IONIS® InBrief
22 March 2022

Investigational olezarsen significantly reduced apoC-III, triglycerides and atherogenic lipoproteins in hypertriglyceridemia patients with or at high risk for CVD

European Heart Journal: Results from Phase 2 study of olezarsen show targeting apoC-III is effective in lowering elevated triglycerides

Apolipoprotein C-III (apoC-III) is a protein produced in the liver that plays a key role in the metabolism of triglycerides (TG) and triglyceride-rich lipoproteins (TRL). High levels of apoC-III are associated with hypertriglyceridemia (HTG) and increased risk for pancreatitis and atherosclerotic cardiovascular events, even in patients receiving appropriate lipid-lowering therapies.

KEY TAKEAWAY

In the context of the current and other studies targeting apoC-III, olezarsen may treat the continuum of elevated TG levels, including familial and multifactorial chylomicronemia syndrome, severe hypertriglyceridemia, and mild hypertriglyceridemia.

Olezarsen is an investigational antisense medicine that uses Ionis' advanced **Li**gand-**C**onjugated **A**ntisense (LICA) technology and is designed to inhibit production of apoC-III in patients at risk for cardiovascular disease (CVD) due to elevated TG levels. Results from a Phase 2 clinical study recently published in the European Heart Journal demonstrate that olezarsen significantly reduced TG levels in HTG patients with or at high risk for CVD, with a favorable safety and tolerability profile.

The randomized, double-blind, placebo-controlled, Phase 2 dose-ranging study was conducted in 114 patients with fasting serum TG 200–500 mg/dL (2.26–5.65 mmol/L) to evaluate the effect of apoC-III inhibition on TG levels in patients at high risk for or with established CVD. Patients received olezarsen in monthly, bi-weekly or weekly dosing regimens, with total monthly doses ranging from 10 mg to 50 mg (10 or 50 mg every 4 weeks, 15 mg every 2 weeks, or 10 mg every week) or placebo via subcutaneous injection for at least six months. The primary endpoint was the percent change in fasting TG levels from baseline at Month 6. More information about the study is available at ClinicalTrials.gov, identifier: NCT03385239.

In the Phase 2 study (n=114), olezarsen met its primary and key secondary endpoints by significantly reducing TG and apoC-III levels in the treatment of patients with HTG (≥200 to ≤500 mg/dL) who have established CVD or are at risk for CVD. Importantly, 91% of patients receiving 50 mg of

olezarsen every 4 weeks achieved a normal TG level of <150 mg/dL (<1.7 mmol/L) with olezarsen (vs. 4% in placebo group).* In addition, up to 46% of patients treated with olezarsen achieved a fasting TG level of <100 mg/dL (<1.13 mmol/L), compared to none of the placebo patients.

Substantial reductions in TG levels were shown with olezarsen across dosing regimens

At six months, statistically significant reductions in fasting TG from a mean baseline of 262 mg/dL were observed in **all** olezarsen groups. Treatment with olezarsen resulted in mean TG reductions of:

- 60% with 50 mg every 4 weeks
- 60% with 10 mg every week
- 56% with 15 mg every 2 weeks
- 23% with 10 mg every 4 weeks

These reductions with olezarsen contrasted with an increase in TG of 6% for the pooled placebo group (p-values ranged from 0.0042 to <0.0001 compared with placebo).

Moreover, the TG-lowering effect was observed within the first month of treatment and reached near-maximal effect by Week 17 in the three higher dose groups.

Olezarsen also resulted in significant reductions in apolipoproteins and atherogenic lipids

Mean reductions with the highest monthly dose of olezarsen (50 mg every 4 weeks) were (compared with placebo at six months):

- 74% for apoC-III (p<0.0001)
- 58% for very low-density lipoprotein cholesterol (VLDL-C; p<0.0001)
- 20% for non-high-density lipoprotein cholesterol (non-HDL-C; p=0.009)
- and 10% for apolipoprotein B (apoB; p=0.024)

Meanwhile, **HDL-C levels** increased in all olezarsen treated groups up to 42% (10 mg weekly dose) (p<0.0001). No dose-dependent effects of olezarsen on LDL-C levels were observed.

**The percent of patients achieving a fasting TG level of <150 mg/dL at six months with olezarsen ranged from 14% in the group that received 10 mg every 4 weeks, to 91% in the group that received 50 mg every 4 weeks, compared to 4% of patients in the placebo group.*

Favorable safety and tolerability profile

Adverse events were similar among patients taking olezarsen or placebo, with the majority being mild to moderate. The most frequent adverse events in patients treated with olezarsen compared with the placebo group were injection site erythema (15.6% vs. 0%), arthralgia (12.2% vs. 0%),

nasopharyngitis (12.2% vs. 8.3%), and upper respiratory tract infection (11.1% vs. 8.3%). None of the serious adverse events (10% of the patients receiving olezarsen and 4.2% of those receiving placebo) were considered drug-related.

Olezarsen is one of several wholly owned medicines in Ionis' leading cardiovascular franchise that the company plans to commercialize and is part of a broad clinical program that includes two Phase 3 studies, BALANCE in patients with familial chylomicronemia syndrome and CORE in patients with severe hypertriglyceridemia.

Key Findings

- Olezarsen has the potential to address unmet therapeutic needs in subjects with uncontrolled TG levels and CVD.
- Olezarsen demonstrated significant reductions in TG levels in patients with elevated TG, across multiple dose ranges, with 91% of patients achieving below 150mg/dl at the 50mg Q4 week dose.
- Adverse events were similar among patients taking olezarsen or placebo, with the majority being mild to moderate.