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ORIGINAL ARTICLE

Olezarsen for Hypertriglyceridemia in Patients at High Cardiovascular Risk

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Elevated triglyceride-rich lipoprotein and triglyceride levels are associated with heightened cardiovascular risk, and hypertriglyceridemia has direct clinical consequences (e.g., an increased risk of acute pancreatitis), particularly when the condition is severe.

Reducing the level of triglyceriderich lipoproteins remains an unmet clinical need.

Apolipoprotein C-III (APOC3), which is synthesized primarily in the liver and to a lesser extent in the intestine, increases plasma triglyceride levels through several mechanisms, including inhibition of lipoprotein lipase and reduction of hepatic clearance of triglyceride-rich lipoproteins.

Loss of-function variants in APOC3 are associated with lower triglyceride levels and reduced cardiovascular risk. Trials of volanesorsen, an unconjugated antisense oligonucleotide targeting APOC3 messenger RNA (mRNA), in healthy volunteers or patients with chylomicronemia syndromes showed significant reductions in triglyceride levels.In a recent meta-analysis, volanesorsen reduced the risk of acute pancreatitis events.

Olezarsen (ISIS 678354) is an investigational N-acetylgalactosamine–conjugated antisense oligonucleotide targeting APOC3 mRNA that has been evaluated in a phase 1 study involving healthy volunteers and in a small, phase 2, doseranging study.

We designed the Bridge–TIMI (Thrombolysis in Myocardial Infarction) 73a trial to assess the efficacy and safety of olezarsen in patients with moderate hypertriglyceridemia (triglyceride level, 150 to 499 mg per deciliter [1.7 to 5.6 mmol per liter]) plus elevated cardiovascular risk and in those with severe hypertriglyceridemia (triglyceride level, ≥500 mg per deciliter)

Methods

In this phase 2b, randomized, placebo-controlled, double-blind trial, we assigned adults who were receiving stable lipid-lowering therapy and had either moderate hypertriglyceridemia plus elevated cardiovascular risk or severe hypertriglyceridemia in a 1:1 ratio to either a 50-mg or 80-mg cohort. Patients were then assigned in a 3:1 ratio to receive monthly subcutaneous olezarsen or matching placebo within each cohort.

The objective of this phase 2b trial was to assess the efficacy of these two doses of olezarsen across several lipid measures of clinical importance, while also providing additional safety data.

- The treatment period was 12 months, followed by a 13-week follow-up period.

  All the patients provided written informed consent

Adults (≥18 years of age) were eligible for the trial if they had either moderate hypertriglyceridemia plus an increased risk of atherosclerotic cardiovascular disease or severe hypertriglyceridemia.

Patients were **excluded** if they had poorly controlled, severe, or newly recognized diabetes mellitus; a recent acute coronary syndrome, cerebrovascular event, or arterial revascularization; recent acute pancreatitis; or important hepatic or renal laboratory abnormalities.

At the time of enrollment, patients were expected to be receiving stable lipidlowering therapy, according to the local standard of care.

Qualifying and follow-up laboratory tests were obtained in the fasting state.

If a qualifying triglyceride value fell below the required level, two additional tests were allowed, with the average of all values used to determine eligibility for trial enrollment.

Outcomes

The **primary outcome** was the percent change in the triglyceride level from baseline to 6 months, reported as the difference between each olezarsen dose group and placebo.

secondary outcomes were changes in other lipid measures, including APOC3, very-low-density lipoprotein (VLDL) cholesterol, total apolipoprotein B, non–high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol at 6 months; changes in lipid levels at 12 months; the proportion of patients with moderate hypertriglyceridemia at baseline who had a triglyceride level of less than 150 mg per deciliter (the generally accepted clinical threshold for normal reference value) at 6 months and 12 months; and pancreatitis events .

Assessments of key **safety outcomes included** monitoring for abnormalities in renal function, platelet counts, and liver enzymes, as well as adverse clinical events. For patients in the 80-mg group, a blinded dose reduction from 80 mg to 50 mg could be considered in patients with a decrease in the platelet count to a level of 50,000 to 100,000 per microliter or for other safety or adverse-event concerns. Blood and urine samples were measured centrally by Medpace Reference Laboratories with the use of commercial assays.

Pancreatitis events were to be adjudicated by a central committee in a blinded manner.

We determined that the enrollment of 152 patients would provide the trial with at least 80% power to show a 60% lower triglyceride level for each dose of olezarsen as compared with placebo.

Baseline lipid measurements were defined as the mean of the predose level on day 1 and all levels during the qualification period.

Month 6 levels were defined as the mean of week 25 and week 27 levels, and month 12 levels were defined as the average of week 51 and week 53 levels.

We used the Markov chain Monte Carlo method under the multivariate normality assumption to impute the missing values according to trial group.

Results

Patients were recruited at 24 sites in the United States and Canada from June through September 2022.

A total of 154 patients underwent randomization to receive 50 mg of olezarsen (58 patients), 80 mg of olezarsen (57 patients), or placebo (39 patients) once a month.

Premature discontinuation of olezarsen or placebo occurred in 14 of 58 patients (24%) in the olezarsen 50-mg group, in 7 of 57 patients (12%) in the olezarsen 80-mg group, and in 3 of 39 patients (8%) in the placebo group .

One patient (2%) in the olezarsen 80-mg group had a dose reduction to 50 mg.

In the three groups, 1 patient died (in the olezarsen 50-mg group), 2 were lost to follow-up (1 in each of the olezarsen groups)

and 1 withdrew consent (in the olezarsen 50-mg group).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Olezarsen, 50 mg (N=58)	Olezarsen, 80 mg (N=57)	Placebo (N=39)
Median age (IQR) — yr	63 (54–71)	60 (54–69)	63 (58–71)
Female sex — no. (%)	24 (41)	17 (30)	24 (62)
Race and ethnic group — no. (%)†			
White	54 (93)	52 (91)	35 (90)
Non-Hispanic or Latino	34 (59)	29 (51)	25 (64)
Hispanic or Latino	20 (34)	23 (40)	10 (26)
Black	3 (5)	5 (9)	4 (10)
Non-Hispanic or Latino	2 (3)	5 (9)	1 (3)
Hispanic or Latino	1 (2)	0	3 (8)
Asian	1 (2)	0	0
Median body-mass index (IQR)‡	32.9 (29.7–38.4)	32.4 (27.6–36.6)	33.0 (30.7–37.9)
Medical history — no. (%)			
Pancreatitis	2 (3)	0	0
Atherosclerotic cardiovascular disease	16 (28)	12 (21)	6 (15)
Diabetes mellitus	37 (64)	38 (67)	30 (77)
Chronic kidney disease	8 (14)	9 (16)	5 (13)
Laboratory values			
Triglycerides			
Median value (IQR) — mg/dl	230.0 (182.5–331.5)	241.5 (179.5–357.5)	249.3 (219.5–284.5)
≥500 mg/dl — no. (%)	5 (9)	7 (12)	4 (10)
Median APOC3 (IQR) — mg/dl	15.3 (12.0–19.3)	13.4 (11.5–17.9)	15.8 (13.2–18.7)
Median VLDL cholesterol (IQR) — mg/dl	41.0 (34.0–62.5)	43.0 (31.0–56.7)	41.5 (36.0–61.0)
Median non-HDL cholesterol (IQR) — mg/dl	132.2 (103.5–156.5)	126.0 (110.0–150.5)	134.5 (110.0–161.5)
Median apolipoprotein B (IQR) — mg/dl	90.8 (75.5–105.0)	93.0 (78.0–107.0)	94.0 (78.0–114.5)
Median LDL cholesterol (IQR) — mg/dl	83.8 (59.5–106.0)	80.5 (62.0–102.0)	81.5 (62.0–104.5)
Median glycated hemoglobin (IQR) — %	6.3 (5.9–7.3)	6.4 (5.8–7.0)	6.6 (6.0–7.3)
Median creatinine (IQR) — mg/dl	0.8 (0.7–1.0)	0.9 (0.8–1.1)	0.8 (0.7–0.9)
Median platelet count (IQR) — no./μl	239,000 (198,000–283,000)	237,000 (196,000–288,000)	238,000 (223,000–295,000)
Lipid-lowering therapy — no. (%)			
Any	57 (98)	53 (93)	39 (100)
Statin	49 (84)	46 (81)	32 (82)
Ezetimibe	5 (9)	2 (4)	3 (8)
Fibrate	5 (9)	9 (16)	11 (28)
N–3 fatty acids	12 (21)	14 (25)	8 (21)
Niacin	0	0	1 (3)
PCSK9 inhibitor	3 (5)	1 (2)	1 (3)
≥2 therapies	14 (24)	17 (30)	16 (41)

* To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. APOC3 denotes apolipoprotein C-III, HDL high-density lipoprotein, IQR interquartile range, LDL low-density lipoprotein, PCSK9 proprotein convertase subtilisin kexin type 9, and VLDL very-low-density lipoprotein.
† Race and ethnic group were reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

The median age was 62 years (interquartile range, 55 to 70), 90% of the patients had moderate hypertriglyceridemia, and 42% were women; 92% were White (among whom 38% identified as Hispanic or Latino), and 8% identified as Black.

Two thirds of the patients had diabetes, 97% were receiving lipid-lowering therapy, and 31% were receiving two or more lipidlowering therapies.

At 6 months, triglyceride levels were significantly reduced by both doses of olezarsen as compared with placebo.
Patients in the placebo group had a mean decrease of **7.8%** (95% confidence interval [CI], 0.2 to 15.3) from baseline in the triglyceride level, whereas patients in the olezarsen 50-mg group had a mean decrease of **57.1%** (95% CI, 50.9 to 63.2) and those in the 80-mg group had a mean decrease of **60.9%** (95% CI, 54.7 to 67.1).
These results led to an absolute difference in the olezarsen groups as compared with the placebo group of 49.3 percentage points (95% CI, 39.5 to 59.0) in the 50-mg group and 53.1 percentage points (95% CI, 43.4 to 62.9) in the 80-mg group ($P<0.001$ for both comparisons)

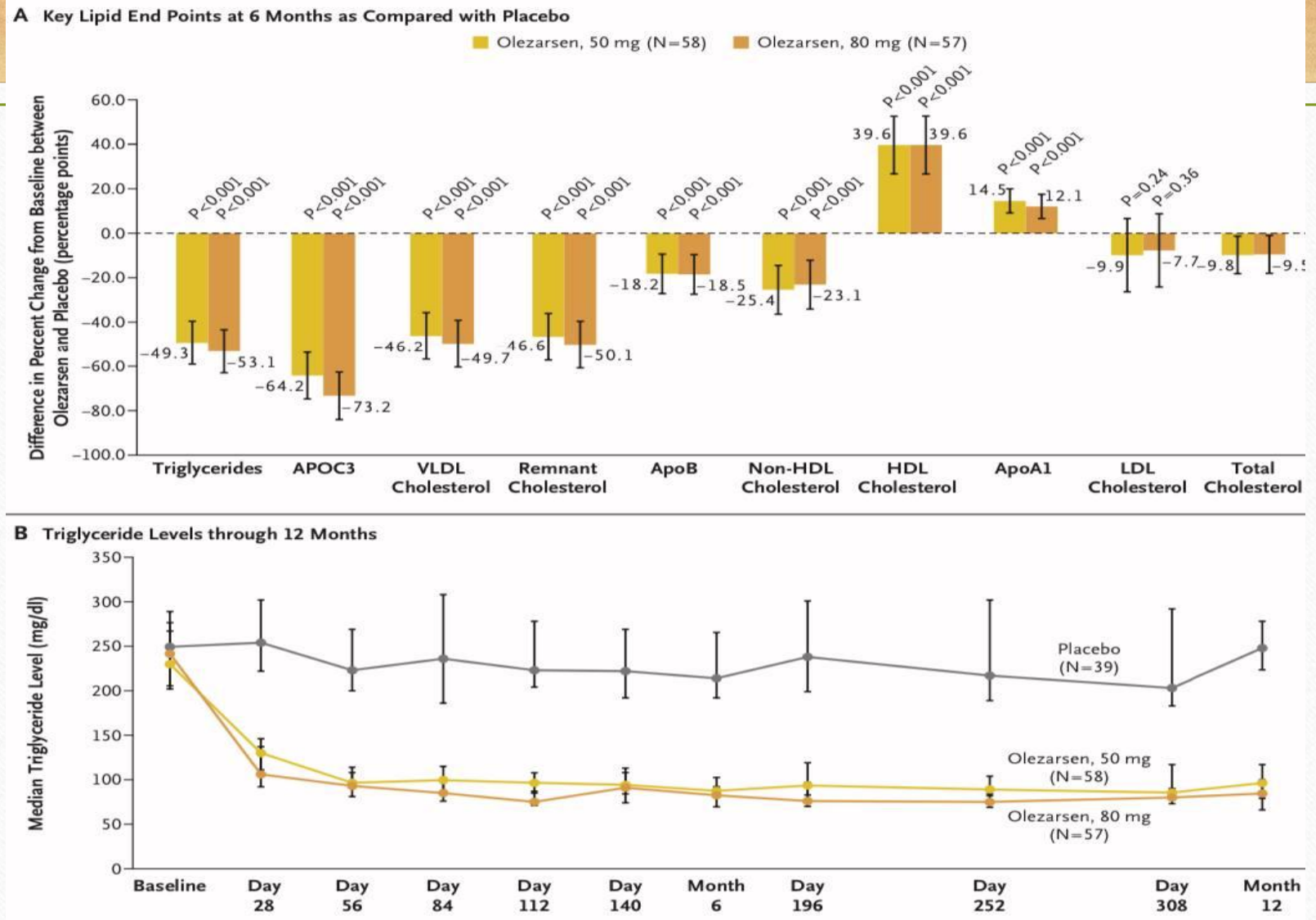

Figure 1. Effect of Olezarsen on Key Lipid Levels at 6 Months and Triglyceride Levels through 12 Months.

Panel A shows the effect of the two doses of olezarsen (50 mg and 80 mg) on key lipid outcomes at 6 months, as compared with placebo. P values are shown for the percent change from baseline for each dose group as compared with the change in the placebo group. Because of the hierarchical order of testing for secondary outcomes, no P values could be reported for the between-group differences in total cholesterol levels. Panel B shows median triglyceride levels from randomization through 12 months. Values at 6 months were calculated as the mean of day 168 and day 182 values. Values at 12 months were calculated as the mean of day 350 and day 364 values. In Panels A and B, I bars indicate 95% confidence intervals. Remnant cholesterol is calculated as the total cholesterol level minus high-density lipoprotein (HDL) and low-density lipoprotein (LDL). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. ApoA1 denotes apolipoprotein A1, ApoB apolipoprotein B, APOC3 apolipoprotein C-III, and VLDL very-low-density lipoprotein.

Among 128 patients with moderate hypertriglyceridemia at baseline and nonmissing triglyceride values at 6 months, a triglyceride level of less than 150 mg per deciliter at 6 months was reported in 42 of 49 patients (86%) in the olezarsen 50-mg group and in 42 of 45 patients (93%) in the olezarsen 80-mg group, as compared with 4 of 34 patients (12%) in the placebo group ($P<0.001$ for the comparison of each olezarsen dose with placebo)

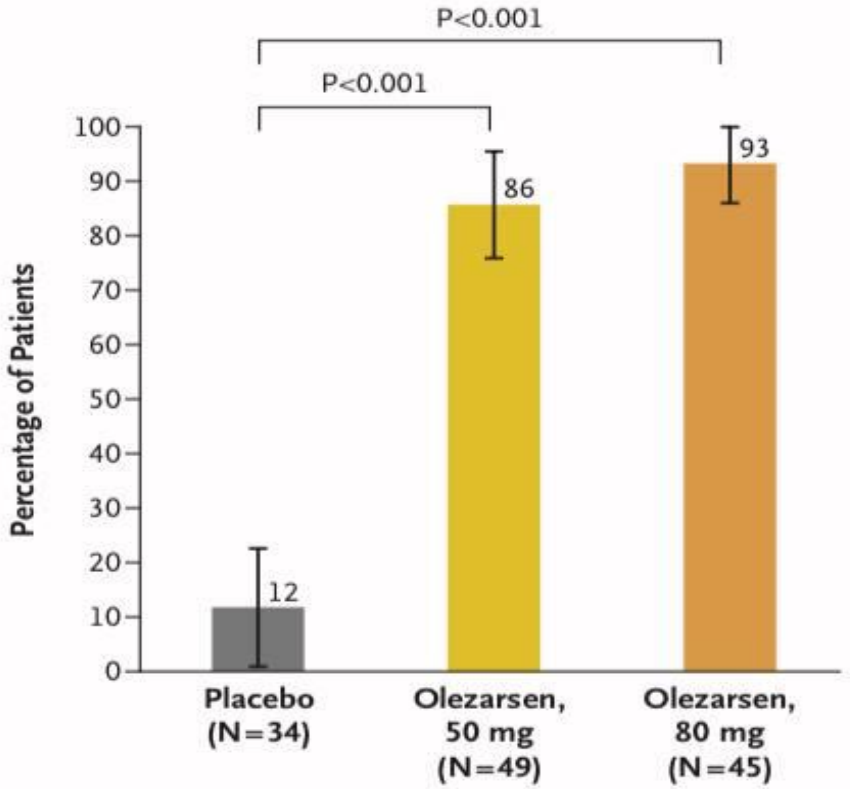

Figure 2. Patients with Moderate Hypertriglyceridemia at Baseline Who Had a Normal Triglyceride Level at 6 Months.

Among 128 patients with moderate hypertriglyceridemia at baseline and nonmissing triglyceride values at 6 months, a triglyceride level of less than 150 mg per deciliter (the generally accepted clinical threshold for normal reference value) at 6 months was reported in 42 of 49 patients (86%) in the olezarsen 50-mg group and in 42 of 45 patients (93%) in the olezarsen 80-mg group, as compared with 4 of 34 patients (12%) in the placebo group. I bars indicate 95% confidence intervals.

The effect of olezarsen on triglyceride levels was evident as soon as 1 month after the initiation of treatment and persisted through the 12-month follow-up.

Safety and Adverse Events

The proportions of patients who had an adverse event during treatment through 28 days after the last dose of olezarsen or placebo were similar in the trial groups.

Table 2. Key Safety Measures (Safety Population).*

Safety Measure	Placebo (N=39)	Olezarsen, 50 mg (N=58)	Risk Ratio vs. Placebo (95% CI)	P Value vs. Placebo	Olezarsen, 80 mg (N=57)	Risk Ratio vs. Placebo (95% CI)	P Value vs. Placebo
	no. (%)				*no. (%)*		
Adverse event							
Any event	29 (74)	42 (72)	0.97 (0.76–1.24)	0.83	38 (67)	0.90 (0.69–1.16)	0.42
Leading to discontinuation of olezarsen or placebo	0	7 (12)	NA	0.04	3 (5)	NA	0.27
Serious event	2 (5)	4 (7)	1.34 (0.26–6.99)	1.00	7 (12)	2.39 (0.52–10.92)	0.30
Leading to discontinuation of olezarsen or placebo	0	1 (2)	NA	1.00	1 (2)	NA	1.00
Hepatic abnormality†							
Any adverse event	2 (5)	7 (12)	2.35 (0.52–10.74)	0.31	5 (9)	1.71 (0.35–8.37)	0.70
ALT or AST ≥3 times ULN	0	4 (7)	NA	0.15	1 (2)	NA	1.00
ALT ≥ULN							
Any elevation	1 (3)	27 (47)	18.16 (2.57–128.15)	<0.001	21 (37)	14.37 (2.02–102.45)	<0.001
≥3 times ULN	0	4 (7)	NA	0.15	1 (2)	NA	1.00
≥5 times ULN	0	2 (3)	NA	0.51	0	NA	NA
AST ≥ULN							
Any elevation	4 (10)	18 (31)	3.03 (1.11–8.26)	0.025	21 (37)	3.59 (1.34–9.65)	0.004
≥3 times ULN	0	3 (5)	NA	0.27	0	NA	NA
≥5 times ULN	0	1 (2)	NA	1.00	0	NA	NA
Renal abnormality							
Any adverse event	5 (13)	2 (3)	0.27 (0.05–1.32)	0.11	1 (2)	0.14 (0.02–1.13)	0.04
Decrease in eGFR‡							
≥25%	11 (28)	10 (17)	0.61 (0.29–1.30)	0.20	9 (16)	0.56 (0.26–1.22)	0.14
≥30%	8 (21)	6 (10)	0.50 (0.19–1.34)	0.16	4 (7)	0.34 (0.11–1.06)	0.06

Urinary protein:creatinine ratio§							
≥500	10 (26)	8 (14)	0.54 (0.23–1.24)	0.14	8 (14)	0.55 (0.24–1.26)	0.15
≥1000	4 (10)	4 (7)	0.67 (0.18–2.53)	0.71	3 (5)	0.51 (0.12–2.17)	0.44
Platelet count¶							
Thrombocytopenia adverse event	1 (3)	0	NA	0.40	2 (4)	1.37 (0.13–14.57)	1.00
Bleeding	2 (5)	3 (5)	1.01 (0.18–5.76)	1.00	3 (5)	1.03 (0.18–5.86)	1.00
Count <140,000/μl	1 (3)	10 (17)	6.72 (0.90–50.44)	0.046	10 (18)	6.84 (0.91–51.31)	0.03
Count <100,000/μl	1 (3)	0	NA	0.40	3 (5)	2.05 (0.22–19.02)	0.64
Other							
Possible hypersensitivity reaction‖	0	6 (10)	NA	0.08	1 (2)	NA	1.00

* Data are shown through 28 days after the last dose of olezarsen or placebo. The safety population included all the patients who had received at least one dose of olezarsen or placebo. No pancreatitis events were reported in any group. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, eGFR estimated glomerular filtration rate, NA not applicable, and ULN upper limit of normal range.

† No patient had total bilirubin elevation of 2 or more times the ULN. Patients were eligible to enroll in the trial if they had an ALT or AST level up to three times the ULN. An ALT level that was higher than the ULN at baseline occurred in 2 patients (5%) in the placebo group, 6 patients (10%) in the olezarsen 50-mg group, and 4 patients (7%) in olezarsen 80-mg group. An AST level that was higher than the ULN at baseline occurred in 2 patients (5%) in the placebo group, 3 patients (5%) in the olezarsen 50-mg group, and 4 patients (7%) in olezarsen 80-mg group.

‡ No patient had a decrease in the eGFR of 50% or more.

§ Urinary protein was measured in milligrams and urinary creatinine in grams.

¶ No patient had a platelet count of less than 75,000 per microliter. At trial entry, a low platelet count was not an exclusion criterion. A baseline platelet count of less than 140,000 per microliter was reported in 1 patient in the placebo group (3%), in no patients in the olezarsen 50-mg group, and in 2 patients (4%) in olezarsen 80-mg group.

‖ The reported event terms listed for possible hypersensitivity reaction included rash, poison ivy rash, lowered blood pressure, asthmatic bronchitis, exacerbation of asthma, injection-site urticaria, and generalized flushing.

Discussion

In this phase 2b trial involving patients with hypertriglyceridemia and elevated cardiovascular risk, olezarsen significantly reduced triglyceride levels to a greater degree than can be achieved with currently available therapies. This effect was accompanied by significant reductions in apolipoprotein B and non-HDL cholesterol levels. No major safety concerns were identified.

Hypertriglyceridemia is common, and effective therapies that have an effect on triglycerideriderich lipoproteins are limited.

Elevated triglyceride levels put patients at risk for direct clinical consequences, including acute pancreatitis, which is often recurrent when severe hypertriglyceridemia is persistent.

In addition, **triglyceride-rich lipoproteins appear to have at least the same atherogenic potential per particle as LDL cholesterol**. Observational and mendelian randomization studies have shown strong associations between hypertriglyceridemia, prevalent atherosclerosis, and incident ischemic events across vascular territories.

Currently available therapies such as statins, ezetimibe, fibrates, and prescription-strength N−3 fatty acids typically lower triglyceride levels by values ranging from less than 10% to approximately 30 to 40%.

Thus, there is great interest in new therapeutic approaches for reducing circulating levels of triglycerides and triglyceride-rich lipoproteins.

The choice of APOC3 mRNA as a target for triglyceride lowering and cardiovascular risk reduction is supported by genetic and epidemiologic data, as well as the results of early-phase trials.

In previous randomized trials, volanesorsen (an unconjugated antisense oligonucleotide against APOC3) reduced triglyceride levels in patients with familial chylomicronemia syndrome (FCS) or non-FCS with moderate or severe hypertriglyceridemia.

In a meta-analysis of three trials, the use of volanesorsen led to a lower risk of hepatic steatosis and a lower incidence of acute pancreatitis than with placebo.

However, despite promising efficacy results, thrombocytopenia was identified as a potential safety concern with volanesorsen.

Olezarsen is a hepatically directed antisense oligonucleotide targeting APOC3.

In this context, the findings of the Bridge–TIMI 73a trial are encouraging for this therapeutic pathway.

The **two olezarsen doses reduced triglyceride levels to less than 150 mg per deciliter at 6 months in more than 85% of patients who had moderate hypertriglyceridemia at baseline**.

With respect to differences between the two olezarsen doses, although the effects on triglyceride levels were similar at 6 months, the results support a larger reduction with the 80-mg dose at 12 months.

Further trials will inform to what extent the higher dose provides additional efficacy for triglyceride lowering and other lipid measures, especially in patients with severe hypertriglyceridemia

in our current trial, **olezarsen significantly decreased atherogenic particles as reflected by apolipoprotein B and non-HDL cholesterol levels.** However, it is not fully understood how this approach to APOC3 reduction affects the metabolism of LDL cholesterol and particles relative to other therapies targeting this or related pathways.

In patients with predominantly moderate hypertriglyceridemia and elevated cardiovascular risk, the monthly administration of olezarsen at a dose of 50 mg or 80 mg significantly reduced triglyceride levels as compared with placebo without major safety concerns.

Dr Sara Ghadimi