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PCSK9 Inhibitor Achieves Persistent LDL-C Control and Sustained Safety in a Challenging Population

London - In a rigorous demonstration of lipid-lowering efficacy, PCSK9 inhibition has permitted the majority of patients with heterozygous familial hypercholesterolemia (HeFH) to reach treatment goals. In patients on placebo, few reached this benchmark despite high-intensity statins. The data in HeFH, presented at the 2015 ESC Congress, are relevant to other high-risk patients who cannot reach targets on current treatments.

Background

Just months after regulatory approval was granted to the PCSK9 inhibitors alirocumab and evolocumab in the United States and Europe, a summary of the largest lipid-lowering trial experience ever accumulated in HeFH provides evidence of efficacy considered impossible with alternatives. The data provide a compelling demonstration of the ability of PCSK9 inhibition to address unmet needs in lipid control.

In the pooled analysis, conducted with alirocumab, LDL-C levels achieved and sustained "were until now unobtainable," asserted Dr. John JP Kastelein, Chairman, Department of Vascular Medicine, Academic Medical Centre, Amsterdam, the Netherlands. In summarizing the pooled data in HeFH, he employed the term "cure" on the basis that LDL levels in the treated patients "are now lower than in the general population, something we have never seen before."

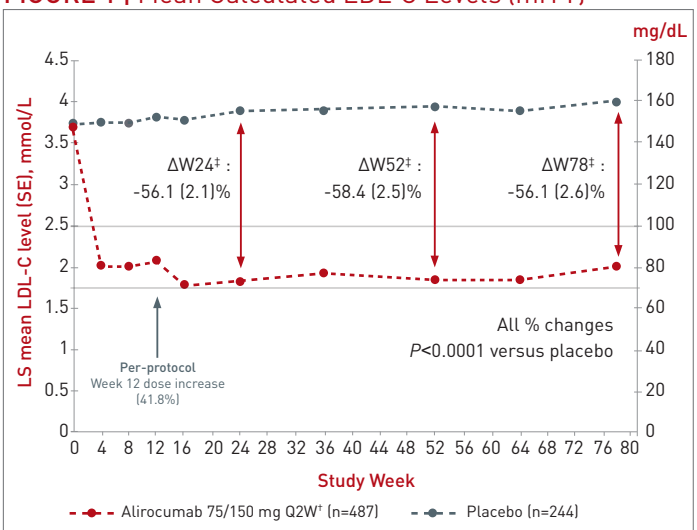
> *"In familial hypercholesterolemia patients on PCSK9 inhibition, LDL-C levels are lower than those seen in the general population, which is something we have never seen before."*

55% LDL-C Reduction over Statins

In this analysis, data on 1257 HeFH patients participating in four placebo-controlled trials with alirocumab were pooled. The average LDL-C at baseline across these studies ranged from 3.65 mmol/L to nearly 4.4 mmol/L. The average reduction in LDL-C on alirocumab relative to placebo, which was the primary endpoint of all 4 trials, climbed to 55% in those with the most severe baseline LDL-C. It has been sustained indefinitely over the course of treatment (Figure 1).

This type of reduction in LDL-C has been reported previously in other populations, but the more impressive result was the proportion reaching treatment goals. Relative to negligible LDL-C goal attainment in placebo patients on maximum-tolerated alternative lipid-lowering therapies (1%), the majority of patients (62.7%) had reached goals on alirocumab (Figure 2).

FIGURE 1 | Mean Calculated LDL-C Levels (mITT)



Pool of FH I and II Studies (Alirocumab 75/150 mg Q2W)
†Alirocumab dose 75 mg Q2W increased to 150 mg Q2W in 41.8% of patients at Week 12 as their LDL-C levels at Week 8 were ≥1.81 mmol/L [70 mg/dL]; ‡ΔW24/52/78 defined as LS mean (SE) % difference versus placebo in calculated LDL-C from baseline to Week 24/52/78. Figure shows on-treatment analysis on modified ITT population, including all lipid data throughout the duration of study collected while the patients were still receiving study treatment.

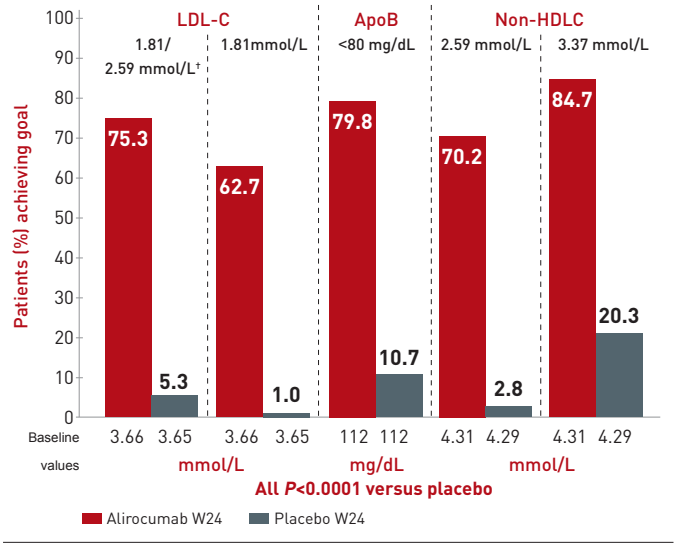
Adapted from Kastelein, JJP et al. As presented during ESC Congress 2015, Abstract 5772.

Prior to PCSK9 inhibition, this degree of lipid control in HeFH patients had been considered "basically impossible," according to Dr. Kastelein. In the HeFH clinic at his center and consistent with the placebo arms he presented, "I have seen very, very few of these patients reach the current guideline goal."

Placebo-like Safety Profile So Far

The rate of incident adverse effects overall and those leading to treatment discontinuation did not differ significantly in these trials (Table 1). Referring to these data and the overall safety data from the large ODYSSEY phase 3 trial program with alirocumab, Dr. Kastelein reported that "we have not seen anything so far that is even remotely worrying."

FIGURE 2 | Goal Attainment (ITT): Pool of FH I and II Studies



Alirocumab dose 75 mg Q2W increased to 150 mg Q2W in 41.8% of patients at Week 12 as their LDL-C levels at Week 8 were ≥1.81 mmol/L; †Depending on CV risk; goals analyzed using multiple imputation followed by logistic regression.
Figure shows ITT analysis performed on ITT population.

Adapted from Kastelein, JJP et al. As presented during ESC Congress 2015, Abstract 5772.

In the United States, alirocumab was awarded a specific indication for treatment of HeFH. Collectively, the studies presented at the 2015 ESC Congress represent the largest trial experience of any agent for this condition. The data are equally compelling in other high-risk patients unable to achieve adequate LDL-C control on alternative therapies. Both alirocumab and evolocumab have been granted approval for the treatment of this larger population in Europe.

In a separate analysis with evolocumab at the 2015 ESC Congress, 3146 patients were pooled from four phase 3 studies (ESC Congress 2015, Abstract 1756). Although not a HeFH analysis, patients enrolled in these studies were also inadequately controlled on statins or other lipid-lowering therapies. LDL-C control was evaluated by stratification for a long list of demographics, risk factors, and other characteristics, such as glucose tolerance status, age above or below 65 years, and likelihood of a cardiovascular (CV) event within the next 10 years.

TABLE 1 I Pooled Safety Data Included in Current Analysis

Pool of HeFH patients (Pool of FH I and II, LONG TERM (HeFH patients only) and HIGH FH)		
	Alirocumab (n=837)	**Placebo (n=418)**
TEAEs, n (%)	674 (80.5)	347 (83.0)
Treatment-emergent SAEs	114 (13.6)	55 (13.2)
TEAEs leading to death	7 (0.8)	2 (0.5)
TEAEs leading to discontinuation	33 (3.9)	15 (3.6)

Table shows safety analysis performed on safety population.
SAE, serious adverse event; TEAE, treatment-emergent adverse event

Adapted from Kastelein, JJP et al. As presented during ESC Congress 2015, Abstract 5772.

"Consistent reductions in LDL-C, regardless of age, gender, race, background statin dose, or CV risk, were observed in the evolocumab group when compared to placebo," confirmed the lead author Dr. Erik S. G. Stroes, who is also affiliated with the Department of Vascular Medicine at the Academic Medical Centre in Amsterdam. His data add evidence to the premise that PCSK9 inhibition provides consistency of effect in patients without other treatment options.

> *"Consistent reductions in LDL-C [are achieved with PCSK9 inhibition] regardless of age, gender, race, background statin dose, or CV risk."*

Conclusion

The PCSK9 inhibitor alirocumab brings more than 60% of HeFH patients to guideline-based LDL-C goals. This is relevant not only to this population but to other high-risk patients unable to achieve treatment goals on alternative agents. Outcome trials are ongoing, but preliminary clinical evidence with PCSK9 inhibition suggests CV risk reductions will be commensurate with LDL-C control. According to Dr. Kastelein, the advent of these drugs represents a "revolution" in the care of high-risk patients.●