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Long Term LDL-C Trajectories under Sequential PCSK9 Inhibition: Descriptive Findings from the ORION-3 Switching Arm

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Abstract

The ORION-3 study offered a unique opportunity to characterize long term LDL-C trajectories within the same individuals undergoing sequential PCSK9 inhibition—initially with evolocumab and subsequently with inclisiran. This secondary descriptive analysis was based exclusively on published aggregate data from ORION-3. LDL-C values were extracted from reported summary statistics. In the switching arm, participants received evolocumab 140 mg every two weeks for one year before transitioning to inclisiran 300 mg every six months from day 361 onward. LDL-C was calculated using the Friedewald formula, and missing values were not imputed. Absolute LDL-C values were summarized descriptively at predefined time points. Evolocumab induced a rapid LDL-C reduction, reaching 45.3 mg/dL at day 90 (n = 88). Day 360 represented the final on treatment assessment during evolocumab therapy (mean LDL-C 64.0 mg/dL; n = 86). After switching to inclisiran, LDL-C remained substantially reduced through long term follow up, with a mean of 70.4 mg/dL at day 1440 (n = 79). Sequential PCSK9 inhibition with evolocumab followed by inclisiran maintained robust LDL-C lowering over four years. These descriptive within patient observations reflect expected pharmacodynamic differences between monoclonal antibody and siRNA based PCSK9 inhibition without implying comparative treatment efficacy.

Keywords

PCSK9 Inhibition, Evolocumab, Inclisiran, LDL-C, ORION-3, siRNA

1. Introduction

Elevated low density lipoprotein cholesterol (LDL-C) is a well-established causal factor in the development and progression of atherosclerotic cardiovascular disease (ASCVD). A large body of genetic, epidemiological, and interventional evi-

dence has consistently demonstrated that cumulative exposure to elevated LDL-C drives atherosclerotic plaque formation and increases the risk of major cardiovascular events. Consequently, LDL-C reduction remains a central therapeutic target in both primary and secondary prevention, as affirmed in the 2025 ESC/EAS Focused Update of the 2019 dyslipidaemia guidelines [1]. Despite the widespread use of statins as the foundation of lipid lowering therapy, a substantial proportion of high-risk patients fail to achieve guideline recommended LDL-C goals even when treated with maximally tolerated doses. This persistent gap in lipid control underscores the need for adjunctive therapies capable of providing additional, sustained LDL-C lowering [2].

Among available non statin options, PCSK9 inhibition has emerged as one of the most effective strategies for achieving substantial LDL-C reductions [3]. Two mechanistically distinct pharmacological approaches are currently approved. The first involves monoclonal antibodies (mAbs), such as evolocumab and alirocumab, which bind circulating PCSK9 and prevent its interaction with the LDL receptor, thereby enhancing receptor recycling and increasing hepatic LDL-C clearance [4]. These agents produce rapid and pronounced LDL-C reductions and require dosing every 2 - 4 weeks. The second approach employs small interfering RNA (siRNA) technology, exemplified by inclisiran, which inhibits hepatic PCSK9 synthesis at the transcriptional level. By reducing intracellular PCSK9 production, inclisiran provides sustained LDL-C lowering with a convenient twice yearly maintenance schedule [5]. Within this evolving therapeutic landscape, ORION-3 study provides valuable long-term data on the use of inclisiran in patients with ASCVD or high cardiovascular risk who had persistently elevated LDL-C despite maximally tolerated statin therapy or documented statin intolerance [6]. ORION-3 was a 4-year, open label extension of the phase 2 ORION-1 trial and included a unique switching arm in which participants received evolocumab for one year before transitioning to inclisiran for the subsequent three years.

This sequential design offers a rare opportunity to observe LDL-C trajectories within the same individuals under two distinct PCSK9 targeting mechanisms, thereby providing descriptive insights into the pharmacodynamic patterns associated with antibody based versus siRNA-based inhibition. The efficacy and durability of inclisiran have been demonstrated in pivotal phase 3 trials, including ORION-10 and ORION-11, which enrolled patients with ASCVD or ASCVD risk equivalents and showed consistent LDL-C reductions across diverse clinical settings [7] [8]. The aim of the present analysis is to characterize LDL-C changes during evolocumab therapy and during subsequent long term inclisiran treatment within the same patient population, focusing specifically on the switching arm of ORION-3.

2. Methods

2.1. Study Population and Methods

This analysis was conducted as a secondary, descriptive evaluation based exclu-

sively on published aggregate data from the ORION-3 trial. All LDL-C values and baseline characteristics were extracted directly from the summary statistics reported in the original publication, without access to participant level data. ORION-3 enrolled a total of 382 patients, of whom 92 were assigned to the switching arm. The modified intention to treat (mITT) population for LDL-C analyses included 88 individuals with at least one post baseline LDL C measurement, consistent with the criteria applied in the parent study. Participants in the switching arm received evolocumab 140 mg administered subcutaneously every two weeks from day 1 through day 360. Beginning on day 361, patients transitioned to inclisiran 300 mg, administered on day 361, day 451, and subsequently every 180 days through day 1440. This sequential regimen reflects the predefined ORION-3 protocol and enables descriptive evaluation of LDL-C trajectories under two mechanistically distinct PCSK9 targeting strategies within the same individuals. LDL-C was calculated using the Friedewald formula, in accordance with the methodology employed in ORION-3. No imputation procedures were applied for missing values; all descriptive summaries reflect the number of participants with available LDL-C measurements at each time point. LDL-C was assessed at baseline and at predefined study visits. For the purposes of the present analysis, three clinically relevant time points were selected: day 90 (representing early steady state response to evolocumab), day 360 (final on treatment assessment during the evolocumab phase), and day 1440 (long term response during inclisiran therapy). The number of participants contributing LDL-C data at each of these time points was as follows: day 90: n = 88, day 360: n = 86, day 1440: n = 79. These values reflect expected attrition over the four years follow up period of an open label extension trial. Given the non-randomized, open label design of ORION-3 and the descriptive nature of this secondary analysis, no inferential statistical testing or between group comparisons were performed.

2.2. Statistical Analysis

Descriptive statistical methods were used to summarize LDL-C values at each predefined time point in the switching arm. Continuous variables were reported as mean values based on the aggregate summary statistics provided in the ORION-3 publication. Because this was a secondary analysis of published aggregate data, no additional transformations, imputations, or recalculations were applied beyond those originally reported. Given the open label, non-randomized design of ORION-3 and the sequential nature of treatment exposure, no inferential statistical testing was performed. Between treatment comparisons were not conducted, as the study design does not support formal evaluation of comparative treatment effects. Instead, LDL-C trajectories were described within patients over time, focusing on the evolution of absolute LDL-C values during the evolocumab phase and following the transition to inclisiran.

3. Results

Evolocumab produced a rapid and pronounced reduction in LDL-C during the

first year of therapy. Mean LDL-C decreased from 122.6 mg/dL at baseline to 45.3 mg/dL at day 90 (n = 88), reflecting the expected early steady state response to monoclonal antibody–mediated PCSK9 inhibition. This substantial reduction was maintained throughout the evolocumab treatment period. By day 360—the final on treatment assessment before the therapeutic transition—mean LDL-C was 64.0 mg/dL (n = 86), indicating continued suppression of circulating LDL-C during the full year of mAb therapy.

Following the switch to inclisiran on day 361, LDL-C levels remained substantially reduced throughout long term follow-up. Inclisiran's twice yearly dosing regimen was associated with stable LDL-C concentrations over the subsequent three years. At day 1440, mean LDL-C was 70.4 mg/dL (n = 79), consistent with the durable lipid lowering profile characteristic of siRNA mediated PCSK9 suppression. The modest numerical increase relative to the evolocumab phase aligns with the known pharmacodynamic differences between antibody based and siRNA-based mechanisms and reflects the expected long term steady state achieved with inclisiran (Figure 1).

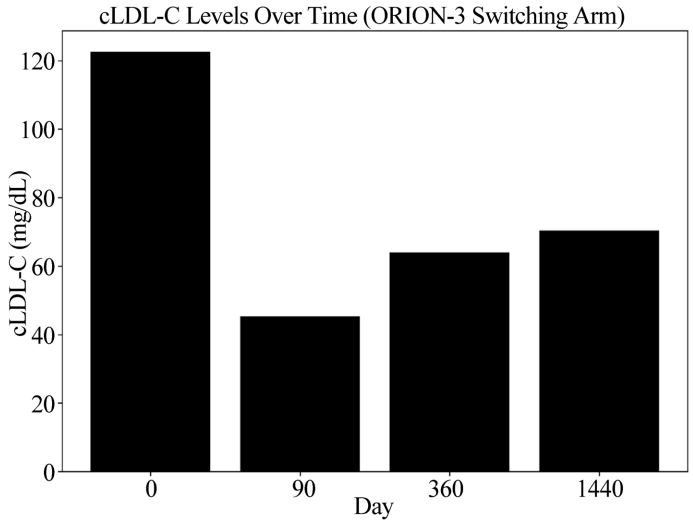

Figure 1. LDL C trajectories during evolocumab and inclisiran therapy.

Across the four-year observation period, these within patient LDL-C trajectories illustrate the temporal patterns associated with sequential PCSK9 targeting strategies. The observed values reflect mechanistic distinctions between mAb and siRNA-based inhibition without implying comparative treatment efficacy, as the ORION-3 design does not support direct treatment comparisons.

4. Discussion

The sequential design of ORION-3 provided a unique opportunity to examine LDL-C trajectories within the same individuals exposed to two mechanistically distinct PCSK9 targeting therapies. This within patient framework minimizes interindividual variability and allows a clearer appreciation of the temporal patterns

associated with monoclonal antibody–based and siRNA based PCSK9 inhibition. As expected, evolocumab produced the most rapid and pronounced early LDL-C reduction, consistent with the immediate suppression of circulating PCSK9 achieved by monoclonal antibodies. In contrast, inclisiran maintained substantial and durable LDL-C lowering over the subsequent three years, reflecting the long acting pharmacodynamic profile characteristic of siRNA mediated hepatic PCSK9 silencing.

The absolute LDL-C values observed across the four year follow up illustrate a coherent and physiologically plausible pattern. The steady state LDL-C level achieved with evolocumab at day 90 remained numerically lower than the long-term values observed during inclisiran therapy. This difference aligns with known pharmacodynamic distinctions between mAbs and siRNA agents, including the continuous receptor level blockade provided by monoclonal antibodies versus the gradual, transcription level suppression produced by inclisiran. Importantly, these observations are descriptive in nature and do not imply comparative treatment efficacy, as the ORION-3 design does not support head-to-head evaluation or inferential comparisons between therapies.

Cardiovascular outcomes were not assessed in ORION-3, and no conclusions regarding clinical benefit can be drawn from the present analysis. References to outcome trials are included solely to contextualize the LDL-C levels achieved and to situate these findings within the broader evidence base, without extrapolating risk reduction estimates or projecting clinical benefit beyond the data collected in ORION-3.

Several limitations should be acknowledged. ORION-3 was an open label, non-randomized extension study, and the switching arm included a relatively small number of participants. The present analysis relied exclusively on published aggregate data, without access to participant level information, which limits the ability to explore variability or perform adjusted analyses. Attrition over the four year follow up period further reduces the number of participants contributing data at later time points, a common feature of long-term extension studies. Despite these limitations, the descriptive patterns observed provide valuable insight into the long-term lipid lowering trajectories achievable with sequential PCSK9 targeting strategies.

5. Conclusion

Sequential PCSK9 inhibition with evolocumab followed by inclisiran maintained robust LDL-C lowering over a four-year period in the ORION-3 switching arm. The within patient trajectories observed in this descriptive analysis illustrate the characteristic temporal patterns associated with monoclonal antibody–based and siRNA based PCSK9 inhibition, highlighting the rapid early response to evolocumab and the durable long-term stability achieved with inclisiran. Although the study design does not allow for comparative efficacy conclusions, these findings underscore the complementary pharmacodynamic profiles of the two therapeutic approaches and their capacity to sustain LDL-C control over extended

treatment durations. More broadly, the results emphasize the value of long-term extension studies in characterizing lipid lowering trajectories across different PCSK9 targeting mechanisms. Such data provide important clinical context for understanding how sequential therapeutic strategies may support persistent LDL-C reduction in high-risk patients who require prolonged lipid management beyond standard statin therapy. The ORION-3 experience contributes to the growing evidence base supporting the long-term feasibility of PCSK9 directed therapies and offers insight into the patterns of LDL-C evolution achievable under extended, mechanism diverse treatment strategies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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