

# Plozasiran Associated With Greater Triglyceride Lowering and Attainment of Triglyceride Goals as Compared to Olezarsen

## A Monte Carlo Simulation Comparing Triglyceride Lowering With Plozasiran versus Olezarsen in Patients With Familial Chylomicronemia Syndrome

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### BACKGROUND

- Familial chylomicronemia syndrome (FCS) is a rare hereditary disorder, characterized by severely elevated triglyceride (TG) levels (>880 mg/dL), that affects 1 to 10 individuals per million.<sup>1,2</sup>
- FCS is associated with an increased risk of acute pancreatitis (AP), a life-threatening condition, and the primary goal of FCS management is to prevent AP episodes.<sup>3</sup>
- Traditional therapies for FCS (e.g., statins, fibrates, fish oils) produce minimal to modest reductions in TG levels in this population.<sup>3</sup>
- A new generation of treatments that inhibit apolipoprotein C-III (APOC3) production and may reduce TGs to below threshold levels for AP (500 mg/dL) are necessary.
- Plozasiran and olezarsen are two novel APOC3 inhibitors that have been evaluated in placebo-controlled phase 3 trials of patients with FCS; however, there is limited evidence evaluating their comparative effectiveness.<sup>4,5</sup>

### DATA & METHODS

- The Monte Carlo simulation method was used to compare post-treatment TG levels in patients with FCS based on results from the PALISADE and BALANCE trials.
- Primary outcomes** were the proportion of patients who achieved TG levels <500 mg/dL at 1 month, 6 months, 10 months, and 12 months post-treatment.
- Secondary outcomes** were mean and median post-treatment TG levels.
- In the base case model, a synthetic pre-treatment cohort of 6,000 patients with FCS was simulated using baseline TG distributions from the PALISADE trial.
- Treatment response was modeled as the percent change in TG levels from baseline and was sampled from beta distributions parameterized at each timepoint by the mean and standard deviation estimates from 25mg plozasiran quarterly arm of PALISADE and 80mg olezarsen monthly arm of BALANCE.
- Measures of statistical significance were not used because microsimulations with a sufficiently large sample size will converge around the expected value with 95% CIs near zero.<sup>6,7</sup>
- In such settings, p-values offer limited interpretability because they can become arbitrarily small.<sup>6,7</sup>
- A base case model and three scenarios were run to assess the impact of uncertainty around the modeling assumptions used in the study design:

Analysis	Description
<b>Base case</b>	Pre-treatment TG levels based on all patients in PALISADE
<b>Scenario 1</b>	Pre-treatment cohort based on pre-treatment TG levels of patients in BALANCE
<b>Scenario 2</b>	Pre-treatment cohort based on the distribution in PALISADE with maximum TG level of 10,000 mg/dL
<b>Scenario 3</b>	Pre-treatment cohort and treatment responses for plozasiran based on <b>genetically confirmed</b> patients in PALISADE



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### SUMMARY

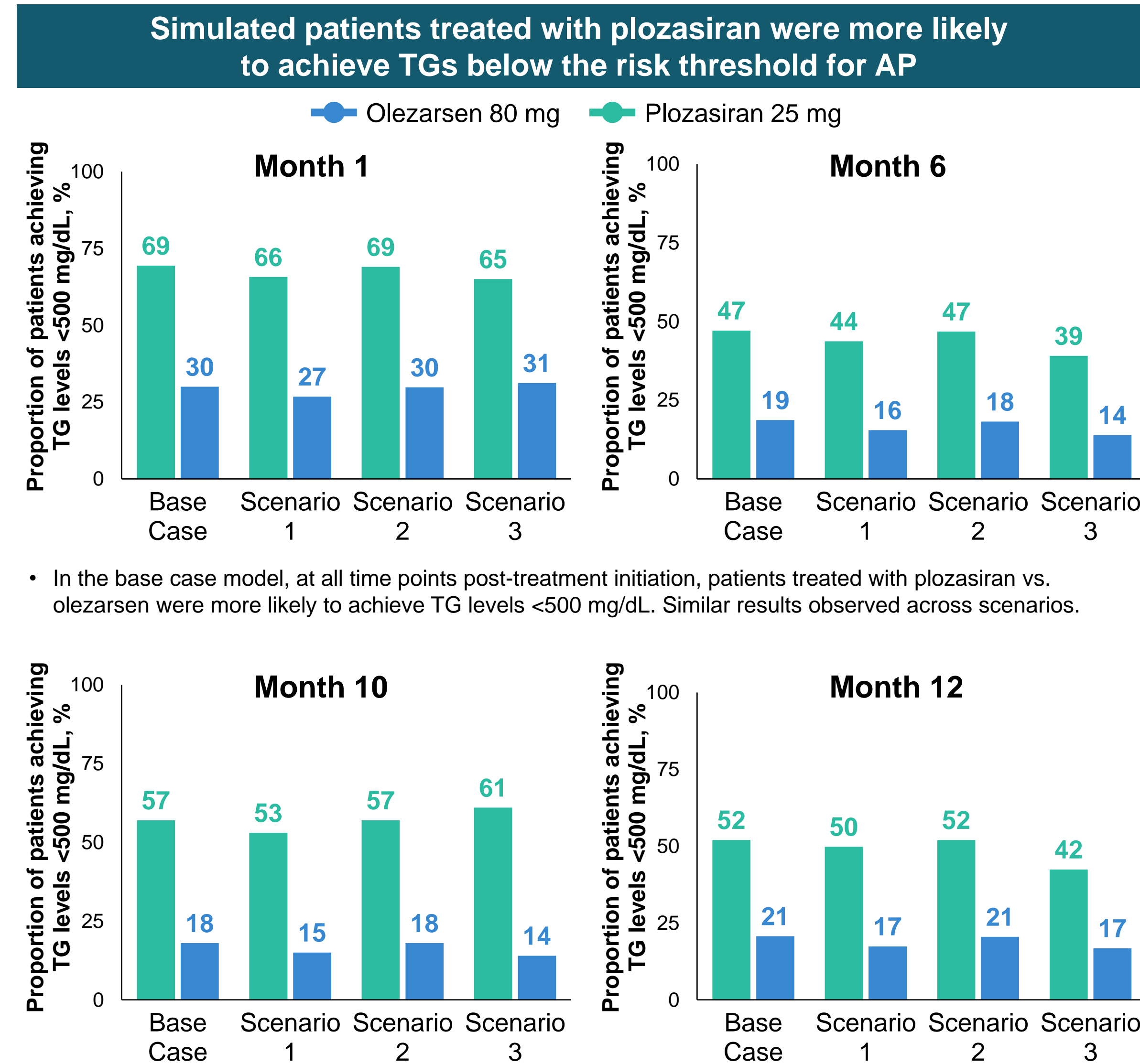
- FCS is a rare disorder caused by severe hypertriglyceridemia which increases risk for life-threatening AP.

- A Monte Carlo simulation model was developed to assess the impact of novel FCS treatments, plozasiran versus olezarsen, on TG levels.

- The model suggests plozasiran's greater effectiveness in TG level reduction, compared to olezarsen, in FCS. Greater reductions in TG levels may prevent AP events.

### RESULTS

**Figure 1. Proportion of patients achieving TG levels <500 mg/dL post-treatment with plozasiran or olezarsen**



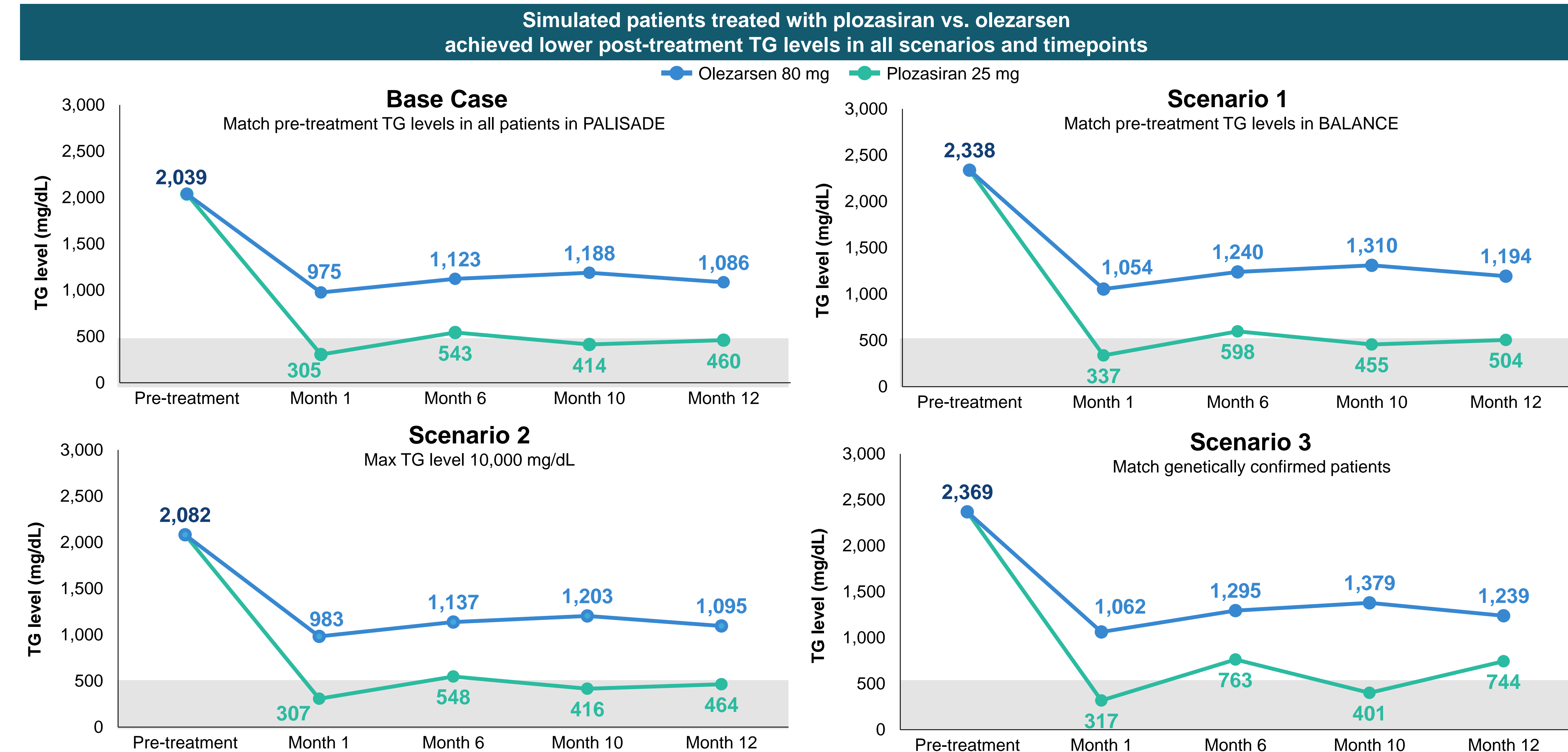
### DISCUSSION

- This analysis suggests that plozasiran is more effective than olezarsen at achieving TG levels <500 mg/dL among patients with FCS.
- The results were robust across modeling scenarios, including the scenario which considered only patients with genetically confirmed FCS from PALISADE, suggesting that the difference in TG lowering between plozasiran and olezarsen was not due to differences in trial populations.

### LIMITATIONS

- The model's findings depend on the validity of the modeling assumptions, which were tested and found to be robust in scenario analyses.
- The model's inputs are from clinical trials that differ in design, sites, and inclusion criteria.
- Aggregate-level data are used in the model, which reduces the model's ability to adjust for potential differences between treatment groups.

**Figure 2. Median TG level among simulated patients treated with plozasiran or olezarsen**



- In the base case model, the overall pre-treatment mean (median) TG level was 2,425 mg/dL (2,039 mg/dL) and both plozasiran and olezarsen lowered TG levels as early as month 1. Similar results were found across all scenarios and timepoints.
- Simulated patients treated with plozasiran achieved lower post-treatment mean and median TG levels than patients treated with olezarsen at all timepoints, in the base case model and all scenarios.

### Reductions in TGs apparent at 1 month and sustained thereafter within the thresholds of AP risk

### CONCLUSIONS

This microsimulation model suggests plozasiran's increased potency compared to olezarsen at reducing TG levels in patients with FCS.

In this analysis of patients with FCS, plozasiran was more effective than olezarsen in achieving TG levels <500 mg/dL.

Elevated TG levels >500 mg/dL increase the risk of AP, which is associated with higher mortality, morbidity, inpatient hospitalization, and healthcare costs.<sup>8</sup>

Reduction of TGs to below thresholds for AP may prevent life-threatening AP events.

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### DISCLOSURES

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