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Primary Hyperlipidemia: Fresh look at an LDL-C Therapy and its Long-Term Data

Announcer
Welcome to ReachMD. This medical industry feature, titled "*Fresh Look at an LDL-C Therapy for Primary Hyperlipidemia, Including Long-Term Data*" is sponsored by Novartis Pharmaceuticals Corporation and this program is intended for US health care professionals.

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Dr Tadwalkar
Hello and thank you for tuning into ReachMD. I'm your host Dr Rigved Tadwalkar, a partner and consultative cardiologist with the Pacific Heart Institute from Santa Monica, California. In today's program, Dr Briana Costello, a cardiologist from The Texas Heart Institute Center for Cardiovascular Care in Houston, Texas, and I will discuss clinical perspectives on the efficacy and safety of LEQVIO (inclisiran), including data from the ORION-8 trial, the role of LEQVIO on low-density lipoprotein cholesterol (LDL-C) management in patients with primary hyperlipidemia, and any questions that cardiologists may have regarding the use of LEQVIO.

As you know, LEQVIO was previously approved to lower LDL-C in patients with atherosclerotic cardiovascular disease, or ASCVD, or heterozygous familial hypercholesterolemia as an adjunct to diet and maximally tolerated statin therapy.[1] In July 2023, the Food and Drug Administration approved an expanded indication for LEQVIO.[1] LEQVIO injection is indicated as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia, to reduce LDL-C.[1]

Dr Costello
Thank you for having me, Dr Tadwalkar. I have been considering prescribing LEQVIO for some of my patients.

I was curious to see if efficacy and the safety profile were over a longer period of time and I am glad that the data are finally available to be shared. Long-term control of LDL-C has been proven to be pivotal in risk factor modification for patients with ASCVD and those at increased risk for CVD.[2-4]

I know LEQVIO is a first-in-class small interfering RNA, or siRNA, therapy that selectively targets the liver to prevent production of the PCSK9 protein and therefore regulating the LDL-C levels.[1,5] I've been considering LEQVIO for my patients who have difficulty achieving LDL-C targets with traditional lipid-lowering therapies or struggle with the side effects of statins, in particular. One patient who comes to mind is a younger woman, she is less than 60, with known atherosclerotic disease and a severe intolerance to statins. The baseline LDL-C level of this patient is more than 180 mg/dL.

LEQVIO may be a good option for this patient because it's a twice-yearly injection after the 2 initial doses, it's HCP-administered, has demonstrated to lower LDL-C levels, and was well tolerated in the pivotal clinical trials for up to 18 months.[1]

Dr Tadwalkar
I'm glad you agree, Briana. Before we discuss the long-term data for LEQVIO, why don't we review some of the key Phase 3 data for this treatment? LEQVIO was studied in ORION-10 and in ORION-11 Phase 3 multicenter, double-blind, randomized, placebo-controlled 18-month trials.[6] ORION-10 enrolled patients with ASCVD.[6] ORION-11 enrolled patients with ASCVD and patients at increased risk of CVD.[6]

Factors that increased the risk of CVD included heterozygous familial hypercholesterolemia, type 2 diabetes, or a 10-year risk greater than or equal to 20%.[6] The primary end point of these studies was the percentage change in LDL-C from baseline to day 510 or month

17.[6] And in ORION-10 and -11, there was a 52% and 50% LDL-C reduction, respectively, with LEQVIO compared to placebo groups from baseline to month 17, when LEQVIO was administered in patients on maximally tolerated dose of statin, with or without ezetimibe.[1,6]

Dr Costello
I am also aware that ORION-10 and ORION-11 evaluated the number of patients who achieved guideline-recommended LDL-C thresholds by month 17.[7,8] I think that's important to look at in terms of understanding if patients reach their targets with LEQVIO.

Dr Tadwalkar
Yes, they did, Briana! In ORION-10, 84% of LEQVIO-treated patients with ASCVD achieved LDL-C levels less than 70 mg/dL at month 17 compared with 18% of placebo-treated patients.[1,7] In ORION-11, 81% of LEQVIO-treated patients with ASCVD or at an increased risk of CVD achieved LDL-C guideline-recommended target at month 17 compared with 18% of placebo-treated patients.[1,7]

The LDL-C target was <70 mg/dL for patients with ASCVD and <100 mg/dL for patients with increased risk for CVD.[7]

Dr Costello
The data for ORION-10 and ORION-11 look very promising; however, I'm interested to know whether LEQVIO will continue to show LDL-C reduction and will be well tolerated for patients over the long term.

Dr Tadwalkar
Absolutely, let me address your question. The long-term efficacy and safety of LEQVIO was studied in ORION-8.[9] ORION-8 is a Phase 3 long-term extension trial, including greater than 3000 patients from Phase 2 ORION-3 trial and the Phase 3 trials ORION-9, ORION-10, or ORION-11.[9]

This trial included patients with ASCVD, increased risk for CVD, or heterozygous familial hypercholesterolemia with elevated LDL-C despite ongoing treatment with statin therapy with or without ezetimibe.[9,10] The primary end points were proportion of patients achieving pre-specified lipid goals at the end of the study and safety.[9]

End of study was defined as day 1080 or ≥ 90 days after the last LEQVIO dose.[9] The key secondary end point was the percentage change in LDL-C from baseline to end of study.[9] There are some limitations of the trial, that is, it was not blinded nor controlled and includes inherent self-selection bias for continuing onto the extension trial. The open-label design and absence of a control group may present difficulties in the interpretation of results, allowing comparisons only to baseline values.[10]

Dr Costello
I appreciate that study overview of ORION-8, Rigved, in terms of the actual data I know that in Phase 3 trials,patients treated with LEQVIO achieved consistent reductions in LDL-C levels.[9] Was this similar to what was found in ORION-8?

Dr Tadwalkar
Yes, they were! In ORION-8, 78% of patients achieved target LDL-C levels. As a reminder, LDL-C threshold for patients with ASCVD is less than 70 mg/dL while that for patients with increased risk of CVD is less than 100 mg/dL.[9]Also, there was an approximately 50% reduction in LDL-C levels at the end of the study.[9]

These results from ORION-8, which included some patients receiving LEQVIO for over 6 years, were consistent with the data seen in the pivotal ORION-10 and ORION-11 trials.[9] I am very excited about the long-term data results from ORION-8 and what it means for my clinical practice. We're all aware that LDL-C is a major risk factor for cardiovascular disease, and lowering LDL-C may help reduce the risk of developing a cardiovascular event.[2,3]

The ability of LEQVIO to provide sustained lowering is a huge win clinically. I want to note thatthe effect of LEQVIO on cardiovascular morbidity and mortality, however, has not been determined.[4,11-13] I've been using LEQVIO in my appropriate patients since its approval, and I have been very impressed with the results. I've seen many patients achieve their LDL-C goals with LEQVIO. One of the things that I like most about LEQVIO is that it is a twice-yearly injection after the initial 2 doses,[1] which resonates tremendously with my patients.

I have 1 patient, a man in his 60s, who's been on maximum dose of statin for many years and has not achieved his LDL-C goal. After conversations, it was decided to start him on LEQVIO, and it's made a big difference. His LDL-C levels have dropped by >50%, and he's finally able to achieve his target goal. He is also quite happy with the twice-yearly dosing schedule after the 2 initial doses. He tells me this is a "convenient option" for him and I'm so glad that I'm able to offer him this treatment option.

Dr Costello
Nice, that data and patient experience are very encouraging to hear, Rigved.I know from the Phase 3 trials that LEQVIO had a well tolerated safety profile.[14] Is there more information about the long-term safety of LEQVIO?

Dr Tadwalkar
That's a good question. So, to begin, in Phase 3 clinical trials over 18 months, the most common adverse reactions occurring in ≥3% of patients treated with LEQVIO, and more frequently than placebo, were injection site reaction, arthralgia, and bronchitis.[1,6]

And adverse reactions leading to discontinuation occurred in 2.5% of patients treated with LEQVIO vs 1.9% of patients receiving placebo.[1] Injection site reactions were most common causes for treatment discontinuation observed in 0.2% of patients taking LEQVIO vs 0% taking placebo.[1]

The majority of adverse events were mild to moderate.[14] The safety profile of LEQVIO was consistent across all subgroups, including elderly, mild-to-moderate hepatic, and renally impaired patient populations.[1] In ORION-8, long-term safety data beyond 6 years was consistent with the Phase 3 trials. LEQVIO was well tolerated and there were no new safety signals.[9]

Dr Costello
That's definitely compelling to hear that the safety profile was consistent over time and among patients being treated. In terms of dosing, does the schedule for LEQVIO change depending on how long the patient has been treated with LEQVIO?

Dr Tadwalkar
LEQVIO dosing does not change based on how long the patient's been on treatment.[1] The recommended dosage of LEQVIO, in combination with statin therapy, is 284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months thereafter.[1]

Also, we discussed in the beginning of the podcast, LEQVIO is HCP-administered.[1] So, once it's administered, I'm confident that my patient has their dose to cover 6 months.

Dr Costello
Thank you, Dr Tadwalkar, for talking with me today and sharing your perspectives and clinical experiences. As clinicians, we want to know that our treatments are both efficacious and well tolerated – and that our patients are actually taking it, so we can achieve our goal.

Dr Tadwalkar
Anytime, Briana. Knowing that LEQVIO has demonstrated powerful and consistent LDL-C reduction in the Phase 3 studies and has consistent long-term data beyond 6 years from ORION-8 is very reassuring for me and my patients.[1,9] And with the expanded indication for LEQVIO, I am happy to see that certain patients with primary hyperlipidemia may also be able to benefit from it. As these final thoughts bring us to the end of our program, on behalf of Briana and myself, I'd like to thank you all for joining.

Announcer
For more information about LEQVIO please visit LEQVIOHCP.COM/expert-perspectives

Important Safety Information: Adverse reactions in clinical trials (≥3% of patients treated with LEQVIO and more frequently than placebo) were injection site reaction, arthralgia, and bronchitis.

Please see LEQVIO full Prescribing Information on this site or at **LEQVIOHCP.com**

Important Safety Information for LEQVIO is available underneath the player of this audio presentation.

This program was sponsored by Novartis Pharmaceuticals Corporation. If you missed any part of this discussion, visit ReachMD.com/industry feature. This is ReachMD. Be part of the knowledge.

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