24) n (%)	120 mg Q4W (N=23) n (%)	80 mg Q2W (N=45) n (%)	160 mg Q4W (N=45) n (%)	120 mg Q2W (N=46) n (%)	160 mg Q2W (N=36) n (%)
Disposition phase: Treatment								
Discontinued	2 (4.5)	5 (21.7)	4 (16.7)	6 (26.1)	12 (26.7)	8 (17.8)	9 (19.6)	14 (38.9)
Reason for discontinuation								
Adverse Event	1 (2.3)	2 (8.7)	3 (12.5)	3 (13.0)	9 (20.0)	4 (8.9)	7 (15.2)	14 (38.9)
Lost to Follow-Up	0	1 (4.3)	0	0	0	0	0	0
Protocol Deviation	0	0	0	1 (4.3)	0	0	0	0
Withdrawal By Participant	0	2 (8.7)	1 (4.2)	0	1 (2.2)	0	0	0
Other	1 (2.3)	0	0	2 (8.7)	2 (4.4)	4 (8.9)	2 (4.3)	0
Completed	42 (95.5)	18 (78.3)	20 (83.3)	17 (73.9)	33 (73.3)	37 (82.2)	37 (80.4)	22 (61.1)
Disposition phase: Follow-Up								
Discontinued	0	1 (4.3)	1 (4.2)	2 (8.7)	2 (4.4)	0	0	0
Reason for discontinuation								
Adverse Event	0	0	1 (4.2)	0	1 (2.2)	0	0	0
Lost to Follow-Up	0	0	0	0	0	0	0	0
Protocol Deviation	0	0	0	0	0	0	0	0
Withdrawal By Participant	0	0	0	0	1 (2.2)	0	0	0
Other	0	1 (4.3)	0	2 (8.7)	0	0	0	0
Completed	44 (100.0)	22 (95.7)	23 (95.8)	21 (91.3)	43 (95.6)	45 (100.0)	46 (100.0)	36 (100.0)

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Table S3. Disposition Events Summary - All Randomized Participants(Protocol C4491011_FCSR)

	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)
Number (%) of Participants	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**

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Table 14.1.1.2.2 Vupanorsen is for Pfizer internal use.

Demographic characteristics were balanced across dose groups (Table S4). The majority of participants were male (55.9%), White (87.4%), and not Hispanic or Latino (90.6%). The mean age of participants was 63.57 years and 38.1% were in the 55 to 64 and 65 to 74 age range.

Table S4. Demographic Characteristics - All Randomized Participants(Protocol C4491011_FCSR)

	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)	Total (N=286)
Age (Years), n (%)									
<40	0	0	0	0	0	0	0	0	0
40-54	5 (11.4%)	2 (8.7%)	4 (16.7%)	5 (21.7%)	7 (15.6%)	8 (17.8%)	6 (13.0%)	5 (13.9%)	42 (14.7%)
55-64	18 (40.9%)	9 (39.1%)	7 (29.2%)	8 (34.8%)	16 (35.6%)	15 (33.3%)	24 (52.2%)	12 (33.3%)	109 (38.1%)
65-74	16 (36.4%)	10 (43.5%)	10 (41.7%)	10 (43.5%)	18 (40.0%)	17 (37.8%)	12 (26.1%)	16 (44.4%)	109 (38.1%)
>=75	5 (11.4%)	2 (8.7%)	3 (12.5%)	0	4 (8.9%)	5 (11.1%)	4 (8.7%)	3 (8.3%)	26 (9.1%)
Unspecified	0	0	0	0	0	0	0	0	0
Median	64.00	66.00	65.50	60.00	64.00	64.00	63.00	65.00	64.00
Mean	64.23	65.78	64.21	61.04	63.38	63.09	62.74	64.47	63.57
Std Dev	8.09	7.27	9.92	9.31	8.41	8.80	8.64	7.74	8.48
Range(Min,Max)	(45.00, 81.00)	(52.00, 78.00)	(48.00, 88.00)	(42.00, 74.00)	(44.00, 77.00)	(45.00, 82.00)	(40.00, 84.00)	(49.00, 82.00)	(40.00, 88.00)
Gender, n (%)									
Male	27 (61.4%)	10 (43.5%)	17 (70.8%)	14 (60.9%)	21 (46.7%)	28 (62.2%)	26 (56.5%)	17 (47.2%)	160 (55.9%)
Female	17 (38.6%)	13 (56.5%)	7 (29.2%)	9 (39.1%)	24 (53.3%)	17 (37.8%)	20 (43.5%)	19 (52.8%)	126 (44.1%)
Race, n (%)									
White	38 (86.4%)	20 (87.0%)	21 (87.5%)	21 (91.3%)	38 (84.4%)	44 (97.8%)	37 (80.4%)	31 (86.1%)	250 (87.4%)
Black or African American	0	1 (4.3%)	1 (4.2%)	0	4 (8.9%)	1 (2.2%)	4 (8.7%)	1 (2.8%)	12 (4.2%)
Asian	4 (9.1%)	2 (8.7%)	2 (8.3%)	1 (4.3%)	3 (6.7%)	0	4 (8.7%)	4 (11.1%)	20 (7.0%)
American Indian or Alaska Native	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0

Table S4. Demographic Characteristics - All Randomized Participants(Protocol C4491011_FCSR)

	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)	Total (N=286)
Other	0	0	0	0	0	0	0	0	0
Not reported	2 (4.5%)	0	0	1 (4.3%)	0	0	1 (2.2%)	0	4 (1.4%)
Ethnicity, n (%)									
Hispanic or Latino	5 (11.4%)	2 (8.7%)	1 (4.2%)	6 (26.1%)	4 (8.9%)	6 (13.3%)	2 (4.3%)	1 (2.8%)	27 (9.4%)
Not Hispanic or Latino	39 (88.6%)	21 (91.3%)	23 (95.8%)	17 (73.9%)	41 (91.1%)	39 (86.7%)	44 (95.7%)	35 (97.2%)	259 (90.6%)
Weight (KG)									
Median	90.90	92.90	91.30	94.00	91.50	95.25	88.55	85.05	91.10
Mean	92.32	93.39	93.07	93.85	89.98	95.64	89.11	87.15	91.58
Std Dev	17.75	17.94	16.48	14.72	16.26	17.41	18.57	14.62	16.93
Range(Min,Max)	(52.00, 124.2)	(60.10, 121.7)	(56.00, 122.5)	(66.70, 123.4)	(58.50, 126.1)	(62.00, 126.2)	(53.48, 135.0)	(66.20, 129.0)	(52.00, 135.0)
BMI									
Median	31.07	32.32	33.66	33.84	32.51	32.58	30.45	30.02	32.30
Mean	31.74	34.16	32.29	33.53	32.39	33.29	31.57	31.01	32.35
Std Dev	5.53	6.31	4.89	5.32	5.19	4.88	6.18	4.38	5.38
Range(Min,Max)	(23.17, 44.45)	(24.52, 51.87)	(22.21, 39.39)	(23.84, 44.29)	(23.25, 46.93)	(24.78, 42.06)	(22.52, 50.52)	(23.36, 41.84)	(22.21, 51.87)

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Table 14.1.2.1 Vupanorsen is for Pfizer internal use.

Table S5. Participant Evaluation Groups - All Participants (Protocol C4491011_FCSR)

	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)	Total (N=286)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Screened: 727 Screened Failure: 391 Not Screen Failure but not Randomized: 50									
Assigned to Treatment	44 (100.0)	23 (100.0)	24 (100.0)	23 (100.0)	45 (100.0)	45 (100.0)	46 (100.0)	36 (100.0)	286 (100.0)
Treated	44 (100.0)	23 (100.0)	24 (100.0)	23 (100.0)	45 (100.0)	45 (100.0)	46 (100.0)	36 (100.0)	286 (100.0)
Not Treated	0	0	0	0	0	0	0	0	0
Safety Population	44 (100.0)	23 (100.0)	24 (100.0)	23 (100.0)	45 (100.0)	45 (100.0)	46 (100.0)	36 (100.0)	286 (100.0)
Evaluable Population	44 (100.0)	23 (100.0)	24 (100.0)	23 (100.0)	45 (100.0)	45 (100.0)	46 (100.0)	36 (100.0)	286 (100.0)
Full Analysis Set	44 (100.0)	23 (100.0)	24 (100.0)	23 (100.0)	43 (95.6)	45 (100.0)	46 (100.0)	36 (100.0)	284 (99.3)
Full Analysis Set (Primary)	44 (100.0)	23 (100.0)	23 (95.8)	23 (100.0)	42 (93.3)	45 (100.0)	46 (100.0)	35 (97.2)	281 (98.3)
Full Analysis Set - PS	44 (100.0)	16 (69.6)	16 (66.7)	16 (69.6)	31 (68.9)	34 (75.6)	35 (76.1)	20 (55.6)	212 (74.1)
PK Population	0	23 (100.0)	24 (100.0)	23 (100.0)	42 (93.3)	45 (100.0)	45 (97.8)	36 (100.0)	238 (83.2)
ADA Population	0	23 (100.0)	24 (100.0)	23 (100.0)	45 (100.0)	45 (100.0)	46 (100.0)	36 (100.0)	242 (84.6)

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Table 14.1.1.1 Vupanorsen is for Pfizer internal use.

Efficacy Results:

Non-HDL-C at Week 24 Primary Endpoint Results

Vupanorsen treatment led to statistically significant reductions in the primary endpoint, percent change from baseline in non-HDL-C at Week 24, compared to placebo at all doses. The LS mean (95% CI) reductions (all endpoint results are presented as placebo-adjusted) in non-HDL-C ranged from -22.0% (95% CI: -31.7, -12.4) for the 60 mg Q2W group to -27.7% (95% CI: -35.7, -19.6) for the 80 mg Q2W group (Table S6 and Figure S1). There was no clear dose response.

Table S6. Percent Change from Baseline in non-HDL-C (mg/dL) at Week 24 - MMRM (Hypothetical) - Full Analysis Set (Primary)(Protocol C4491011_FCSR)

Statistics	Placebo (N = 44)	80 mg Q4W (N = 23)	60 mg Q2W (N = 23)	120 mg Q4W (N = 23)	80 mg Q2W (N = 42)	160 mg Q4W (N = 45)	120 mg Q2W (N = 46)	160 mg Q2W (N = 35)
n	44	23	23	23	42	45	46	35
Mean Baseline	135.7	146.7	148.5	142.1	143.0	135.9	143.0	138.1
LS Mean (SE)	-1.1 (2.76)	-23.5 (4.08)	-23.2 (4.02)	-25.3 (4.23)	-28.8 (3.02)	-27.8 (2.88)	-25.8 (2.84)	-27.6 (3.57)
Difference from Placebo LS Mean (SE)		-22.4 (4.93)	-22.0 (4.88)	-24.1 (5.05)	-27.7 (4.09)	-26.6 (3.98)	-24.7 (3.96)	-26.5 (4.51)
95% CI for the difference from Placebo		(-32.1, -12.7)	(-31.7, -12.4)	(-34.1, -14.2)	(-35.7, -19.6)	(-34.5, -18.8)	(-32.5, -16.9)	(-35.4, -17.6)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Results are obtained from a Mixed Effects Repeated Measures Analysis of Covariance Model; baseline, treatment, visit and interaction term of treatment by visit will be treated as fixed effects with unstructured (un) covariance structure.
n = number of participants who contribute to the MMRM model.
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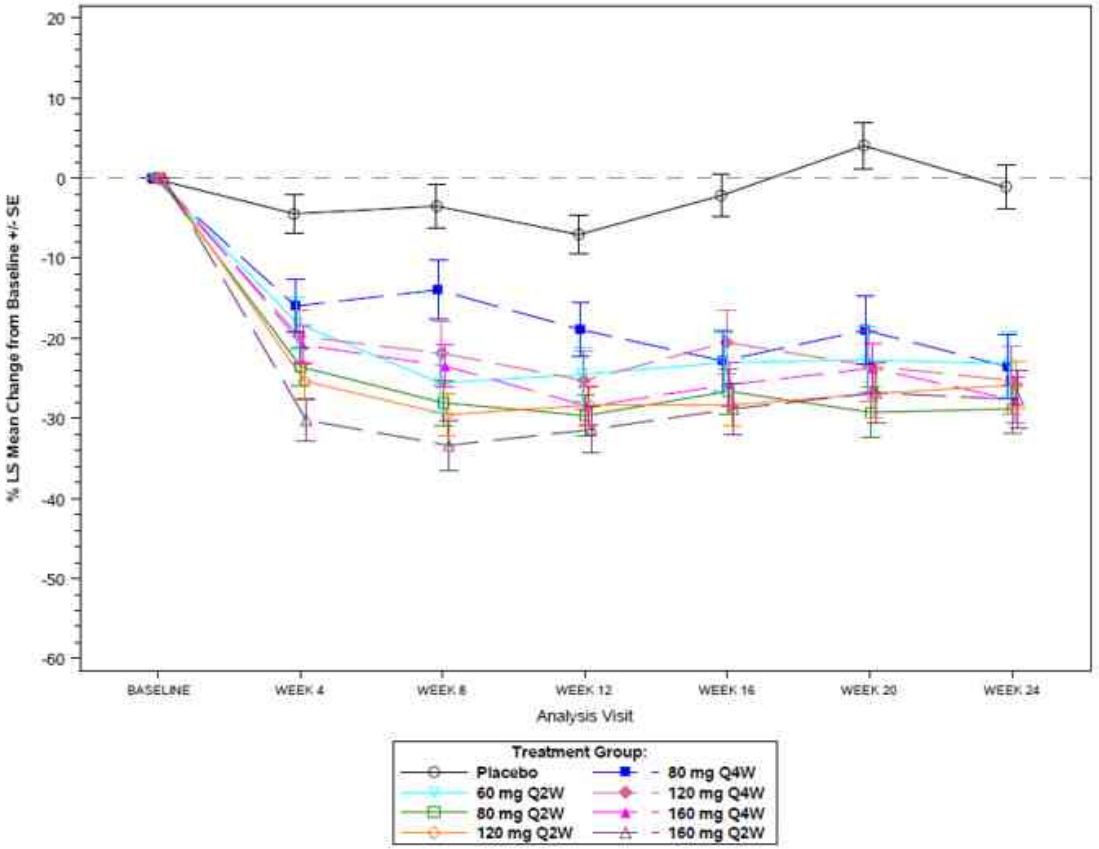
Table 14.2.1.1.1 Vupanorsen is for Pfizer internal use.

Figure S1. LS Mean Plot of Percent Change From Baseline Over Time Until Week 24 in Non-HDL-C (mg/dL) - MMRM - Full Analysis Set (Primary)



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The TP supplemental analysis results are presented in Table S7.

Table S7. Percent Change from Baseline in non-HDL-C (mg/dL) at Week 24 - MMRM (TP) - Full Analysis Set(Protocol C4491011_FCSR)

Statistics	Placebo (N = 44)	80 mg Q4W (N = 23)	60 mg Q2W (N = 24)	120 mg Q4W (N = 23)	80 mg Q2W (N = 43)	160 mg Q4W (N = 45)	120 mg Q2W (N = 46)	160 mg Q2W (N = 36)
n	44	23	24	23	43	45	46	36
Mean Baseline	135.7	146.7	147.6	142.1	142.6	135.9	143.0	138.1
LS Mean (SE)	-2.9 (3.36)	-22.5 (4.71)	-23.0 (4.69)	-22.8 (4.76)	-24.0 (3.43)	-22.6 (3.36)	-22.8 (3.33)	-15.3 (3.70)
Difference from Placebo LS Mean (SE)		-19.7 (5.79)	-20.2 (5.77)	-19.9 (5.83)	-21.1 (4.81)	-19.8 (4.75)	-19.9 (4.74)	-12.5 (5.00)
95% CI for the difference from Placebo		(-31.1, -8.3)	(-31.6, -8.8)	(-31.4, -8.4)	(-30.6, -11.7)	(-29.1, -10.4)	(-29.3, -10.6)	(-22.3, -2.6)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.013

Results are obtained from a Mixed Effects Repeated Measures Analysis of Covariance Model; baseline, treatment, visit and interaction term of treatment by visit will be treated as fixed effects with unstructured (un) covariance structure.
n = number of participants who contribute to the MMRM model.
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Table 14.2.1.1.2 Vupanorsen is for Pfizer internal use.

The MI-RD supplementary analysis of the percent change from baseline in non-HDL-C at Week 24 is presented in Table S8.

Table S8. Percent Change from Baseline in non-HDL-C (mg/dL) at Week 24 - MI-RD - Full Analysis Set(Protocol C4491011_FCSR)

Statistics	Placebo (N = 44)	80 mg Q4W (N = 23)	60 mg Q2W (N = 24)	120 mg Q4W (N = 23)	80 mg Q2W (N = 43)	160 mg Q4W (N = 45)	120 mg Q2W (N = 46)	160 mg Q2W (N = 36)
n	43	23	23	23	42	45	46	35
Mean Baseline	136.1	146.7	148.5	142.1	143.0	135.9	143.0	138.1
LS Mean (SE)	-2.6 (3.55)	-22.6 (6.04)	-22.1 (5.40)	-20.6 (5.16)	-24.8 (3.69)	-21.5 (3.77)	-23.0 (3.53)	-16.7 (3.93)
Difference from Placebo LS Mean (SE)		-20.1 (6.99)	-19.5 (6.48)	-18.0 (6.26)	-22.2 (5.11)	-19.0 (5.17)	-20.4 (5.01)	-14.1 (5.29)
95 % CI for the difference from Placebo		(-33.8, -6.4)	(-32.2, -6.8)	(-30.3, -5.8)	(-32.2, -12.2)	(-29.1, -8.8)	(-30.2, -10.6)	(-24.5, -3.7)
P-value		0.004	0.003	0.004	<0.001	<0.001	<0.001	0.008

n = number of participants who contribute to the model. This includes completers and retrieved drop-outs. In case >4 drop-outs are available per treatment then values for dropouts can be calculated.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Table Generation: 16FEB2022 (09:16)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/tmirdnhdlc
Table 14.2.1.1.3 Vupanorsen is for Pfizer internal use.

Secondary Endpoints Results

Triglycerides at Week 24

All vupanorsen treatment groups demonstrated a statistically significant reduction in percent change from baseline in TG versus placebo (difference from placebo LS mean [95% CI] ranged from -41.3% [95% CI: -54.8, -27.8] for the 120 mg Q4W group to -56.8% [95% CI: -68.9, -44.7] for the 160 mg Q2W group [Table S9]).

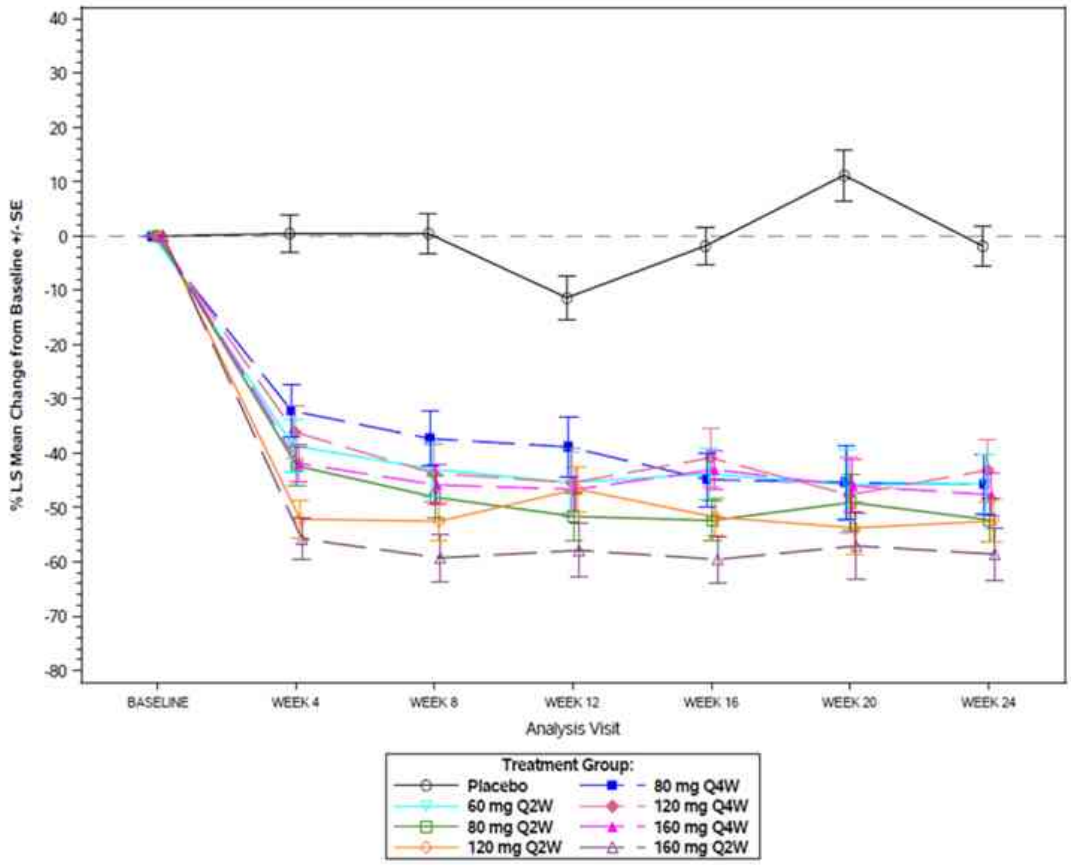
LS mean plot of percent change from baseline over time until Week 24 for TG obtained from MMRM is provided in Figure S2.

Table S9. Percent Change from Baseline in TG (mg/dL) at Week 24 - MMRM (Hypothetical) - Full Analysis Set (Primary)(Protocol C4491011_FCSR)

Statistics	Placebo (N = 44)	80 mg Q4W (N = 23)	60 mg Q2W (N = 23)	120 mg Q4W (N = 23)	80 mg Q2W (N = 42)	160 mg Q4W (N = 45)	120 mg Q2W (N = 46)	160 mg Q2W (N = 35)
n	44	23	23	23	42	45	46	35
Mean Baseline	228.6	236.0	241.1	249.2	245.7	236.6	224.4	228.4
LS Mean (SE)	-1.8 (3.71)	-45.8 (5.53)	-45.6 (5.50)	-43.1 (5.76)	-52.3 (4.10)	-47.7 (3.90)	-52.5 (3.85)	-58.6 (4.90)
Difference from Placebo LS Mean (SE)		-44.0 (6.66)	-43.8 (6.64)	-41.3 (6.85)	-50.5 (5.54)	-45.9 (5.38)	-50.7 (5.35)	-56.8 (6.14)
95% CI for the difference from Placebo		(-57.1, -30.8)	(-56.9, -30.7)	(-54.8, -27.8)	(-61.4, -39.6)	(-56.5, -35.2)	(-61.2, -40.1)	(-68.9, -44.7)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Results are obtained from a Mixed Effects Repeated Measures Analysis of Covariance Model; baseline, treatment, visit and interaction term of treatment by visit will be treated as fixed effects with unstructured (un) covariance structure.
n = number of participants who contribute to the MMRM model.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Table Generation: 16FEB2022 (09:25)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/tmmprtg
Table 14.2.1.2.1 Vupanorsen is for Pfizer internal use.

Figure S2. LS Mean Plot of Percent Change From Baseline Over Time Until Week 24 in TG (mg/dL) - MMRM - Full Analysis Set (Primary)



PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Date of Generation: 16FEB2022 (11:38)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: /CSR/C4491011_FCSR/flsmpctg

The TP supplementary analysis results in Table S10 were similar to the main analysis results (Table S9) in that the reductions were statistically significant. However, LS means were generally smaller for the MMRM-TP analysis.

Table S10. Percent Change from Baseline in TG (mg/dL) at Week 24 - MMRM (TP) - Full Analysis Set(Protocol C4491011_FCSR)

Statistics	Placebo (N = 44)	80 mg Q4W (N = 23)	60 mg Q2W (N = 24)	120 mg Q4W (N = 23)	80 mg Q2W (N = 43)	160 mg Q4W (N = 45)	120 mg Q2W (N = 46)	160 mg Q2W (N = 36)
n	44	23	24	23	43	45	46	36
Mean Baseline	228.6	236.0	243.9	249.2	243.9	236.6	224.4	225.7
LS Mean (SE)	-2.1 (4.70)	-46.2 (6.60)	-41.2 (6.60)	-35.3 (6.68)	-43.6 (4.80)	-40.8 (4.70)	-46.2 (4.67)	-47.2 (5.17)
Difference from Placebo LS Mean (SE)		-44.1 (8.10)	-39.1 (8.10)	-33.1 (8.17)	-41.5 (6.72)	-38.7 (6.65)	-44.1 (6.63)	-45.1 (6.99)
95% CI for the difference from Placebo		(-60.0, -28.1)	(-55.1, -23.2)	(-49.2, -17.1)	(-54.7, -28.3)	(-51.8, -25.6)	(-57.1, -31.0)	(-58.9, -31.4)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Results are obtained from a Mixed Effects Repeated Measures Analysis of Covariance Model; baseline, treatment, visit and interaction term of treatment by visit will be treated as fixed effects with unstructured (un) covariance structure.
n = number of participants who contribute to the MMRM model.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Table Generation: 16FEB2022 (09:25)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/tmmfastg
Table 14.2.1.2.2 Vupanorsen is for Pfizer internal use.

The MI-RD supplementary analysis results in Table S11 show smaller reductions in TG for most dose groups than the primary analysis MMRM (hypothetical) (Table S9).

Table S11. Percent Change from Baseline in TG (mg/dL) at Week 24 - MI-RD - Full Analysis Set(Protocol C4491011_FCSR)

Statistics	Placebo (N = 44)	80 mg Q4W (N = 23)	60 mg Q2W (N = 24)	120 mg Q4W (N = 23)	80 mg Q2W (N = 43)	160 mg Q4W (N = 45)	120 mg Q2W (N = 46)	160 mg Q2W (N = 36)
n	43	23	23	23	42	45	46	35
Mean Baseline	225.6	236.0	241.1	249.2	245.7	236.6	224.4	228.4
LS Mean (SE)	-2.0 (5.14)	-47.1 (7.17)	-40.5 (9.61)	-29.0 (8.10)	-42.2 (5.42)	-40.5 (5.17)	-44.9 (5.45)	-47.8 (5.70)
Difference from Placebo LS Mean (SE)		-45.1 (8.82)	-38.5 (10.94)	-27.0 (9.62)	-40.2 (7.48)	-38.5 (7.30)	-42.9 (7.49)	-45.8 (7.67)
95 % CI for the difference from Placebo		(-62.4, -27.8)	(-59.9, -17.0)	(-45.9, -8.2)	(-54.9, -25.6)	(-52.8, -24.2)	(-57.6, -28.2)	(-60.8, -30.7)
P-value		<0.001	<0.001	0.005	<0.001	<0.001	<0.001	<0.001

n = number of participants who contribute to the model. This includes completers and retrieved drop-outs. In case >4 drop-outs are available per treatment then values for dropouts can be calculated.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Table Generation: 16FEB2022 (09:25)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/tmirdtg
Table 14.2.1.2.3 Vupanorsen is for Pfizer internal use.

ApoB at Week 24

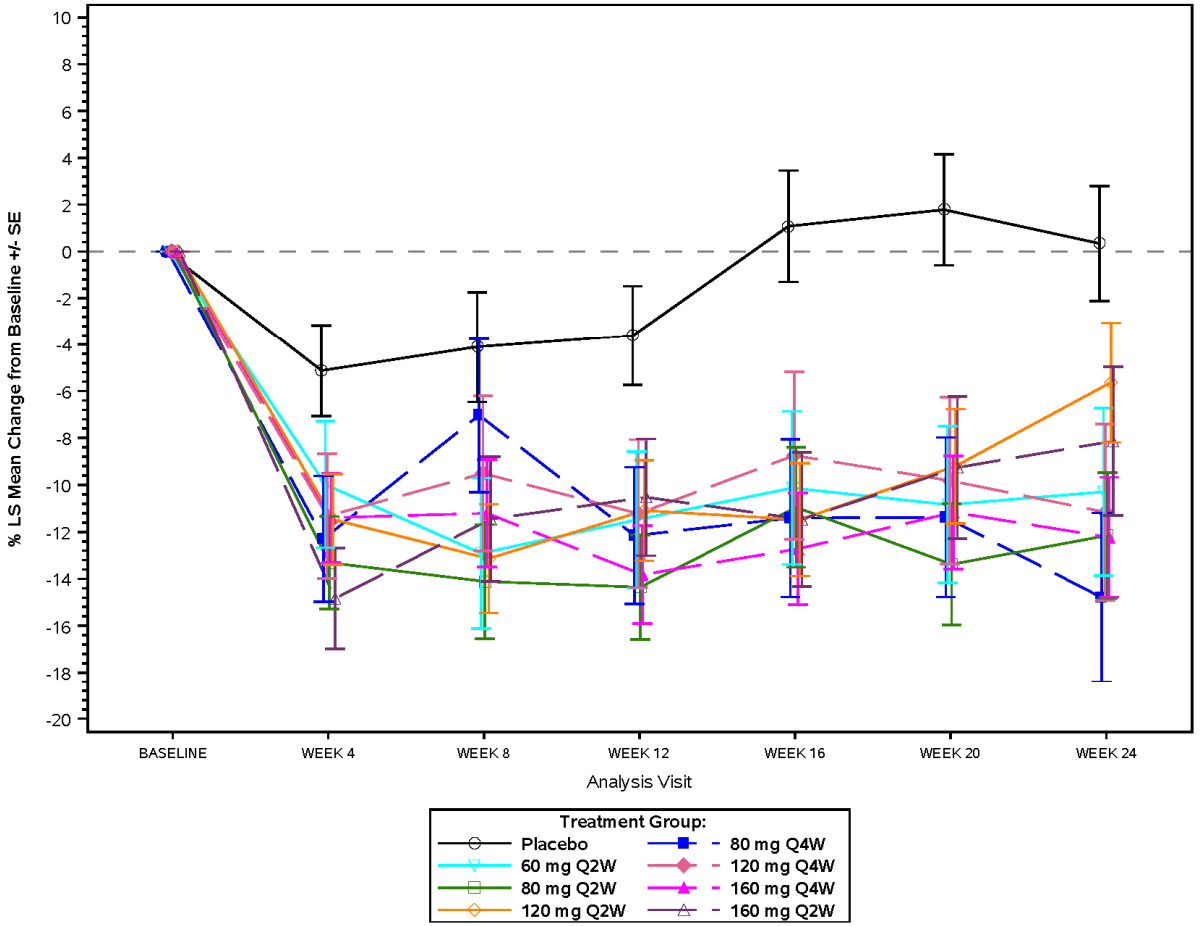
In ApoB, all vupanorsen treatment groups except for 120 mg Q2W showed statistically significant reductions in percent change from baseline versus placebo (Table S12 and Figure S3). The difference from placebo LS mean (95% CI) in ApoB at Week 24 ranged from -6.0% (95% CI: -13.0, 1.0) for the 120 mg Q2W group to -15.1% (95% CI: -23.7, -6.5) for the 80 mg Q4W group.

Table S12. Percent Change from Baseline in ApoB (mg/dL) at Week 24 - MMRM (Hypothetical) - Full Analysis Set (Primary)(Protocol C4491011_FCSR)

Statistics	Placebo (N = 44)	80 mg Q4W (N = 23)	60 mg Q2W (N = 23)	120 mg Q4W (N = 23)	80 mg Q2W (N = 42)	160 mg Q4W (N = 45)	120 mg Q2W (N = 46)	160 mg Q2W (N = 35)
n	42	22	22	23	41	45	44	35
Mean Baseline	96.6	103.2	106.8	101.7	101.1	100.1	102.4	99.2
LS Mean (SE)	0.3 (2.46)	-14.8 (3.60)	-10.3 (3.57)	-11.2 (3.76)	-12.2 (2.68)	-12.2 (2.55)	-5.6 (2.57)	-8.1 (3.17)
Difference from Placebo LS Mean (SE)		-15.1 (4.36)	-10.6 (4.34)	-11.5 (4.49)	-12.5 (3.64)	-12.6 (3.54)	-6.0 (3.56)	-8.5 (4.01)
95% CI for the difference from Placebo		(-23.7, -6.5)	(-19.2, -2.1)	(-20.3, -2.7)	(-19.7, -5.3)	(-19.5, -5.6)	(-13.0, 1.0)	(-16.4, -0.6)
P-value		<0.001	0.015	0.011	<0.001	<0.001	0.095	0.036

Results are obtained from a Mixed Effects Repeated Measures Analysis of Covariance Model; baseline, treatment, visit and interaction term of treatment by visit will be treated as fixed effects with unstructured (un) covariance structure.
n = number of participants who contribute to the MMRM model.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Table Generation: 16FEB2022 (09:32)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/tmmprapob
Table 14.2.1.3.1 Vupanorsen is for Pfizer internal use.

Figure S3. LS Mean Plot of Percent Change From Baseline Over Time Until Week 24 in ApoB (mg/dL) - MMRM - Full Analysis Set (Primary)



PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Date of Generation: 16FEB2022 (11:38)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/flsapbpc

Direct LDL-C at Week 24

Only the 80 mg Q2W and 160 mg Q4W treatment groups showed a statistically significant percent change from baseline versus placebo in direct LDL-C (Table S13).

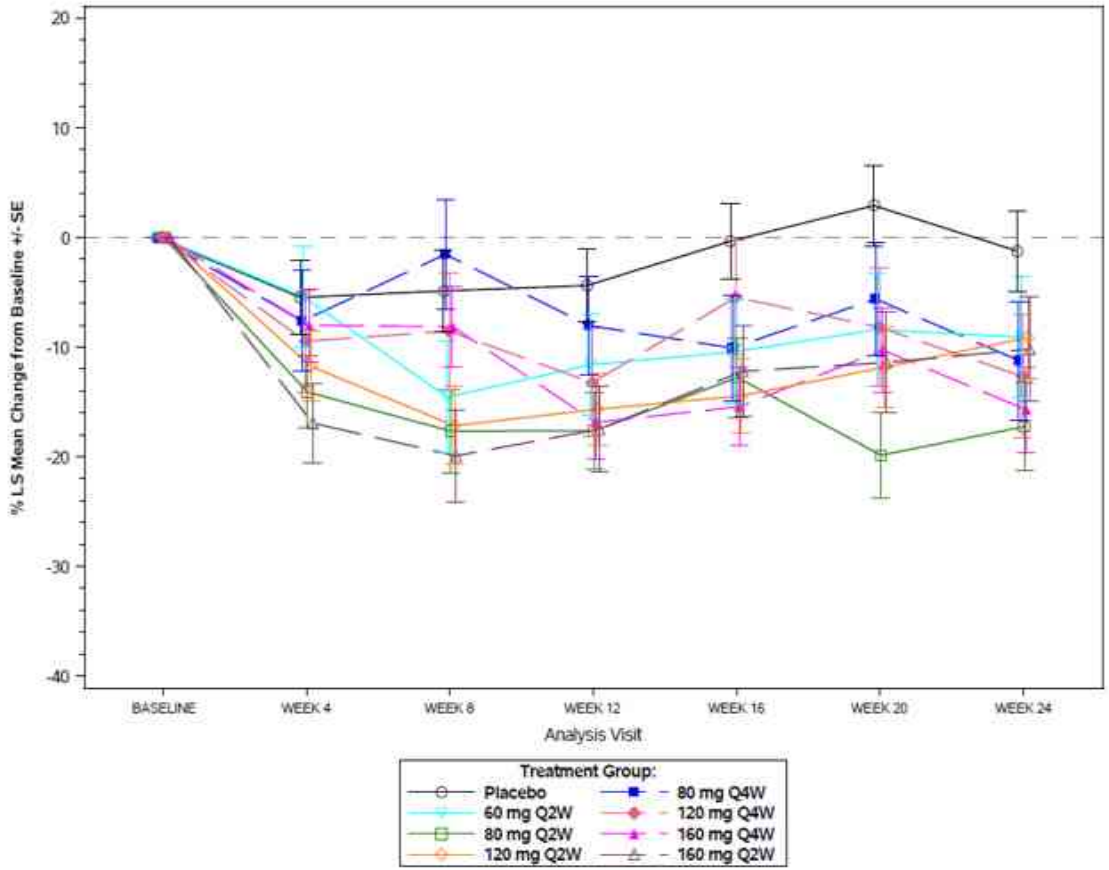
The difference from placebo LS mean (95% CI) in direct LDL-C at Week 24 ranged from -7.9% (95% CI: -21.0, 5.2) for the 60 mg Q2W group and -7.9% (95% CI: -18.3, 2.5) for the 120 mg Q2W group to -16.0% (95% CI: -26.7, -5.3) for the 80 mg Q2W group (Table S13 and Figure S4).

Table S13. Percent Change from Baseline in Direct LDL-C (mg/dL) at Week 24 - MMRM (Hypothetical) - Full Analysis Set (Primary)(Protocol C4491011_FCSR)

Statistics	Placebo (N = 44)	80 mg Q4W (N = 23)	60 mg Q2W (N = 23)	120 mg Q4W (N = 23)	80 mg Q2W (N = 42)	160 mg Q4W (N = 45)	120 mg Q2W (N = 46)	160 mg Q2W (N = 35)
n	43	23	22	22	42	43	46	35
Mean Baseline	91.4	100.1	100.7	89.3	95.6	88.9	98.3	93.8
LS Mean (SE)	-1.2 (3.69)	-11.2 (5.41)	-9.1 (5.52)	-12.7 (5.63)	-17.3 (4.00)	-15.7 (3.92)	-9.1 (3.77)	-10.2 (4.74)
Difference from Placebo LS Mean (SE)		-10.0 (6.55)	-7.9 (6.65)	-11.4 (6.73)	-16.0 (5.44)	-14.5 (5.38)	-7.9 (5.28)	-9.0 (6.01)
95% CI for the difference from Placebo		(-22.9, 2.9)	(-21.0, 5.2)	(-24.7, 1.8)	(-26.7, -5.3)	(-25.1, -3.9)	(-18.3, 2.5)	(-20.8, 2.9)
P-value		0.129	0.238	0.090	0.004	0.008	0.136	0.138

Results are obtained from a Mixed Effects Repeated Measures Analysis of Covariance Model; baseline, treatment, visit and interaction term of treatment by visit will be treated as fixed effects with unstructured (un) covariance structure.
n = number of participants who contribute to the MMRM model.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Table Generation: 16FEB2022 (09:32)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/tmmprldlc
Table 14.2.1.4.1 Vupanorsen is for Pfizer internal use.

Figure S4. LS Mean Plot of Percent Change From Baseline Over Time Until Week 24 in Direct LDL-C (mg/dL) - MMRM - Full Analysis Set (Primary)



PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Date of Generation: 16FEB2022 (11:38)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: /CSR/C4491011_FCSR/flspcldc

ANGPTL3 at Week 24

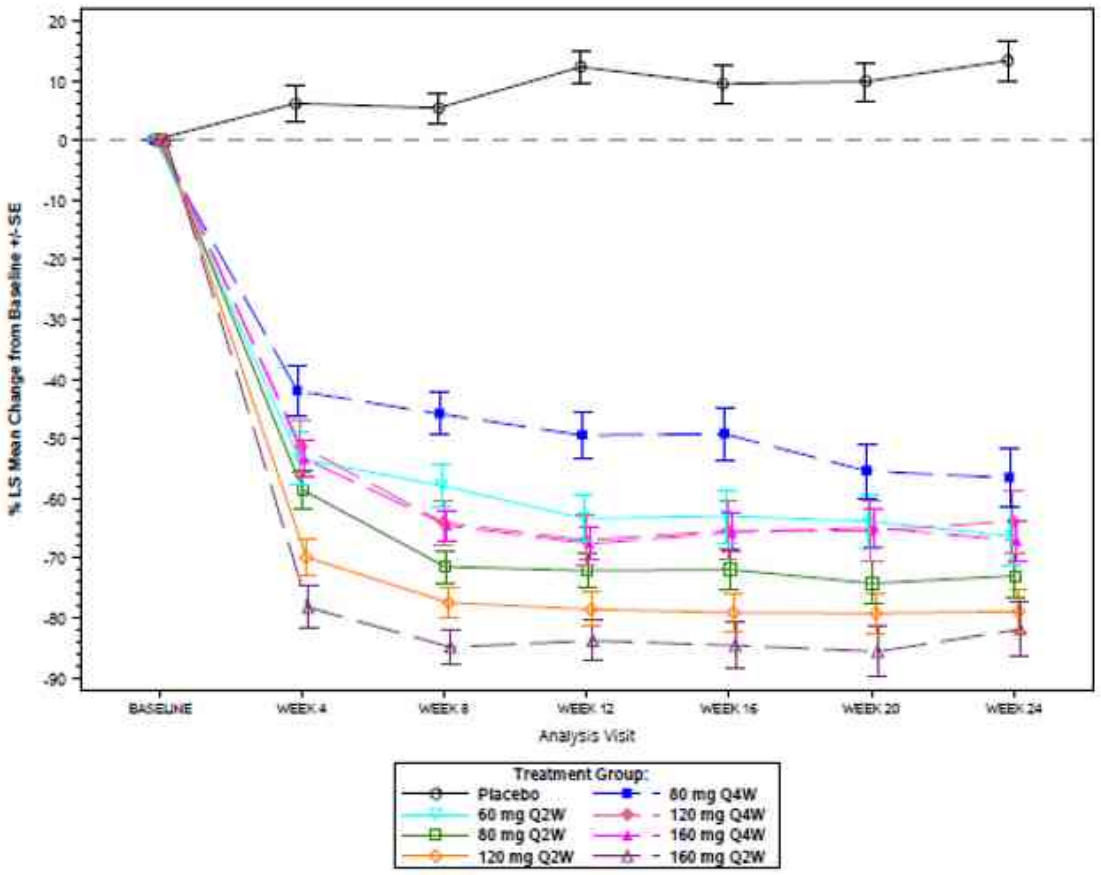
There was a statistically significant reduction in percent change from baseline in ANGPTL3 at Week 24 for all treatment groups ($p < 0.001$). The difference from placebo LS mean (95% CI) in ANGPTL3 at Week 24 ranged from -69.9% (95% CI: -81.6, -58.1) for the 80 mg Q4W group to -95.2% (95% CI: -106.2, -84.2) for the 160 mg Q2W group (Table S14 and Figure S5).

Table S14. Percent Change from Baseline in ANGPTL3 (ng/mL) at Week 24 - MMRM (Hypothetical) - Full Analysis Set (Primary)(Protocol C4491011_FCSR)

Statistics	Placebo (N = 44)	80 mg Q4W (N = 23)	60 mg Q2W (N = 23)	120 mg Q4W (N = 23)	80 mg Q2W (N = 42)	160 mg Q4W (N = 45)	120 mg Q2W (N = 46)	160 mg Q2W (N = 35)
n	42	22	21	22	40	45	42	33
Mean Baseline	94.2	113.5	104.8	106.4	97.8	96.5	105.7	97.3
LS Mean (SE)	13.3 (3.36)	-56.6 (4.92)	-66.3 (5.01)	-63.8 (5.22)	-73.0 (3.76)	-67.1 (3.46)	-78.9 (3.58)	-81.9 (4.48)
Difference from Placebo LS Mean (SE)		-69.9 (5.97)	-79.6 (6.03)	-77.1 (6.22)	-86.3 (5.04)	-80.4 (4.82)	-92.2 (4.92)	-95.2 (5.59)
95% CI for the difference from Placebo		(-81.6, -58.1)	(-91.5, -67.7)	(-89.4, -64.9)	(-96.2, -76.3)	(-89.9, -70.9)	(-101.9, -82.6)	(-106.2, -84.2)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Results are obtained from a Mixed Effects Repeated Measures Analysis of Covariance Model; baseline, treatment, visit and interaction term of treatment by visit will be treated as fixed effects with unstructured (un) covariance structure.
n = number of participants who contribute to the MMRM model.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Table Generation: 16FEB2022 (09:37)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/tmmprangptl3
Table 14.2.1.5.1 Vupanorsen is for Pfizer internal use.

Figure S5. LS Mean Plot of Percent Change From Baseline Over Time Until Week 24 in ANGPTL3 (ng/mL) - MMRM - Full Analysis Set



PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Date of Generation: 16FEB2022 (11:38)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/fsangpt

Pharmacokinetic and Pharmacodynamic Results: Vupanorsen concentration in plasma increased in a dose-dependent manner at trough and 2 hours to 4 hours after administration (as defined in the protocol) with no significant accumulation with repeated dosing in ADA-Negative participants. In ADA-Positive participants, the trough concentrations increased over time but not the peak concentrations.

The overall incidence of ADA with vupanorsen treatment was 30.7%, with 26.5% as treatment-induced and 4.2% as treatment-boosted (Table S15). No apparent difference was observed between ADA-Positive and ADA-Negative participants in serum ANGPTL3, non-HDL-C, TG, direct LDL-C, and ApoB percent change from baseline in the PK/PD population.

Table S15. Incidence of Anti-Vupanorsen Antibody (ADA) - Safety Population(Protocol C4491011_FCSR)

	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)	Total (N=242)
Total number of participants with >= 1 ADA result	23	24	23	45	45	46	36	242
ADA evaluable participants (N1)	23	24	23	42	45	45	36	238
Evaluable participants with pre-existing antibody, n/N1 (%)	1/23 (4.3)	2/24 (8.3)	0/23 (0.0)	2/42 (4.8)	3/45 (6.7)	4/45 (8.9)	4/36 (11.1)	16/238 (6.7)
Baseline-positive participants with non-boosted antibody response, n1/N1 (%)	1/23 (4.3)	1/24 (4.2)	0/23 (0.0)	0/42 (0.0)	1/45 (2.2)	2/45 (4.4)	1/36 (2.8)	6/238 (2.5)
Overall Incidence, n2/N1 (%)	6/23 (26.1)	9/24 (37.5)	4/23 (17.4)	15/42 (35.7)	8/45 (17.8)	15/45 (33.3)	16/36 (44.4)	73/238 (30.7)
Treatment-induced	6/23 (26.1%)	8/24 (33.3%)	4/23 (17.4%)	13/42 (31.0%)	6/45 (13.3%)	13/45 (28.9%)	13/36 (36.1%)	63/238 (26.5%)
Treatment-boosted	0/23 (0.0%)	1/24 (4.2%)	0/23 (0.0%)	2/42 (4.8%)	2/45 (4.4%)	2/45 (4.4%)	3/36 (8.3%)	10/238 (4.2%)

Baseline is defined as the pre-dose measurement on Day 1.
N=Number of Participants in the safety analysis population; N1=Number of Participants with >=1 post-treatment ADA result; n=number of ADA evaluable participants with positive ADA at baseline; n1=Number of ADA-evaluable participants with positive ADA at baseline but did not become boosted post-treatment; n2= Number of ADA-positive Participants (treatment-induced or treatment-boosted).
A Participants is ADA positive if (1) baseline titer is missing or negative and participant has >=1 post-treatment positive titer (treatment-induced), or (2) positive titer at baseline and has a >=4-fold dilution increase in titer from baseline in >=1 post-treatment sample (treatment-boosted). Participants who are ADA positive at baseline but do not become boosted post-treatment are considered as ADA negative.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adisda Table Generation: 16FEB2022 (11:39)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/adisda_s002
Table 14.4.4.3 Vupanorsen is for Pfizer internal use.

Safety Results:

11.1. Extent of Exposure

A total of 220 (76.9%) participants received study drug for >24 weeks to ≤30 weeks (Table S16). The overall mean duration of treatment was 152.9 days.

Table S16. Duration of Treatment - Safety Population(Protocol C4491011_FCSR)

	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)	Total (N=286)
Duration of Treatment (Days)[a]									
n	44	23	24	23	45	45	46	36	286
Mean (SD)	168.5 (22.69)	158.4 (27.70)	160.3 (33.15)	143.1 (53.42)	142.6 (53.62)	156.3 (38.68)	157.2 (35.75)	135.1 (52.74)	152.9 (42.17)
Median	173.0	173.0	173.0	173.0	173.0	173.0	173.0	172.5	173.0
Range (min,max)	(47, 180)	(89, 174)	(33, 176)	(33, 176)	(19, 177)	(33, 180)	(59, 182)	(19, 180)	(19, 182)
Number of Doses									
n	44	23	24	23	45	45	46	36	286
Mean (SD)	14.0 (6.31)	5.4 (1.12)	10.8 (2.60)	9.7 (3.92)	9.7 (3.84)	10.7 (2.74)	21.3 (5.13)	18.3 (7.39)	13.2 (6.74)
Median	12.0	6.0	12.0	12.0	12.0	12.0	24.0	23.0	12.0
Range (min,max)	(3, 24)	(3, 6)	(2, 12)	(2, 12)	(1, 12)	(2, 12)	(8, 24)	(2, 24)	(1, 24)
Category (Weeks)									
<=4wk	0	0	0	0	3 (6.7)	0	0	1 (2.8)	4 (1.4)
>4wk - <=8wk	1 (2.3)	0	1 (4.2)	2 (8.7)	3 (6.7)	2 (4.4)	0	3 (8.3)	12 (4.2)
>8wk - <=12wk	0	0	0	3 (13.0)	2 (4.4)	0	6 (13.0)	4 (11.1)	15 (5.2)
>12wk - <=16wk	1 (2.3)	2 (8.7)	1 (4.2)	1 (4.3)	3 (6.7)	5 (11.1)	0	2 (5.6)	15 (5.2)
>16wk - <=20wk	0	2 (8.7)	2 (8.3)	0	1 (2.2)	1 (2.2)	2 (4.3)	5 (13.9)	13 (4.5)
>20wk - <=24wk	0	2 (8.7)	0	0	1 (2.2)	1 (2.2)	2 (4.3)	1 (2.8)	7 (2.4)
>24wk - <=30wk	42 (95.5)	17 (73.9)	20 (83.3)	17 (73.9)	32 (71.1)	36 (80.0)	36 (78.3)	20 (55.6)	220 (76.9)
>30wk	0	0	0	0	0	0	0	0	0

Table S16. Duration of Treatment - Safety Population(Protocol C4491011_FCSR)

	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)	Total (N=286)

a. The Total Number of weeks of treatment from first injection to 2 or 4 weeks after the last injection.

Note: The number of doses reflects the number of syringes used. For the four 120 and 160 mg dose groups, there were 2 syringes per dosing.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (12:00) Source Data: adex Table Generation: 05APR2022 (07:52)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011 FCSR/adex s002
Table 14.4.1.1 Vupanorsen is for Pfizer internal use.

Adverse Events

All AEs were all-causality and treatment-emergent unless otherwise specified (Table S17).

- The proportion of participants with AEs was greatest in the 160 mg Q2W group (86.1%) and lowest in the 120 mg Q4W group (52.2%) compared to the other vupanorsen groups versus 70.5% for placebo.
- The proportion of participants with SAEs was highest in the 80 mg Q2W group (13.3%) and lowest in the 120 mg Q4W group (0%) versus placebo (9.1%). None of the SAEs were considered related to treatment.
- The proportion of participants who experienced a severe AE was approximately 2 times greater in the 60 mg Q2W group (16.7%) compared to the 80 mg Q4W (8.7%) and 80 mg Q2W (8.9%) groups. The proportion of participants with severe AEs was lowest in the 120 mg Q2W (4.3%), 160 mg Q4W (4.4%), and 160 mg Q2W (5.6%) groups. No severe AEs were reported in the 120 mg Q4W group (0%). The proportion of participants with severe AEs for placebo was 11.4%.
- All treatment groups had participants who discontinued study drug due to AEs and continued in the study. The proportion of participants who discontinued study drug due to AEs and continued in the study ranged from 8.3% in the 60 mg Q2W group to 38.9% in the 160 mg Q2W group. The proportion of participants who discontinued study drug due to AEs and continued in the study in the placebo group was 2.3%.
- The proportion of participants who discontinued the study due to AEs was low (4.2% in the 60 mg Q2W group and 2.2% in the 80 mg Q2W group). None of the participants discontinued the study due to AEs in the other vupanorsen treatment groups. There were no participants in the placebo group who discontinued the study due to AEs.

Table S17. Treatment-Emergent Adverse Events (All Causalities) - Safety Population (Protocol C4491011_FCSR)

Number (%) of Participants	Placebo n (%)	80 mg Q4W n (%)	60 mg Q2W n (%)	120 mg Q4W n (%)	80 mg Q2W n (%)	160 mg Q4W n (%)	120 mg Q2W n (%)	160 mg Q2W n (%)
Participants evaluable for adverse events	44	23	24	23	45	45	46	36
Number of adverse events	87	35	46	40	102	78	79	84
Participants with adverse events	31 (70.5)	15 (65.2)	17 (70.8)	12 (52.2)	31 (68.9)	28 (62.2)	30 (65.2)	31 (86.1)
Participants with serious adverse events	4 (9.1)	2 (8.7)	2 (8.3)	0	6 (13.3)	1 (2.2)	3 (6.5)	1 (2.8)
Participants with severe adverse events	5 (11.4)	2 (8.7)	4 (16.7)	0	4 (8.9)	2 (4.4)	2 (4.3)	2 (5.6)
Participants discontinued from study due to adverse events[a]	0	0	1 (4.2)	0	1 (2.2)	0	0	0
Participants discontinued study drug due to AE and continue Study[b]	1 (2.3)	2 (8.7)	2 (8.3)	3 (13.0)	9 (20.0)	4 (8.9)	7 (15.2)	14 (38.9)
Participants with dose reduced or temporary discontinuation due to adverse events[c]	0	1 (4.3)	3 (12.5)	1 (4.3)	2 (4.4)	1 (2.2)	4 (8.7)	5 (13.9)

Includes all data collected since the first dose of study drug.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Participant to be discontinued from Study
c. Participants with dose reduced or temporary discontinuation due to adverse events: Participants did not have the option to reduce dose and the count is reflective of only dose interruptions.
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:00) Source Data: adae Table Generation: 16FEB2022 (09:32)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011 FCSR/adae s010
Table 14.3.1.2.2 Vupanorsen is for Pfizer internal use.

Incidence of Adverse Events

Treatment-emergent adverse events (TEAEs) by system organ class (SOC) and preferred term (PT) (All Causalities) that occurred in ≥5% of participants are listed in Table S18. Injection site reactions (ISRs) were among the most common TEAEs in all dose groups and alanine aminotransferase (ALT) increased was the most common in the 2 highest dose groups.

The most common TEAEs in each vupanorsen dose group are listed below (Table S18).

- 80 mg Q4W group: diarrhea, fatigue, injection site erythema, ISR, urinary tract infection, arthralgia, back pain, and headache (1 participant, 4.3% each)
- 60 mg Q2W group: ISR, pain in extremity (3 participants, 12.5% each), injection site recall reaction, urine analysis abnormal, gout, back pain, osteoarthritis, and acute kidney injury (2 participants, 8.3% each)
- 120 mg Q4W group: ISR (4 participants, 17.4%), injection site erythema and anxiety (2 participants, 8.7% each)
- 80 mg Q2W group: back pain (6 participants, 13.3%), ISR and arthralgia (4 participants, 8.9% each)
- 160 mg Q4W group: ISR (4 participants, 8.9%), myalgia and headache (3 participants, 6.7% each)
- 120 mg Q2W group: ISR (6 participants, 13.0%), injection site recall reaction (5 participants, 10.9%), ALT increased (4 participants, 8.7%)
- 160 mg Q2W group: ALT increased (9 participants, 25.0%), ISR (8 participants, 22.2%), transaminases increased (6 participants, 16.7%), aspartate aminotransferase (AST) increased and injection site erythema (4 participants, 11.1% each), hepatic enzyme increased, injection site recall reaction, urinary tract infection, muscular weakness, and hypertension (3 participants, 8.3% each), diarrhoea, gastrooesophageal reflux disease, and flank pain (2 participants, 5.6% each)

Table S18. Treatment-Emergent Adverse Events occurring in >=5% of Participants by System Organ Class and Preferred Term (All Causalities) - Safety Population (Protocol C4491011_FCSR)

Number of Participants Evaluable for AEs	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With Any adverse event	17 (38.6)	6 (26.1)	14 (58.3)	8 (34.8)	24 (53.3)	13 (28.9)	21 (45.7)	27 (75.0)
GASTROINTESTINAL DISORDERS	3 (6.8)	1 (4.3)	0	0	1 (2.2)	3 (6.7)	2 (4.3)	4 (11.1)
Diarrhoea	3 (6.8)	1 (4.3)	0	0	1 (2.2)	1 (2.2)	2 (4.3)	2 (5.6)
Gastrooesophageal reflux disease	0	0	0	0	0	2 (4.4)	0	2 (5.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (4.5)	3 (13.0)	5 (20.8)	6 (26.1)	7 (15.6)	7 (15.6)	11 (23.9)	11 (30.6)
Fatigue	2 (4.5)	1 (4.3)	1 (4.2)	0	1 (2.2)	2 (4.4)	3 (6.5)	0
Injection site erythema	0	1 (4.3)	1 (4.2)	2 (8.7)	2 (4.4)	1 (2.2)	3 (6.5)	4 (11.1)
Injection site reaction	0	1 (4.3)	3 (12.5)	4 (17.4)	4 (8.9)	4 (8.9)	6 (13.0)	8 (22.2)
Injection site recall reaction	0	0	2 (8.3)	1 (4.3)	2 (4.4)	0	5 (10.9)	3 (8.3)
HEPATOBILIARY DISORDERS	0	0	0	0	1 (2.2)	0	3 (6.5)	0
Drug-induced liver injury	0	0	0	0	1 (2.2)	0	3 (6.5)	0
INFECTIONS AND INFESTATIONS	4 (9.1)	1 (4.3)	1 (4.2)	1 (4.3)	3 (6.7)	1 (2.2)	1 (2.2)	3 (8.3)
Urinary tract infection	4 (9.1)	1 (4.3)	1 (4.2)	1 (4.3)	3 (6.7)	1 (2.2)	1 (2.2)	3 (8.3)
INVESTIGATIONS	2 (4.5)	0	3 (12.5)	0	3 (6.7)	1 (2.2)	7 (15.2)	18 (50.0)
Alanine aminotransferase increased	2 (4.5)	0	0	0	1 (2.2)	1 (2.2)	4 (8.7)	9 (25.0)

Table S18. Treatment-Emergent Adverse Events occurring in >=5% of Participants by System Organ Class and Preferred Term (All Causalities) - Safety Population (Protocol C4491011_FCSR)

Number of Participants Evaluable for AEs	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Aspartate aminotransferase increased	1 (2.3)	0	0	0	0	0	2 (4.3)	4 (11.1)
Hepatic enzyme increased	0	0	1 (4.2)	0	0	0	2 (4.3)	3 (8.3)
Transaminases increased	0	0	0	0	2 (4.4)	0	1 (2.2)	6 (16.7)
Urine analysis abnormal	0	0	2 (8.3)	0	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	1 (2.3)	0	2 (8.3)	0	0	0	0	0
Gout	1 (2.3)	0	2 (8.3)	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	6 (13.6)	2 (8.7)	8 (33.3)	0	11 (24.4)	5 (11.1)	5 (10.9)	5 (13.9)
Arthralgia	2 (4.5)	1 (4.3)	1 (4.2)	0	4 (8.9)	1 (2.2)	3 (6.5)	1 (2.8)
Back pain	2 (4.5)	1 (4.3)	2 (8.3)	0	6 (13.3)	1 (2.2)	0	0
Flank pain	0	0	0	0	0	0	0	2 (5.6)
Muscular weakness	0	0	0	0	0	0	0	3 (8.3)
Myalgia	1 (2.3)	0	0	0	2 (4.4)	3 (6.7)	0	0
Osteoarthritis	0	0	2 (8.3)	0	1 (2.2)	0	0	0
Pain in extremity	1 (2.3)	0	3 (12.5)	0	3 (6.7)	0	2 (4.3)	0
NERVOUS SYSTEM DISORDERS	2 (4.5)	1 (4.3)	1 (4.2)	1 (4.3)	2 (4.4)	3 (6.7)	1 (2.2)	0
Headache	2 (4.5)	1 (4.3)	1 (4.2)	1 (4.3)	2 (4.4)	3 (6.7)	1 (2.2)	0
PSYCHIATRIC DISORDERS	0	0	0	2 (8.7)	1 (2.2)	2 (4.4)	0	0
Anxiety	0	0	0	2 (8.7)	1 (2.2)	2 (4.4)	0	0
RENAL AND URINARY DISORDERS	0	0	2 (8.3)	0	0	0	0	0
Acute kidney injury	0	0	2 (8.3)	0	0	0	0	0
VASCULAR DISORDERS	3 (6.8)	0	0	0	0	0	0	3 (8.3)

Table S18. Treatment-Emergent Adverse Events occurring in >=5% of Participants by System Organ Class and Preferred Term (All Causalities) - Safety Population (Protocol C4491011_FCSR)

Number of Participants Evaluable for AEs	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hypertension	3 (6.8)	0	0	0	0	0	0	3 (8.3)

Participants are only counted once per treatment per event.
Totals for the No. of Participants at a higher-level are not necessarily the sum of those at the lower levels since a Participant may report two or more different adverse events within the higher level category.
Includes data up to lag days after last dose of study drug.
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:00) Source Data: adae Table Generation: 16FEB2022 (13:29)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/adae_s0311a
Table 14.3.1.2.3a Vupanorsen is for Pfizer internal use.

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The number of participants (percent) in each vupanorsen treatment group with severe TEAEs is listed below.

- 160 mg Q4W group: 1 (2.2%) acute myocardial infarction, 1 (2.2%) infection parasitic, 1 (2.2%) radiculopathy
- 60 mg Q2W group: 1 (4.2%) urinary tract infection, 1 (4.2%) muscle rupture, 1 (4.2%) intervertebral disc disorder, 1 (4.2%) osteoarthritis, 1 (4.2%) acute kidney injury
- 80 mg Q2W group: 1 (2.2%) nausea, 1 (2.2%) head injury, 1 (2.2%) osteoarthritis, 1 (2.2%) acoustic neuroma, 1 (2.2%) alopecia
- 120 mg Q2W group: 1 (2.2%) acute coronary syndrome, 1 (2.2%) SARS-CoV-2 test positive
- 80 mg Q4W group: 1 (4.3%) gastroenteritis, 1 (4.3%) back pain, 1 (4.3%) thrombosis
- 160 mg Q2W group: 1 (2.8%) ischaemic stroke, 1 (2.8%) injection site erythema

Analysis of Adverse Events

Permanent Discontinuations Due to Adverse Events

Discontinuations from study drug due to AEs (and continued in the study) ranged from 2 (8.3%) participants in the 60 mg Q2W group to 14 (38.9%) participants in the 160 mg Q2W group compared to 1 (2.3%) participant in the placebo group (Table S17). Of participants who discontinued study drug due to AEs, the greatest number discontinued for ISR AEs. At the 2 highest vupanorsen doses, liver-related AEs were the most common reason for discontinuation from study drug (Table S19).

The most common PTs in any vupanorsen dose group that led to discontinuation from study drug are summarized in Table S19.

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Table S19. Summary of Participant Discontinuations From Study Drug Due to Adverse Events - Safety Population(Protocol C4491011_FCSR)

Number of Participants Evaluable for AEs	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Participants with any AE	1 (2.3)	2 (8.7)	2 (8.3)	3 (13.0)	9 (20.0)	4 (8.9)	7 (15.2)	14 (38.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	0	0	0	0	1 (2.8)
Eosinophilia	0	0	0	0	0	0	0	1 (2.8)
CARDIAC DISORDERS	0	0	0	0	1 (2.2)	1 (2.2)	0	0
Acute myocardial infarction	0	0	0	0	0	1 (2.2)	0	0
Atrial fibrillation	0	0	0	0	1 (2.2)	0	0	0
GASTROINTESTINAL DISORDERS	0	0	0	1 (4.3)	0	1 (2.2)	0	0
Crohn's disease	0	0	0	0	0	1 (2.2)	0	0
Nausea	0	0	0	1 (4.3)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (4.3)	2 (8.3)	2 (8.7)	4 (8.9)	2 (4.4)	3 (6.5)	5 (13.9)
Injection site erythema	0	0	0	1 (4.3)	1 (2.2)	1 (2.2)	1 (2.2)	2 (5.6)
Injection site rash	0	1 (4.3)	0	0	0	0	0	0
Injection site reaction	0	0	2 (8.3)	1 (4.3)	3 (6.7)	1 (2.2)	2 (4.3)	3 (8.3)
Injection site recall reaction	0	0	0	0	1 (2.2)	0	0	1 (2.8)
HEPATOBILIARY DISORDERS	1 (2.3)	0	0	0	1 (2.2)	0	1 (2.2)	0

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Table S19. Summary of Participant Discontinuations From Study Drug Due to Adverse Events - Safety Population(Protocol C4491011_FCSR)

Number of Participants Evaluable for AEs	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Cholangitis	1 (2.3)	0	0	0	0	0	0	0
Drug-induced liver injury	0	0	0	0	1 (2.2)	0	1 (2.2)	0
INVESTIGATIONS	0	0	0	0	0	0	3 (6.5)	9 (25.0)
Alanine aminotransferase increased	0	0	0	0	0	0	0	4 (11.1)
Aspartate aminotransferase increased	0	0	0	0	0	0	0	3 (8.3)
Hepatic enzyme increased	0	0	0	0	0	0	1 (2.2)	2 (5.6)
SARS-CoV-2 test positive	0	0	0	0	0	0	1 (2.2)	0
Transaminases increased	0	0	0	0	0	0	1 (2.2)	3 (8.3)
METABOLISM AND NUTRITION DISORDERS	0	0	0	1 (4.3)	0	0	0	0
Decreased appetite	0	0	0	1 (4.3)	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	0	1 (2.2)	0	0	0
Acoustic neuroma	0	0	0	0	1 (2.2)	0	0	0
NERVOUS SYSTEM DISORDERS	0	0	0	1 (4.3)	0	0	0	0
Migraine	0	0	0	1 (4.3)	0	0	0	0
PSYCHIATRIC DISORDERS	0	0	0	0	1 (2.2)	0	0	0
Anxiety	0	0	0	0	1 (2.2)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	1 (4.3)	0	0	0	0
Epistaxis	0	0	0	1 (4.3)	0	0	0	0

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Table S19. Summary of Participant Discontinuations From Study Drug Due to Adverse Events - Safety Population(Protocol C4491011_FCSR)

Number of Participants Evaluable for AEs	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=24)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=36)
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (4.3)	0	1 (4.3)	1 (2.2)	0	0	0
Erythema	0	0	0	1 (4.3)	0	0	0	0
Rash	0	1 (4.3)	0	0	0	0	0	0
Skin lesion	0	0	0	0	1 (2.2)	0	0	0

Participants are only counted once per treatment per event.
Totals for the No. of Participants at a higher level are not necessarily the sum of those at the lower levels since a participant may report two or more different adverse events within the higher level category.
Includes data up to lag days after last dose of study drug.
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:00) Source Data: adae Table Generation: 16FEB2022 (09:32)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/adae_s185
Table 14.3.1.1.1 Vupanorsen is for Pfizer internal use.

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Deaths (None)

No participants died during this study.

Other Serious Adverse Events

There were 22 SAE cases that occurred in 21 participants (Table S20). None of the events were considered treatment-related by the investigator or the sponsor. SAEs occurred in all treatment groups except 120 mg Q4W (Table S20).

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Table S20. Summary of Serious Adverse Events by System Organ Class and Preferred Terms (All Adverse Events) - Safety Population (Protocol C4491011_FCSR)

Number of Participants Evaluable for Adverse Events	Pre-randomization (N=2)	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=23)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=35)
Number (%) of Participants with Serious Adverse Events[a]: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Cardiac disorders	0	0	0	0	0	1 (2.2)	1 (2.2)	1 (2.2)	0
Acute coronary syndrome	0	0	0	0	0	0	0	1 (2.2)	0
Acute myocardial infarction	0	0	0	0	0	0	1 (2.2)	0	0
Atrial fibrillation	0	0	0	0	0	1 (2.2)	0	0	0
General disorders and administration site conditions	1 (50.0)	0	0	0	0	3 (6.7)	0	0	0
Chest pain	0	0	0	0	0	1 (2.2)	0	0	0
Condition aggravated	1 (50.0)	0	0	0	0	2 (4.4)	0	0	0
Hepatobiliary disorders	0	1 (2.3)	0	0	0	0	0	0	0
Cholangitis	0	1 (2.3)	0	0	0	0	0	0	0
Infections and infestations	0	1 (2.3)	1 (4.3)	1 (4.3)	0	0	0	1 (2.2)	0
COVID-19	0	0	0	0	0	0	0	1 (2.2)	0
Gastroenteritis	0	0	1 (4.3)	0	0	0	0	0	0
Urinary tract infection	0	1 (2.3)	0	1 (4.3)	0	0	0	0	0

CLINICAL STUDY REPORT SYNOPSIS

Table S20. Summary of Serious Adverse Events by System Organ Class and Preferred Terms (All Adverse Events) - Safety Population (Protocol C4491011_FCSR)

Number of Participants Evaluable for Adverse Events	Pre-randomization (N=2)	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=23)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=35)
Number (%) of Participants with Serious Adverse Events[a]: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Metabolism and nutrition disorders	0	1 (2.3)	0	0	0	0	0	0	0
Dehydration	0	1 (2.3)	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (4.3)	0	0	2 (4.4)	0	0	0
Back pain	0	0	1 (4.3)	0	0	0	0	0	0
Osteoarthritis	0	0	0	0	0	1 (2.2)	0	0	0
Spinal stenosis	0	0	0	0	0	1 (2.2)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (50.0)	1 (2.3)	0	1 (4.3)	0	1 (2.2)	0	0	0
Acoustic neuroma	0	0	0	0	0	1 (2.2)	0	0	0
Basal cell carcinoma	0	0	0	1 (4.3)	0	0	0	0	0
Bladder cancer	0	1 (2.3)	0	0	0	0	0	0	0
Transitional cell carcinoma	1 (50.0)	0	0	0	0	0	0	0	0
Nervous system disorders	1 (50.0)	0	0	0	0	1 (2.2)	0	0	1 (2.9)
Carotid artery stenosis	1 (50.0)	0	0	0	0	0	0	0	0
Ischaemic stroke	0	0	0	0	0	0	0	0	1 (2.9)
Seizure	0	0	0	0	0	1 (2.2)	0	0	0
Psychiatric disorders	0	0	0	0	0	0	0	1 (2.2)	0
Depression	0	0	0	0	0	0	0	1 (2.2)	0

CLINICAL STUDY REPORT SYNOPSIS

Table S20. Summary of Serious Adverse Events by System Organ Class and Preferred Terms (All Adverse Events) - Safety Population (Protocol C4491011_FCSR)

Number of Participants Evaluable for Adverse Events	Pre-randomization (N=2)	Placebo (N=44)	80 mg Q4W (N=23)	60 mg Q2W (N=23)	120 mg Q4W (N=23)	80 mg Q2W (N=45)	160 mg Q4W (N=45)	120 mg Q2W (N=46)	160 mg Q2W (N=35)
Number (%) of Participants with Serious Adverse Events[a]: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Vascular disorders	0	0	1 (4.3)	0	0	0	0	0	0
Thrombosis	0	0	1 (4.3)	0	0	0	0	0	0
Total preferred term events[b]	3	4	3	2	0	8	1	3	1
Total Number of Cases[c]	2	4	3	2	0	6	1	3	1
Total Number of Participants with Serious Adverse Events[d]	2	4	2	2	0	6	1	3	1
Total Number of Participants with Serious Adverse Events[e] 21									

A case is a single event or a series of related events not separated in time occurring in a single participant.
a. SAEs are counted at MedDRA preferred term/Treatment group with each individual SAE counted only once per participant per treatment group
b. Total number of events per participant per Treatment group
c. Number of cases that started in the Treatment group
d. Total number of participants having an event that started in the Treatment group
e. Overall count of participants that had a Serious adverse Event in any Treatment group
Source of Actual treatment Group is OC(Oracle Clinical) or PIMS(Phase I Management System). Source of SAE is SDW(Safety Data Warehouse)
f. Reporting period: Cumulative Through - Cut off date 24JAN2022.
PFIZER CONFIDENTIAL SDTM Creation: 21JAN2022 (12:09) Source Data: adsae Table Generation: 23FEB2022 (15:08)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/adsae_s001
Table 14.3.2.2.3 Vupanorsen is for Pfizer internal use.

CLINICAL STUDY REPORT SYNOPSIS

Other Significant Adverse Events

ISRs were defined as an adverse event of special interest (AESI) in the protocol. ISRs included bruising, dermatitis, erythema, pain, rash, vesicles, recall, cellulitis, discomfort, and general reactions. Recall reactions were defined as ISRs that occurred at a prior injection site after a subsequent injection treatment at a different site. All treatment groups had participants who experienced ISRs. The percentage of participants in the vupanorsen treatment groups who had ISRs ranged from 13.3% to 33.3% and was higher than the placebo group (4.5%). The largest percentage of participants experiencing ISRs was in the highest treatment group (160 mg Q2W) followed by the 120 mg Q4W group. Injection site recall reactions occurred in 5 of the 7 vupanorsen treatment groups and did not appear dose-related. The percentage of participants with recall reactions ranged from 4.3% to 10.9%, with the highest percentage in the 120 mg Q2W group. TEAEs by SOC and PT (ISRs) are summarized in Table S21.

CLINICAL STUDY REPORT SYNOPSIS

Table S21. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Injection Site Reactions) - Safety Population(Protocol C4491011_FCSR)

Number of Participants Evaluable for AEs	Placebo (N=44)		80 mg Q4W (N=23)		60 mg Q2W (N=24)		120 mg Q4W (N=23)		80 mg Q2W (N=45)		160 mg Q4W (N=45)		120 mg Q2W (N=46)		160 mg Q2W (N=36)	
Number (%) of Participants or Occurrences: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**
With adverse events	2 (4.5)		4 (17.4)		4 (16.7)		6 (26.1)		6 (13.3)		7 (15.6)		10 (21.7)		12 (33.3)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (2.3)	1	4 (17.4)	7	4 (16.7)	11	6 (26.1)	16	6 (13.3)	12	7 (15.6)	14	10 (21.7)	22	12 (33.3)	39
Injection site bruising	0	0	0	0	0	0	0	0	0	0	1 (2.2)	1	1 (2.2)	1	1 (2.8)	1
Injection site dermatitis	0	0	0	0	0	0	1 (4.3)	3	0	0	1 (2.2)	4	0	0	1 (2.8)	1
Injection site erythema	0	0	1 (4.3)	2	1 (4.2)	1	2 (8.7)	2	2 (4.4)	3	1 (2.2)	2	3 (6.5)	5	4 (11.1)	6
Injection site pain	1 (2.3)	1	1 (4.3)	1	0	0	0	0	0	0	0	0	1 (2.2)	1	0	0
Injection site rash	0	0	1 (4.3)	2	1 (4.2)	1	0	0	0	0	0	0	1 (2.2)	1	0	0
Injection site reaction	0	0	1 (4.3)	2	3 (12.5)	7	4 (17.4)	10	4 (8.9)	5	4 (8.9)	7	6 (13.0)	9	8 (22.2)	27
Injection site recall reaction	0	0	0	0	2 (8.3)	2	1 (4.3)	1	2 (4.4)	3	0	0	5 (10.9)	5	3 (8.3)	4
Injection site vesicles	0	0	0	0	0	0	0	0	1 (2.2)	1	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	0	0	0	0	0	0	0	0	0	0	0	0	1 (2.2)	1	0	0
Injection site cellulitis	0	0	0	0	0	0	0	0	0	0	0	0	1 (2.2)	1	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (2.3)	1	0	0	0	0	0	0	0	0	1 (2.2)	1	0	0	0	0

CLINICAL STUDY REPORT SYNOPSIS

Table S21. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Injection Site Reactions) - Safety Population(Protocol C4491011_FCSR)

Number of Participants Evaluable for AEs	Placebo (N=44)		80 mg Q4W (N=23)		60 mg Q2W (N=24)		120 mg Q4W (N=23)		80 mg Q2W (N=45)		160 mg Q4W (N=45)		120 mg Q2W (N=46)		160 mg Q2W (N=36)	
Number (%) of Participants or Occurrences: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**	**n (%)**	**n1[a]**
Injection related reaction	0	0	0	0	0	0	0	0	0	0	1 (2.2)	1	0	0	0	0
Post procedural discomfort	1 (2.3)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

n: The number of participants in this reporting group affected by any occurrence of this adverse event, All Causalities.
a. n1:The number of Occurrences of Treatment Emergent All Causalities adverse events.
Includes data up to LAG days after last dose of study drug.
Totals for the No. of Participants at a higher level are not necessarily the sum of those at the lower levels since a participant may report two or more different adverse events within the higher level category.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:00) Source Data: adae Table Generation: 16FEB2022 (09:32)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/adae_s176isr
Table 14.3.1.3.3 Vupanorsen is for Pfizer internal use.

CLINICAL STUDY REPORT SYNOPSIS

Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

- There were no deaths in the study.
- Twenty-one participants experienced SAEs (Table S20); none were treatment-related. Forty-two participants discontinued study drug due to AEs and continued the study, with greater proportions of discontinuations due to AEs occurring in the vupanorsen groups than placebo (Table S17 and Table S19).
- ISR AEs were reported in higher numbers among the vupanorsen groups, with the highest incidence in the 160 mg Q2W group (Table S21).
- ALT/AST elevations were also higher among the vupanorsen groups compared to placebo and appeared to be dose-dependent with the highest incidences at the top 2 vupanorsen doses (Table S18).
- No Hy's law cases were observed in the vupanorsen groups (Figure S10 and Figure S11).
- No safety signals were identified with regards to estimated glomerular filtration rate (eGFR) or platelet counts (Table S22, Figure S6, and Figure S7).
- Increases in HFF measured by magnetic resonance imaging derived proton density fat fraction (MRI-PDFF) at Week 24 were observed with vupanorsen treatment compared to placebo for doses of 120 mg Q4W and higher (Table S25).

Clinical Laboratory Evaluation

Platelets and eGFR

The mean change in platelet count from baseline over time until follow-up is shown in Figure S6. One participant (160 mg Q2W) had a platelet count <50 10^9/L (actual count was 7 10^9/L). The platelet count was repeated at a local lab 7 days later and the value was 184 10^9/L, suggesting this was a lab error (Table S22).

There were 3 participants (60 mg Q2W, 80 mg Q2W, 160 mg Q2W) with eGFR decreases ≥50% from baseline, but these were transient and reversible (Table S22). The mean change from baseline over time until follow-up in eGFR is shown in Figure S7.

CLINICAL STUDY REPORT SYNOPSIS

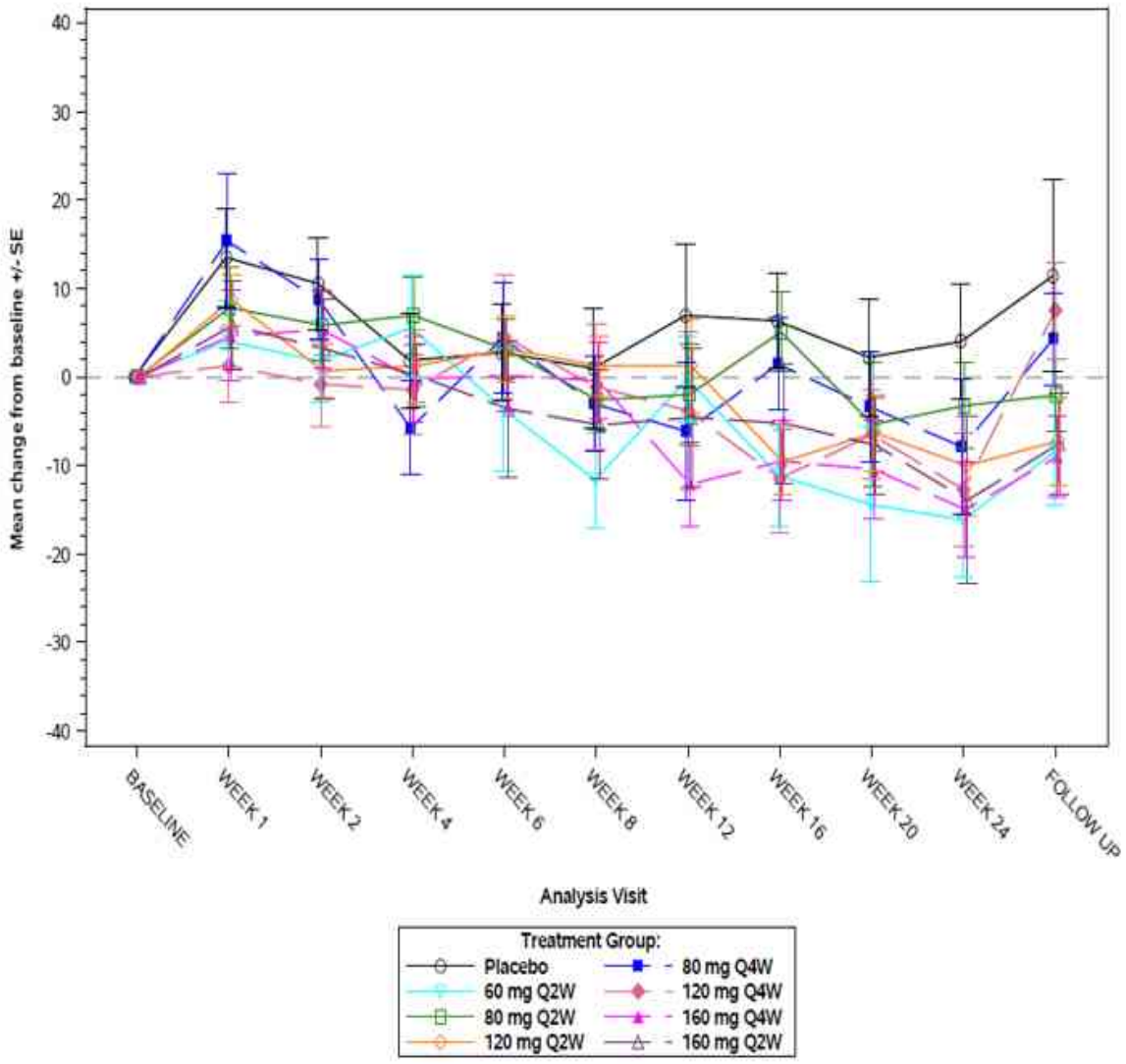
Table S22. Summary of Participants with Laboratory Test Abnormalities (Platelet Counts (10E9/L) and eGFR (mL/min/1.73m2)) - Safety Population (Protocol C4491011_FCSR)

	Placebo (N=44)	80mg Q4W (N=23)	60mg Q2W (N=24)	120mg Q4W (N=23)	80mg Q2W (N=45)	160mg Q4W (N=45)	120mg Q2W (N=46)	160mg Q2W (N=36)
Platelets(10^9/L) < 100	0	0	0	0	0	0	0	1(2.8)
< 100 and >=75	0	0	0	0	0	0	0	0
< 75 and >=50	0	0	0	0	0	0	0	0
< 50	0	0	0	0	0	0	0	1(2.8)
>=30% decrease from baseline	3(6.8)	1(4.3)	3(12.5)	2(8.7)	3(6.7)	4(8.9)	2(4.3)	3(8.3)
>=50% decrease from baseline	1(2.3)	1(4.3)	0	0	0	0	0	1(2.8)
eGFR (mL/min/1.73m^2) >=50% decrease from BL or < 15mL/min/1.73m^2	0	0	1(4.2)	0	1(2.2)	0	0	1(2.8)

PFIZER CONFIDENTIAL SDTM Creation: 16FEB2022 (08:13) Source Data: adlb Table Generation: 13APR2022 (12:37)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/tlbegfr
Table 14.3.4.1.7 Vupanorsen is for Pfizer internal use.

CLINICAL STUDY REPORT SYNOPSIS

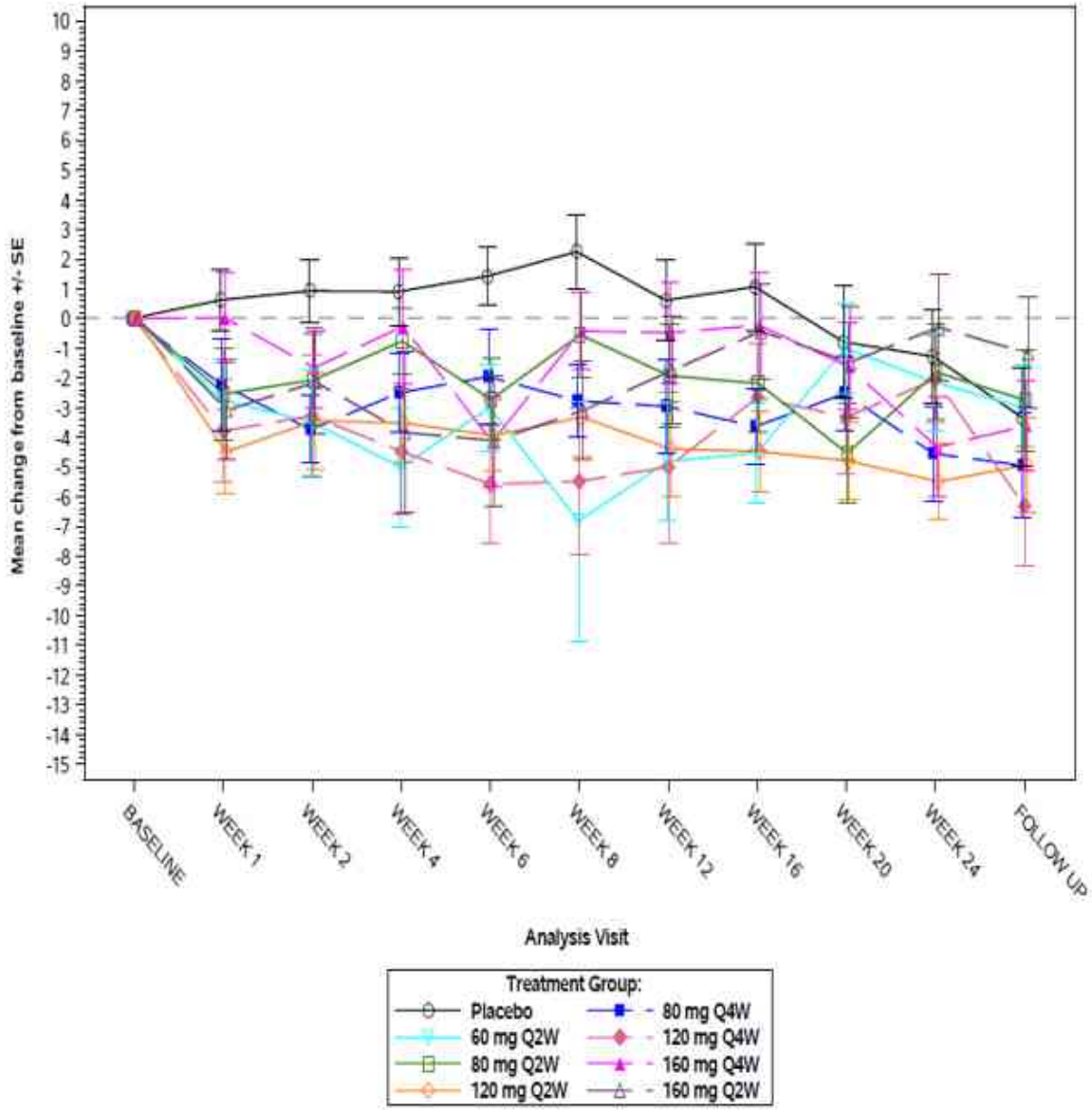
Figure S6. Mean Plot of Change From Baseline Over Time Until Follow-Up in Platelet Counts (10^9/L) - Safety Population



PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Date of Generation: 16FEB2022 (11:38)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/fmpltplat

CLINICAL STUDY REPORT SYNOPSIS

Figure S7. Mean Plot of Change From Baseline Over Time Until Follow-Up in eGFR (mL/min/1.73 m^2) - Safety Population



PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Date of Generation: 16FEB2022 (11:38)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: /CSR/C4491011_FCSR/fmpltegrf

CLINICAL STUDY REPORT SYNOPSIS

ALT, AST, and Bilirubin

Increases in ALT >3 times the upper limit of normal (ULN) occurred more frequently with higher vupanorsen doses and ranged from 0% (80 mg Q4W) to 44.4% (160 mg Q2W) of participants compared to 2.3% in the placebo group. One (2.2%) participant in the 120 mg Q2W group, 3 (8.3%) in the 160 Q2W group, and 1 (2.3%) in the placebo group had ALT elevations >8 times the ULN (Table S23).

Increases in AST >3 times the ULN occurred more frequently with higher vupanorsen doses and ranged from 0% (80 mg Q4W, 120 mg Q4W, and 80 mg Q2W) to 16.7% (160 mg Q2W) of participants compared to 2.3% in the placebo group (Table S23). One (2.8%) participant in the 160 mg Q2W group and 1 (2.3%) in the placebo group had AST elevations >8 times the ULN, meeting the protocol criterion for discontinuation from study treatment. There were no Hy's law cases in the vupanorsen treatment groups (Figure S10 and Figure S11).

Dose-dependent increases in AST and ALT at Week 24 were observed in all vupanorsen treatment groups except 80 mg Q4W when compared to placebo with the greater changes being dose-dependent for both ALT and AST (Figure S8 and Figure S9). eDISH plots of ALT, AST, and total bilirubin are in Figure S10 and Figure S11. The plots are consistent with the trends noted above.

CLINICAL STUDY REPORT SYNOPSIS

Table S23. Summary of Participants with Laboratory Test Abnormalities (AST/ALT(U/L) and Bilirubin(mg/dL))- Safety Population(Protocol C4491011_FCSR)

	Placebo (N=44)	80mg Q4W (N=23)	60mg Q2W (N=24)	120mg Q4W (N=23)	80mg Q2W (N=45)	160mg Q4W (N=45)	120mg Q2W (N=46)	160mg Q2W (N=36)
Participants with at least one ALT, AST or Bilirubin elevation	1(2.3)	0	1(4.2)	1(4.3)	1(2.2)	4(8.9)	11(23.9)	16(44.4)
ALT(U/L) >3xULN[a]	1(2.3)	0	1(4.2)	1(4.3)	1(2.2)	4(8.9)	11(23.9)	16(44.4)
>3[a] and <=5x ULN	0	0	1(4.2)	1(4.3)	0	2(4.4)	8(17.4)	10(27.8)
>5x ULN and <=8xULN	0	0	0	0	1(2.2)	2(4.4)	2(4.3)	3(8.3)
>8xULN	1(2.3)	0	0	0	0	0	1(2.2)	3(8.3)
AST(U/L) >3xULN[a]	1(2.3)	0	1(4.2)	0	0	3(6.7)	3(6.5)	6(16.7)
>3[a] and <=5x ULN	0	0	1(4.2)	0	0	3(6.7)	2(4.3)	4(11.1)
>5x ULN and <=8xULN	0	0	0	0	0	0	1(2.2)	1(2.8)
>8xULN	1(2.3)	0	0	0	0	0	0	1(2.8)
Bilirubin(mg/dL)>2 xULN	1(2.3)	0	0	0	0	0	0	0

CLINICAL STUDY REPORT SYNOPSIS

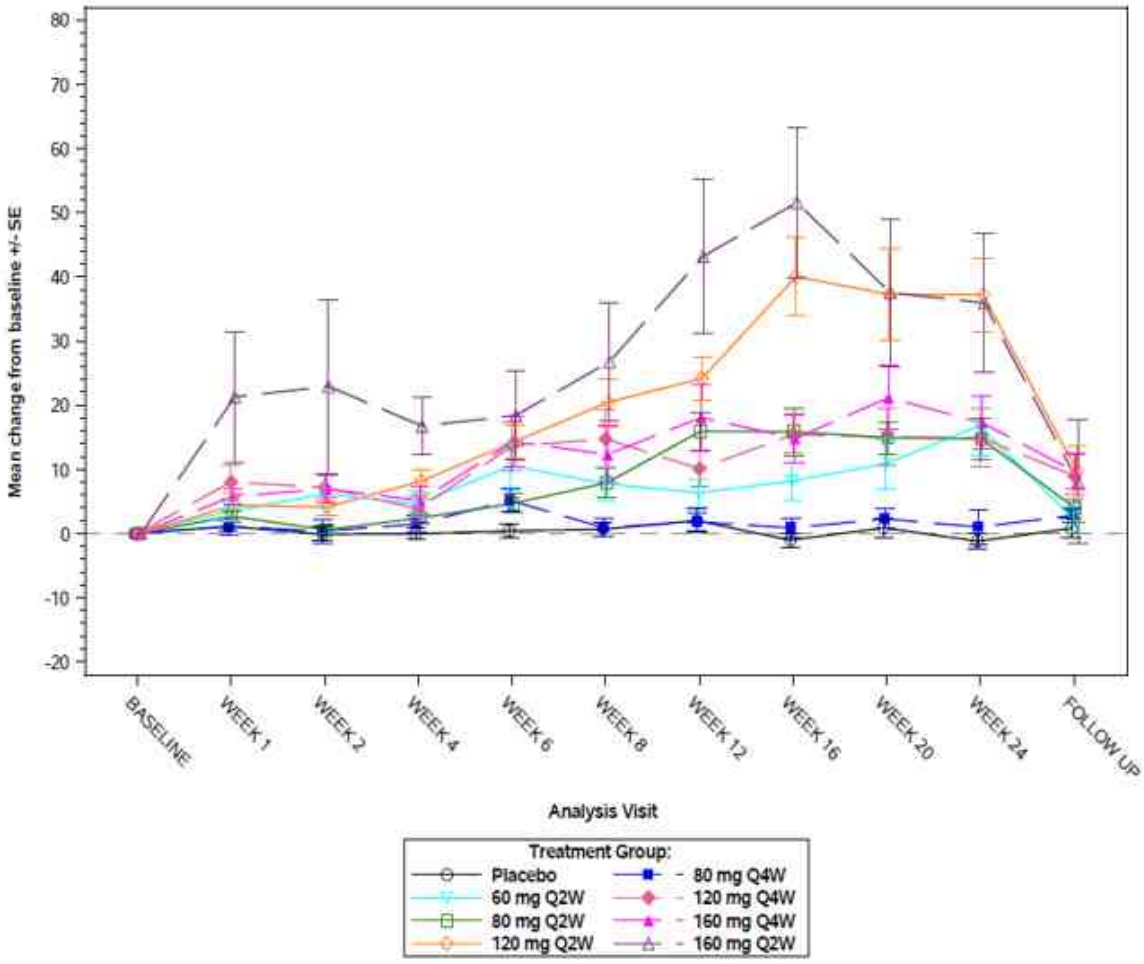
Table S23. Summary of Participants with Laboratory Test Abnormalities (AST/ALT(U/L) and Bilirubin(mg/dL))- Safety Population(Protocol C4491011_FCSR)

	Placebo (N=44)	80mg Q4W (N=23)	60mg Q2W (N=24)	120mg Q4W (N=23)	80mg Q2W (N=45)	160mg Q4W (N=45)	120mg Q2W (N=46)	160mg Q2W (N=36)

a. AST and/or ALT elevation >3 × ULN for participants with baseline AST and ALT within normal limits OR Baseline AST or ALT values above the reference range: AST or ALT values >2 times the baseline values AND >3 × ULN
PFIZER CONFIDENTIAL SDTM Creation: 16FEB2022 (08:13) Source Data: adlb Table Generation: 30MAR2022 (13:36)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/tlbasalt
Table 14.3.4.1.8 Vupanorsen is for Pfizer internal use.

CLINICAL STUDY REPORT SYNOPSIS

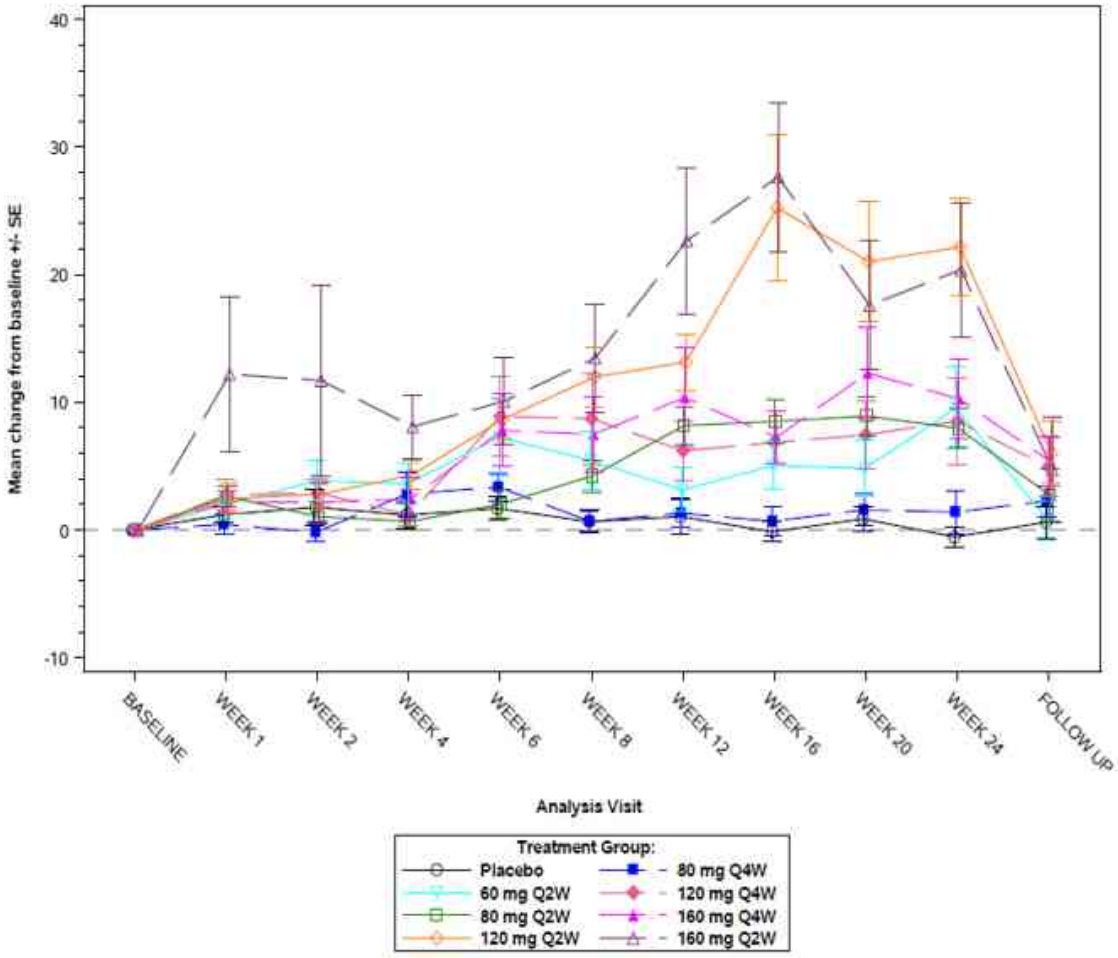
Figure S8. Mean Plot of Change From Baseline Over Time Until Follow-Up in ALT (U/L) - Safety Population



PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Date of Generation: 16FEB2022 (11:34)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: /CSR/C4491011_FCSR/fmpltalt

CLINICAL STUDY REPORT SYNOPSIS

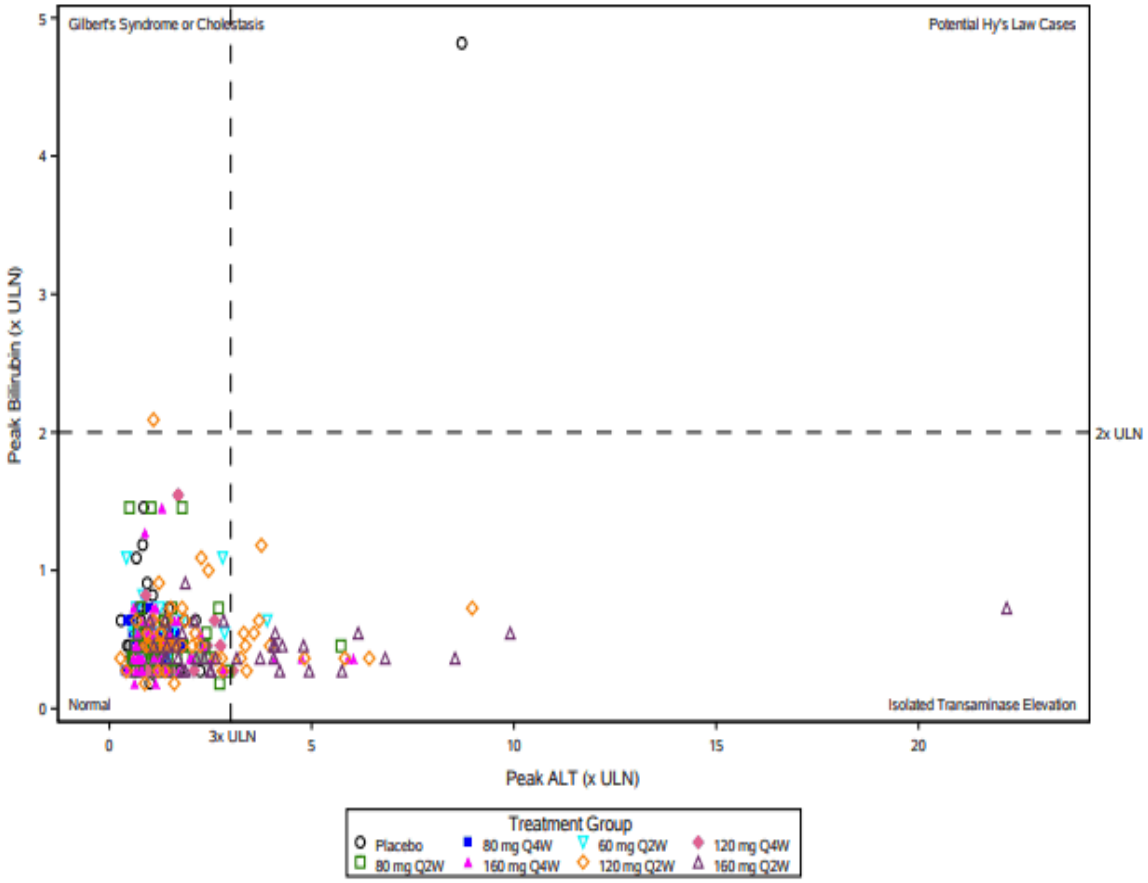
Figure S9. Mean Plot of Change From Baseline Over Time Until Follow-Up in AST (U/L) - Safety Population



PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Date of Generation: 16FEB2022 (11:38)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/fmpltast

CLINICAL STUDY REPORT SYNOPSIS

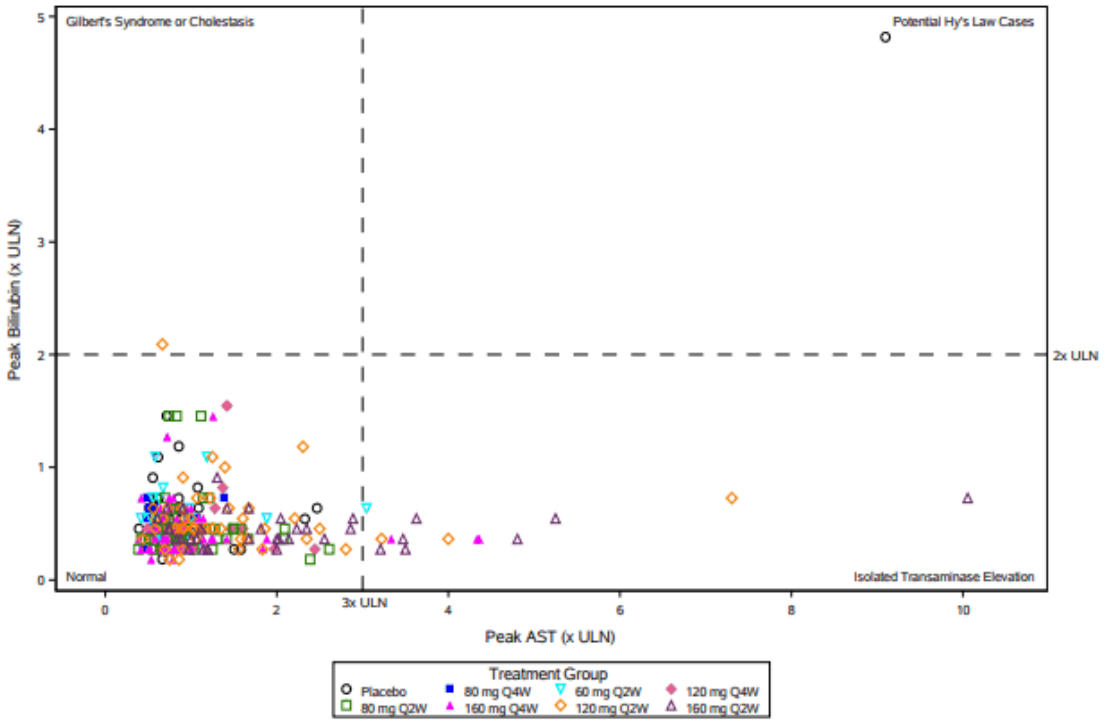
Figure S10. eDISH Plot for ALT (U/L) Safety Population



PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (12:52) Source Data: adlb Date of Generation: 31MAR2022 (10:24)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/fedishalt

CLINICAL STUDY REPORT SYNOPSIS

Figure S11. eDISH Plot for AST (U/L) Safety Population



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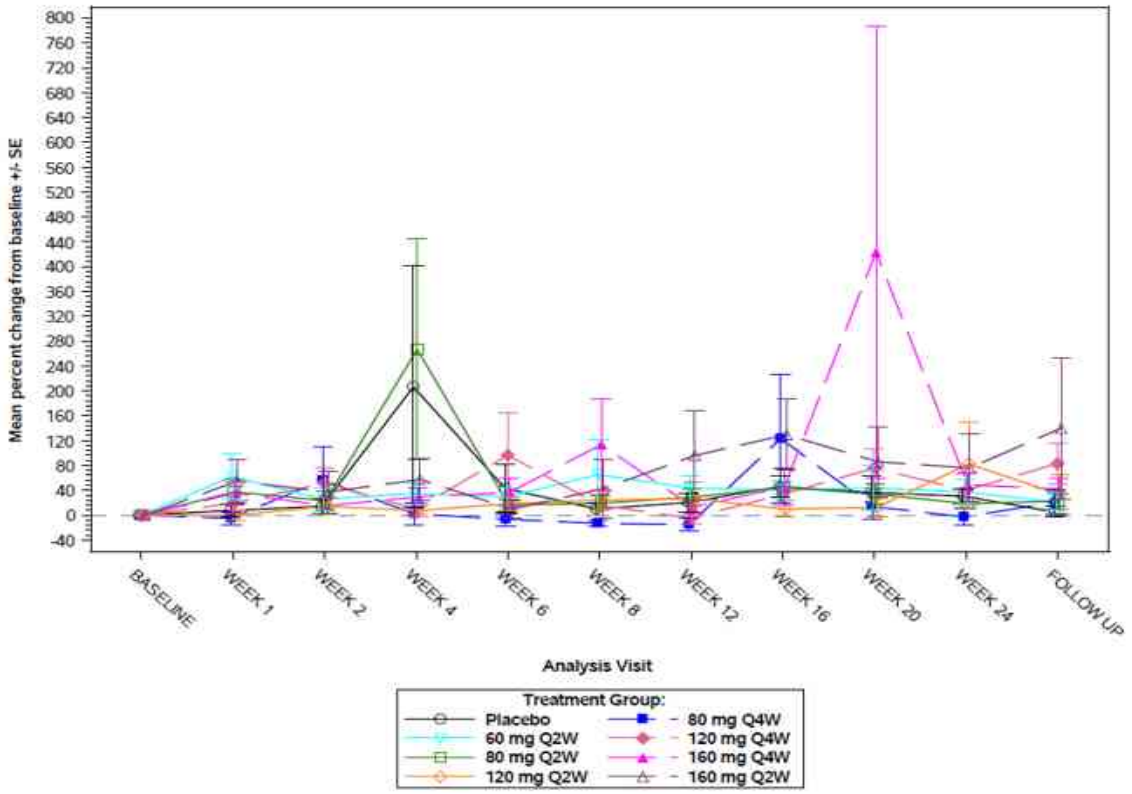
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/fedishast

Urine Albumin Creatinine Ratio(UACR)

Figure S12 shows the mean percent change from baseline over time in UACR.

CLINICAL STUDY REPORT SYNOPSIS

Figure S12. Mean Plot of Percent Change From Baseline Over Time Until Follow-Up in UACR (mg/g) – Safety Population



Note: When either Urine Albumin or Urine Creatinine is undetectable, the corresponding numeric value is used in order to calculate the Urine Albumin/Creatinine ratio. If both Urine Albumin and Urine Creatinine are undetectable, the Urine Albumin/Creatinine ratio is set to 0.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:52) Source Data: adlb Date of Generation: 16FEB2022 (11:38)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/fmpituacr

Glycated Hemoglobin (HbA1c)

Mean HbA1c levels were unchanged from baseline over time in all treatment groups.

Vital Signs, Electrocardiogram, Physical Findings, and Other Observations Related to Safety

No significant changes in vital signs were observed in the study.

ECG

No significant changes in ECG findings were observed in the study (Table S24).

CLINICAL STUDY REPORT SYNOPSIS

Table S24. Categorization of Post Baseline ECG Data - Safety Population - Safety Population(Protocol C4491011_FCSR)

		Placebo (N=44)		80 mg Q4W (N=23)		60 mg Q2W (N=24)		120 mg Q4W (N=23)		80 mg Q2W (N=45)		160 mg Q4W (N=45)		120 mg Q2W (N=46)		160 mg Q2W (N=36)	
Parameter (units)	**Criteria**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
QRS INTERVAL NOT OTHERWISE SPECIFIED (MSEC)	Value>=140 (45-64 Years)	23	0	10	0	11	1 (9.1)	10	0	20	0	22	0	27	1 (3.7)	17	0
	Value>=140 (>=65 Years)	21	2 (9.5)	12	1 (8.3)	13	1 (7.7)	10	1 (10.0)	21	1 (4.8)	20	0	15	0	19	1 (5.3)
	%Chg>=50% (45-64 Years)	23	0	10	0	11	0	10	0	20	1 (5.0)	22	0	27	0	17	0
QT INTERVAL NOT OTHERWISE SPECIFIED (MSEC)	Value>=500	44	0	22	0	24	0	22	0	42	0	42	1 (2.4)	43	0	36	0
QTC INTERVAL NOT OTHERWISE SPECIFIED (MSEC)	450 ms<=Value	44	2 (4.5)	22	1 (4.5)	24	2 (8.3)	22	1 (4.5)	42	4 (9.5)	42	5 (11.9)	43	4 (9.3)	36	4 (11.1)
	480 ms<=Value	44	1 (2.3)	22	0	24	1 (4.2)	22	0	42	0	42	0	43	0	36	0
	Value>=500 ms	44	0	22	0	24	0	22	0	42	3 (7.1)	42	0	43	1 (2.3)	36	0
	30 ms<=Chg	44	0	22	2 (9.1)	24	0	22	0	42	3 (7.1)	42	2 (4.8)	43	2 (4.7)	36	1 (2.8)

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Table S24. Categorization of Post Baseline ECG Data - Safety Population - Safety Population(Protocol C4491011_FCSR)

		Placebo (N=44)		80 mg Q4W (N=23)		60 mg Q2W (N=24)		120 mg Q4W (N=23)		80 mg Q2W (N=45)		160 mg Q4W (N=45)		120 mg Q2W (N=46)		160 mg Q2W (N=36)	
Parameter (units)	**Criteria**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
QTCF - FRIDERICIA'S CORRECTION FORMULA NOT OTHERWISE SPECIFIED (MSEC)	450 ms<=Value	44	0	22	1 (4.5)	24	3 (12.5)	22	2 (9.1)	42	6 (14.3)	42	4 (9.5)	43	4 (9.3)	36	1 (2.8)
	480 ms<=Value	44	1 (2.3)	22	0	24	0	22	0	42	1 (2.4)	42	0	43	0	36	0
	Value>=500 ms	44	0	22	0	24	0	22	0	42	1 (2.4)	42	0	43	0	36	0
	30 ms<=Chg	44	0	22	1 (4.5)	24	0	22	0	42	3 (7.1)	42	2 (4.8)	43	1 (2.3)	36	0
	Chg>=60 ms	44	0	22	0	24	0	22	0	42	1 (2.4)	42	0	43	0	36	0

N=number of Participants evaluated against criteria. n=number of Participants that met criteria.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (12:30) Source Data: adeg Table Generation: 05APR2022 (13:00)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/adeg_s502
Table 14.3.6.2.1 Vupanorsen is for Pfizer internal use.

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HFF

Increases in HFF measured by MRI-PDFF were observed with vupanorsen doses of 120 mg Q4W and higher compared to placebo, with the maximum increase seen in the 160 mg Q2W treatment group where the ratio of LS mean relative change over placebo was 1.79 (95% CI: 1.47, 2.16) (Table S25).

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Table S25. Relative Change in HFF (%) (assessed by MRI PDFF) at Week 24 - ANCOVA -Safety Population(Protocol C4491011_FCSR)

			Relative Change from Baseline		Ratio in Relative Change over Placebo	
Visit	Treatment	N	LSM	95% CI	LSM	95% CI
WEEK 24	Placebo	42	0.99	(0.88,1.11)		
	80 mg Q4W	20	1.13	(0.95,1.34)	1.15	(0.93,1.41)
	60 mg Q2W	21	1.05	(0.89,1.23)	1.06	(0.87,1.30)
	120 mg Q4W	15	1.24	(1.02,1.51)	1.26	(1.01,1.59)
	80 mg Q2W	33	1.21	(1.06,1.38)	1.23	(1.03,1.46)
	160 mg Q4W	35	1.24	(1.09,1.41)	1.26	(1.06,1.50)
	120 mg Q2W	36	1.40	(1.23,1.59)	1.42	(1.19,1.68)
	160 mg Q2W	25	1.76	(1.51,2.05)	1.79	(1.47,2.16)

Relative Change has been calculated for Whole Liver PDFF.
Log-transformed relative changes from baseline were modeled using an ANCOVA with treatment and log-transformed baseline liver fat as a covariate.
Values have been back-transformed from the log scale.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2022 (11:00) Source Data: adgimr Table Generation: 16FEB2022 (09:43)
(Data cutoff date : 24JAN2022 Database snapshot date : 24JAN2022) Output File: ./CSR/C4491011_FCSR/adgimr_s002a
Table 14.3.4.1.13 Vupanorsen is for Pfizer internal use.

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Conclusion(s): Vupanorsen treatment resulted in statistically significant reductions in non-HDL-C, TG, and ANGPTL3 at all doses and ApoB at all doses except 120 mg Q2W. Statistically significant reductions in direct LDL-C were observed only at the 80 mg Q2W and 160 mg Q4W doses. ISRs, liver enzyme abnormalities, HFF increases, ADA, and discontinuations from study treatment due to these AEs were more frequent in the higher monthly vupanorsen dose groups.