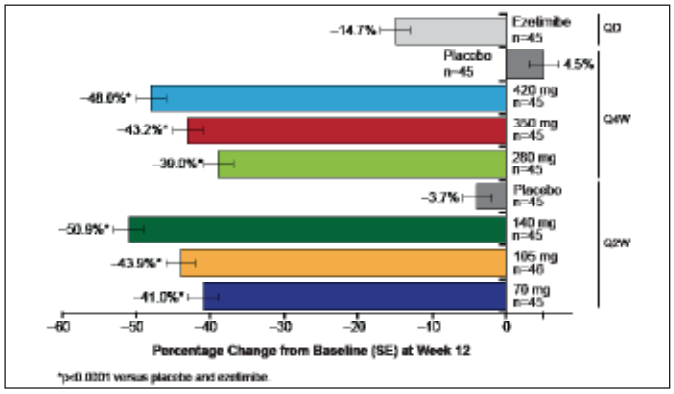
coronary heart disease risk score ≤10% were randomly assigned to 1 of 9 treatment arms: Q2W groups (placebo, or AMG 145 at 70, 105, or 140 mg), Q4W groups (placebo, or AMG 145 at 280, 350, or 420 mg), or oral ezetimibe QD. The primary study endpoint was percentage change in LDL-C by ultracentrifugation from baseline at 12 weeks. Subjects (AMG 145, n=271; placebo, n=90; ezetimibe, n=45) were mean a age of 50 years and mostly white women. Mean baseline LDL-C was between 140 and 145 mg/dL; mean baseline PCSK9 levels were between 341 and 350 ng/mL.

At Week 12, there was a significant dose-dependent reduction in LDL-C levels with both dosing regimens at all doses (Figure 6). Reductions were rapid, with the highest AMG 145 doses leading to the greatest reductions (51% with 140 mg Q2W and 48% with 420 mg Q4W compared with virtually no change with placebo and 15% with ezetimibe). Results were maintained throughout the study and did not vary among any of the prespecified subgroups. As in other studies, treatment with AMG 145 also led to significant reductions in TC, non-HDL-C, ApoB, TC/HDL-C ratio, ApoB/ApoA1 ratio and Lp(a). AEs were similar to those seen in previous trials, and AMG 145 was well tolerated.

Figure 6. Effects of AMG 145 Versus Placebo and Ezetimibe on LDL-C.



LDL-C=low-density lipoprotein cholesterol; Q2W=every 2 weeks; Q4W=every 4 weeks; QD=every day; SE=standard error.

Adapted from MJ Koren, MD. AHA 2012.

Integrating the trials of PCSK9 inhibition for lipid lowering, all have shown that these agents are well tolerated and have potent lipid-lowering effects. This mechanism of therapy has the potential to get substantially more patients to LDL goals when added to currently available therapies [Giugliano RP et al. *Lancet* 2012; Kohli P et al. *Clin Cardiol* 2012]. Well-powered clinical outcome trials are needed in order to evaluate whether LDL lowering through PCSK9 inhibition leads to reductions in adverse CV events.

Effects of 12 Weeks of Treatment with RN316 (PF-04950615) in Hypercholesterolemic Subjects on High and Maximal Dose Statins

Written by ***Phil Vinall***

Results from two Phase 2 trials reported by Barry Gumbiner, MD, Pfizer, Inc., South San Francisco, California, USA, indicate that intravenous infusions of RN316, a humanized IgG2Δa monoclonal antibody that inhibits proprotein convertase subtilisin kexin type 9 (PCSK9), significantly lowers low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects already on high to maximal doses of statins.

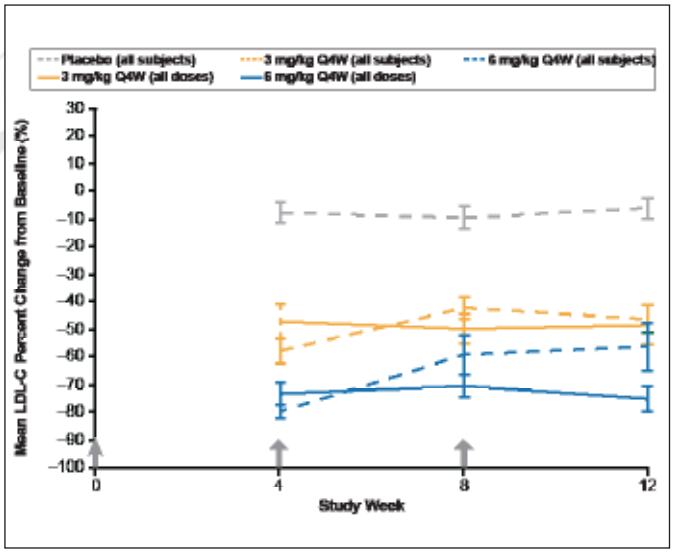
Although statins are first-line therapy for reducing LDL-C and cardiovascular events, many patients are unable to achieve LDL-C goals or tolerate high doses of statin medication. PCSK9, a protein that reduces the number of LDL receptors, leading to diminished hepatic clearance capacity for plasma LDL-C and increased LDL-C levels, is a new therapeutic target for LDL-C lowering. RN316 binds to PCSK9, preventing PCSK9-mediated down-regulation of the LDL receptor, thereby improving LDL-C clearance and reducing LDL-C levels.

Two Phase 2, randomized, double-blind, placebo-controlled, 12-week studies were conducted to assess the efficacy, safety, and tolerability of RN316 when added to high [A Multiple Dose Study of PF-04950615 (RN316) in Subjects on High Doses of Statins; NCT01342211] or maximum [A Multiple Dose Study of PF-04950615 (RN316) In Subjects On Maximum Doses of Statins; NCT01350141] doses of statins (atorvastatin, rosuvastatin, and simvastatin) in subjects with primary hypercholesterolemia. Subjects were eligible if they had an LDL-C ≥100 mgdL in the high-dose statin study and ≥80 mg/dL in the maximal-dose statin study. Subjects in the high-dose statin study were randomized to receive 0.25, 1.0, 3.0, or 6.0 mg/kg doses of intravenous (IV) RN316 or placebo every 4 weeks, while those in the maximal-dose statin study were randomized to 1.0 or 3.0 mg/kg of RN316 or placebo. RN316 dosing was interrupted if LDL-C reached ≤25 mg/dL and resumed once it reached ≥40 mg/dL at a later visit. Subjects were on average aged 55 to 61 years, and overweight or obese with an average body mass index of 30 kg/m^2.

Across the 5 arms, mean baseline LDL-C was ~123 mg/dL, total cholesterol (TC) was ~197 mg/dL, and HDL-C was ~49 mg/dL. Triglycerides ranged from 115 mg/dL to 173 mg/dL. The primary endpoint was the mean percent change in lipid levels from baseline to Week 12.

Data were pooled from the 2 studies (n=135) for this analysis. LDL-C and TC decreased <15% in the placebo, and 0.25 mg/kg and 1 mg/kg RN316-dose groups, with reductions in LDL-C of 46% and 56% with 3- and 6-mg/kg doses of RN316, respectively (p<0.001). For the 3- and 6-mg/kg doses of RN316, there were also significant reductions in TC (30% and 37%, respectively [p<0.001]) and significant increases in HDL-C (7% and 11%, respectively [p<0.05]; Figure 1). There was no significant change in triglyceride levels. More than half of the subjects in the 3- and 6-mg/kg dose groups had at least 1 interrupted dose (19 [59.4%] and 12 [70.6%], respectively). Without dose interruption, overall LDL-C lowering at Week 12 would have been similar to maximal LDL-C lowering observed at Week 4, as confirmed by the sustained LDL-C lowering of 75% in the 6-mg/kg dose subgroup that had no dose interruption.

Figure 1. Mean LDL-C Percent Change from Baseline.



Values are mean ± SE; B1481005 and B1481012 data combined, modified ITT results; results include subjects who had dosing interrupted for LDL-C ≤25 mg/dL; * p<0.05; **p<0.001
Reproduced with permission from B Gumbiner, MD.

Approximately two thirds of all subjects experienced adverse events (AEs) that were mild in nature and resolved without intervention; Dr. Gumbiner said that majority these were reported by the investigators as not likely to be related to the study drug. Overall AEs were balanced between the randomization groups. The development of antidrug antibodies (non-neutralizing) occurred in 5% of subjects receiving RN316, but there were no hypersensitivity reactions. Dr. Gumbiner concluded that overall RN316 appeared to be efficacious, safe, and well tolerated at the doses studied.

Dalcetrapib in Patients with Recent Acute Coronary Syndrome

Written by ***Toni Rizzo***

Observational studies have suggested that spontaneously higher high-density lipoprotein cholesterol (HDL-C) levels are associated with lower cardiovascular (CV) risk; however, it is uncertain whether raising HDL-C by a pharmacologic approach reduces the risk. The cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib raised HDL-C by approximately 30% in Phase 2 trials [Lüscher TF et al. *Eur Heart* 2012; Fayad ZA et al. *Lancet* 2011] without affecting blood pressure (BP) or neurohormones. The objective of the Study of RO4607381 in Stable Coronary Heart Disease Patients With Recent Acute Coronary Syndrome [dal-OUTCOMES; NCT00658515; Schwartz GG et al. *N Engl J Med* 2012] presented by Gregory G. Schwartz, MD, PhD, VA Medical Center and University of Colorado School of Medicine, Denver, Colorado, USA, was to compare the effects of dalcetrapib versus placebo in patients with recent acute coronary syndrome (ACS).

Following a single-blind placebo run-in period of 4 to 12 weeks, patients with recent ACS were randomized to dalcetrapib (n=7938) versus placebo (n=7933) in addition to evidence-based background therapy. Patients with triglycerides >400 mg/dL or under treatment with niacin, fibrates, or bile acid sequestrants were excluded. The primary composite endpoint was time to first occurrence of coronary heart disease death, nonfatal myocardial infarction (MI), ischemic stroke, hospitalization for unstable angina, and cardiac arrest with resuscitation. Secondary endpoints were all-cause mortality and coronary revascularization. The study was terminated for futility at the second prespecified interim analysis (median follow-up 31 months) with 1135 primary endpoint events (71% of projected) since the probability of demonstrating a benefit with dalcetrapib was <20%.

Baseline characteristics, concurrent treatments, and baseline lipid levels were well balanced between the treatment groups. Dalcetrapib raised HDL-C from 43 mg/dL to 59 mg/dL compared with only a slight increase from 43 mg/dL to 45 mg/dL in the placebo group. Low-density lipoprotein cholesterol (LDL-C) averaged 76 mg/dL at baseline in both groups and differed minimally between groups during the study. Despite the effect of dalcetrapib on HDL-C, there was no significant difference in the cumulative percentage of patients reaching the primary endpoint with dalcetrapib (3-year event rate 9.2%) versus placebo (9.1%; HR, 1.04; 95% CI, 0.93 to 1.16; p=0.52).