ACC.14
TCT@ACC-i2 | innovation in intervention

A1375
JACC April 1, 2014
Volume 63, Issue 12

Prevention

RANDOMIZED, PARTIAL BLIND STUDY OF THE PHARMACODYNAMICS, PHARMACOKINETICS AND SAFETY OF MULTIPLE SUBCUTANEOUS DOSES OF ALIROCUMAB, A FULLY HUMAN MONOCLONAL ANTIBODY TO PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9, ADMINISTERED EVERY 4 WEEKS ALONE OR IN COMBINATION WITH EZETIMIBE OR FENOFIBRATE IN HEALTHY SUBJECTS

Poster Contributions
Hall C
Sunday, March 30, 2014, 9:45 a.m.-10:30 a.m.

Session Title: Prevention: Familial Hypercholesterolemia, Novel Therapies and Cardiovascular Risk
Abstract Category: 20. Prevention: Clinical
Presentation Number: 1183-131

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Background: Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) monoclonal antibodies such as alirocumab undergo target mediated clearance by binding PCSK9. Statins are known to increase PCSK9; however, little is known about effects of ezetimibe (EZE) or fenofibrate (FEN) on PCSK9 and consequently their impact on the efficacy of alirocumab dosed every 4 wks (Q4W) in reducing low-density lipoprotein cholesterol (LDL-C).

Methods: Partial-blind study in 3 parallel groups of healthy subjects (LDL-C >130 mg/dL) not on lipid-lowering therapy (NCT01723735). After 4-wk run-in with placebo, 10 mg EZE or 160 mg FEN once daily, subjects received alirocumab 150 mg Q4W and either placebo, EZE or FEN once daily for 8 wks. Primary endpoint was mean % change in LDL-C from day before run-in (day -29).

Results: 72 subjects (24/group) were randomized (32 male, 40 female; 21-65 years). Prior to alirocumab treatment, FEN resulted in increased free PCSK9 levels (from 152 to 217 ng/mL). Maximum mean (standard error of the mean) LDL-C reductions occurred 14 days after 3rd alirocumab dose in all groups ($p<0.0001$): 48.2 (2.3) % with alirocumab alone, 65.3 (2.0) and 66.8 (2.7) % with alirocumab+EZE and +FEN, respectively. Efficacy was sustained over 4-wk dosing interval with alirocumab alone (LDL-C reductions at 4 wks after 3rd alirocumab dose: 47.6 [1.8] %), compared with 59.8 (1.4) % for +EZE, 58.7 (2.8) % for +FEN, suggesting modest loss of efficacy for combinations. Alirocumab exposures were reduced in presence of FEN (geometric mean ratio [95% CI] vs alirocumab alone: 0.64 [0.53 to 0.77]). No serious adverse events or discontinuations occurred; treatment emergent adverse events were reported by 50.0%, 58.3% and 50.0% of subjects for alirocumab alone, +EZE and +FEN, respectively, with headache and nasopharyngitis most frequently reported.

Conclusions: Alirocumab 150 mg Q4W was efficacious as monotherapy or with EZE or FEN over a 4-wk dosing interval. Slight loss in efficacy observed from 2 to 4 wks in FEN combination group may be result of reduced alirocumab exposure due to increase in PCSK9 observed with FEN. Similar incidence of treatment emergent adverse events was reported in all groups.