Lowering LDL-C with alirocumab, an investigational PCSK9 inhibitor

Dr Jay Edelberg speaks to Michael Dowdall, Managing Commissioning Editor

Jay Edelberg is an MD PhD graduate of Duke University in Durham, North Carolina, USA and trained in clinical cardiology at the Beth Israel Deaconess Medical Center in Boston. From 1999 to 2006, Dr Edelberg served as CCU cardiologist and led the Cardiac Vascular Biology Research Laboratory at Weill-Cornell Medical Center, with a specific research focus on cardiovascular stem cells and biomarkers of cardiac aging. In 2006, Dr Edelberg became Director of Cardiovascular Urogenital Biomarker research at GlaxoSmithKline. Two years later, he moved to Bristol-Myers Squibb and progressed to become the US medical lead for Eliquis (apixaban). He joined Sanofi in 2012 as Vice President and Head of the newly formed PCSK9 Development & Launch Unit, reporting to Elias Zerhouni, President, Global R&D and Hanspeter Spek, President, Global Operations, Sanofi. Over the years, Dr Edelberg has published more than 75 peer-reviewed publications and has participated in numerous research and peer-review committees, including those of the National Institutes of Health (NIH), American Heart Association (AHA) and the California Institute for Regenerative Medicine (CIRM). He currently sits on the American Federation for Aging Research Board of Directors and is a Section Editor for the journal Aging Cell.

Q Can you tell us about your career background to date?
I have been the head of the PCSK9 Development and Launch Unit at Sanofi since April of 2012. I previously worked as the Group Director at Bristol-Myers Squibb and served as a director for GlaxoSmithKline. I have been a member of the board of directors for the American Federation for Aging Research since June 2007. Prior to joining GlaxoSmithKline, I was an Associate Professor of Medicine at Weil Cornell Medical College. I received my medical degree from Duke University in 1992, served as a resident in internal medicine at Massachusetts General Hospital and was a cardiology fellow at Beth Israel Hospital in Boston.

Q What does your current role as Head of the PCSK9 Development & Launch Unit at Sanofi-Aventis involve?
In my role as Head of the PCSK9 Development and Launch Unit at Sanofi, I work in close collaboration with Regeneron to devise product strategy and lead clinical and market development for alirocumab, an investigational monoclonal antibody targeting PCSK9.

Q What are the main challenges & benefits of targeting LDL-C (in terms of lipid lowering)?
High low density lipoprotein cholesterol (LDL-C) is a well established major risk factor for cardiovascular disease (CVD), which remains a leading cause of morbidity and mortality across the world, accounting for 24% of all deaths.

Despite the availability of effective lipid-lowering therapy, such as statins, many patients do not achieve optimal LDL-C control and may remain at-risk for cardiovascular (CV) events. This remaining risk is due to multiple factors, including: genetically elevated LDL-C level (familial hypercholesterolemia), previous CV events.
and multiple additional CVD risk factors such as diabetes, and intolerance and inability to adhere to statin therapy.

There is a need to elevate the standard of care in lipid management by providing additional options for people who have a high CV risk and need to lower their cholesterol more aggressively.

Clinical data to date show consistent, positive results in lowering levels of LDL-C, with an encouraging safety and tolerability profile across all Phase III alirocumab trials that Sanofi and Regeneron have reported.

We look forward to potentially providing a new treatment option for patients who may need a more aggressive cholesterol-lowering treatment on top of standard of care.

Q Can you tell us a little more about the investigational PCSK9 inhibitor alirocumab?

Alirocumab is a subcutaneously administered, investigational, fully human monoclonal antibody that targets and inhibits PCSK9, a protein that is known to be a determinant of circulating LDL-C levels because it binds to LDL receptors, resulting in their degradation. Consequently, fewer LDL receptors are available on liver cells (hepatocytes) to remove excess LDL-C from the blood. Inhibiting the PCSK9 pathway is therefore being investigated as a potential mechanism for lowering LDL-C.

Alirocumab is currently under clinical development and its safety and efficacy have not been fully evaluated by any regulatory authority.

Q The ODYSSEY clinical trial program aims to assess the potential of alirocumab in patient groups where there is high unmet need. Can you tell us a little more about the patient groups & the aims/outcomes of some of the individual ODYSSEY trials?

The ODYSSEY program is assessing the LDL-C lowering potential of alirocumab in one or more groups where there is high unmet need: heterozygous familial hypercholesterolemia (HeFH), an inherited form of high cholesterol; high or very high CV risk; and/or with a history of statin intolerance. Entry criteria for all Phase III ODYSSEY studies include LDL-C not at goal despite maximally tolerated lipid-lowering therapy.

The Phase III ODYSSEY program is designed to evaluate the safety and efficacy, with at least 14 global studies at more than 2000 study centers. Overall, the program includes more than 23,500 patients in double-blind, randomized, placebo- and active-controlled studies with alirocumab, ranging from 24 weeks to 5 years in duration. The ODYSSEY program will include approximately 5000 patient-years of exposure at the completion of the Phase III studies, with the exception of ODYSSEY OUTCOMES, a trial that will enroll approximately 18,000 patients and prospectively evaluate the effect of alirocumab on the occurrence of CV events.

ODYSSEY LONG TERM is the ongoing 2341-patient, double-blind trial that is designed to evaluate the long-term safety and efficacy of 150 mg alirocumab every 2 weeks versus placebo in patients with hypercholesterolemia who are at high or very high CV risk, including patients with HeFH. Both study groups are treated with statins at a maximally tolerated dose and some patients also receive additional lipid-lowering therapies. A prespecified interim analysis was performed when all patients reached 1 year and approximately 25% of patients reached 18 months of treatment.

ODYSSEY COMBO II is a double-blind, 720-patient trial designed to evaluate the safety and efficacy of alirocumab compared with ezetimibe in patients with hypercholesterolemia who are at high CV risk and at baseline had inadequate LDL-C reduction despite stable maximally tolerated statin therapy.

The ODYSSEY FH I and FH II trials enrolled a total of 738 HeFH patients and compare alirocumab to placebo. All patients are on maximally tolerated daily statin therapy and the majority of patients also receive ezetimibe. Despite receiving this high level of background therapy, patients in these studies had mean baseline LDL-C levels of 145 mg/dl (FH I) and 134 mg/dl (FH II).

Q ODYSSEY ALTERNATIVE evaluated patients with statin intolerance, what were the main outcomes from this study? With the increase of statin prescriptions & the movement toward ‘statins for all’ for prevention, what do you think the main challenges will present?

The ODYSSEY ALTERNATIVE trial evaluated patients with a history of intolerance to two or more statins (including one at the lowest dose), who were randomized to receive alirocumab, ezetimibe or atorvastatin 20 mg (a ‘calibrator arm’).

One purpose of the ‘calibrator arm’ was to establish the re-challenge failure rate with statin in this population. Dosing for the ‘calibrator arm’ was 20 mg of atorvastatin daily.

Rates of discontinuation for adverse events (AEs) of any type or origin (not just muscle AEs) were 25% for atorvastatin, 25% for ezetimibe and 18% for alirocumab; these differences between treatment groups were not statistically significant.

This trial met its primary efficacy endpoint of a greater percent reduction from baseline in LDL-C at 24 weeks with alirocumab compared with ezetimibe.
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Q The results of nine new Phase III ODYSSEY trials have just been released; can you highlight the main results of these?
Nine new Phase III ODYSSEY trials of alirocumab in people with hypercholesterolemia met their primary efficacy endpoint.

All studies assessed the same primary efficacy endpoint, which was a greater percent reduction from baseline in LDL-C at 24 weeks compared with placebo or active comparator.

Importantly, in the trials that used an individualized approach with 75 and 150 mg doses, the majority of patients reached their LDL-C goal while remaining on a 75 mg dose every 2 weeks.

The potential of alirocumab to demonstrate CV benefit is being prospectively assessed in the ongoing 18,000-patient ODYSSEY OUTCOMES trial.

Q What were the differences in the study designs?
Five studies (ODYSSEY LONG TERM, FH I, FH II, HIGH FH and COMBO I) compared patients treated with alirocumab and standard-of-care-therapy versus patients who only received standard-of-care therapy (placebo).

Four studies (ODYSSEY ALTERNATIVE, COMBO II, OPTIONS I and OPTIONS II) included at least one active comparator other than placebo (e.g., ezetimibe).

Q What were the inclusion criteria?
All trials included patients with LDL-C not at goal with or without a documented history of CVD. In ODYSSEY ALTERNATIVE, patients were eligible for study inclusion if they had a history of intolerance to two or more statins, including one at the lowest dose. As part of the study, some patients were randomized into a ‘calibrator arm’ to establish the re-challenge failure rate with statin in this population.

Q What were the primary end points?
Nine new Phase III ODYSSEY trials of alirocumab in people with hypercholesterolemia met their primary efficacy endpoint. All studies assessed the same primary efficacy endpoint, which was a greater percent reduction from baseline of LDL-C at 24 weeks compared with placebo, or active comparator.

Q Could you comment on the safety & tolerability profile of the administered alirocumab doses?
Alirocumab was generally well tolerated in the nine ODYSSEY trials. The most common AEs were nasopharyngitis and upper respiratory tract infections, which were generally balanced between treatment groups. Injection site reactions occurred more often in the alirocumab group compared with placebo. In the nine trials, serious AEs and deaths were generally balanced between treatment groups as were other key AEs including musculoskeletal, neurocognitive and liver-related events.

Studies are ongoing, so safety information—including the most common AEs—will continue to be collected.

Q What do the main findings of the nine ODYSSEY trials add to the previously reported ODYSSEY MONO trial results?
The nine ODYSSEY trials reported today, along with the previously announced MONO trial, encompass over 5000 patients studied in double-blind trials for 24–104 weeks. ODYSSEY MONO reported positive results in October 2013. All trials included patients with LDL-C not at goal with or without a documented history of CVD. ODYSSEY OPTIONS I, OPTIONS II, COMBO II, MONO and ALTERNATIVE included at least one active comparator (e.g., ezetimibe). The trials evaluated two distinct dosing regimens: 150 mg every 2 weeks or 75 mg every 2 weeks increasing to 150 mg if needed to reach protocol-specified LDL-C targets. The 75 and the 150 mg dose were delivered with a single, self-administered 1 ml injection.

Q Can you comment on the ongoing CHOICE & OUTCOMES studies? Are there any study results due in 2015?
The ODYSSEY clinical trial program remains ongoing. This includes three additional studies, CHOICE I, CHOICE II (both evaluating monthly doses of alirocumab) and OUTCOMES, which are expected to report primary endpoints in 2015 and beyond.

We look forward to discussing more information in the near future, but because we will be presenting detailed results at upcoming medical meetings and/or scientific publications, we cannot disclose detailed information at this time.

Q What are the next developmental stages for alirocumab?
Results from the four ongoing Phase III trials – ODYSSEY LONG TERM, COMBO II, FH I and FH II – were presented as part of the official European Society of Cardiology Congress 2014 Coronary Artery Disease & Lipids Hot Line Session on August 31. Across the four trials, alirocumab showed significant, sustained LDL-C reductions from baseline and consistent safety in combination with maximally tolerated statins, including in the ongoing ODYSSEY
LONG TERM trial, the largest Phase III trial of a PCSK9 inhibitor with the longest follow-up to date.

In ODYSSEY LONG TERM, there was a 62% reduction in LDL-C in alirocumab-treated patients compared with placebo at Week 24. In a post-hoc safety analysis, there was a lower rate of adjudicated major CV events (cardiac death, myocardial infarction, stroke and unstable angina requiring hospitalization) in the alirocumab group compared with placebo, which also included maximally tolerated statins (1.4% compared with 3.0%, nominal p value, p < 0.01). These CV events comprise the composite primary endpoint of the 18,000-patient ODYSSEY OUTCOMES trial, which is prospectively evaluating the potential of alirocumab to demonstrate cardiovascular benefit.

In the three additional trials presented at ESC Congress 2014 (ODYSSEY COMBO II, FH I and FH II), alirocumab-treated patients receive an initial dose of alirocumab 75 mg every 2 weeks, increasing to 150 mg if needed to reach prespecified LDL-C levels. The 75 and 150 mg alirocumab doses were delivered as a single, self-administered 1 ml injection.

Across the four trials, consistent LDL-C reductions were observed throughout a year of treatment, and the majority of patients were able to reach their LDL-C goal.

In these trials, the most common TEAEs (≥5% of patients in one or more trial) across all treatment groups were injection site reactions, nasopharyngitis, upper respiratory tract infection, influenza, accidental overdose, dizziness, headache and muscle pain (myalgia).

The four ODYSSEY trials reported at the ESC Congress 2014, along with results from six other Phase III studies, encompass more than 5000 patients studied in double-blind trials for 24–104 weeks. Results from these four studies form part of the robust data used for global alirocumab regulatory submissions, which will be the largest set of data ever used to support the regulatory filing of an LDL-C lowering therapy. Sanofi and Regeneron anticipate alirocumab regulatory submissions in the United States of America and European Union by the end of 2014. In the United States, the companies intend to use a Priority Review Voucher to obtain priority review status for the alirocumab regulatory submission.

**Q** In your opinion what has been the most influential advancement in the PCSK9 inhibitor field?

The PCSK9 field is a model of modern genetics and state-of-the-art monoclonal antibody technology coming together to develop a new potential medicine for our patients. The results of the clinical studies presented could be predicted from the initial genetic studies that gave rise to the field.

**Q** Where do you see the field of lipidology in 5 years’ time? What advances do you predict will be made & what do you think will be the most important of these advances?

Today, we are seeing the ability of PCSK9 inhibition to markedly lower LDL-C for patients who could not get to treatment targets with standard or care therapy. We look forward to the results of Odyssey Outcomes to demonstrating that this lowering leads to a reduction in CV risk in a large prospective outcomes study.

**Disclaimer**

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Future Medicine Ltd.

**Financial & competing interests disclosure**

J Edelberg is an employee of Sanofi, the company developing Alirocumab. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.