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EFFECT OF DALCETRAPIB PLUS PRAVASTATIN ON LIPOPROTEIN METABOLISM IN DYSLIPIDEMIC PATIENTS: RESULTS OF A PHASE 2B DOSE-RANGING STUDY

ACC Oral Contributions
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Background: As reported earlier, adding the cholesterol ester transfer protein inhibitor dalcetrapib to pravastatin for 12 wk in dyslipidemic patients significantly raised mean high-density lipoprotein cholesterol (HDL-C) levels by up to 36% and apoA-1 by up to 15% in a Phase 2b trial.

Methods: In this same multicenter, randomized, double-blind study, patients with <50 mg/dL HDL-C on 40 mg/d pravastatin received placebo (n=73) or 300 (n=75), 600 (n=67) or 900 (n=72) mg/d dalcetrapib for 12 wk. The % changes from baseline to 12 wk in lipoprotein profile and in HDL and low-density lipoprotein (LDL) subclasses were assessed using nuclear magnetic resonance (NMR) and gradient gel electrophoresis (GGE).

Results: NMR and GGE both showed a shift in the lipoprotein profile at 12 wk in all treatment arms for both HDL and LDL particles. The % of large HDL particles increased with increasing dalcetrapib dose. The % of large LDL particles also increased; this was independent of dose with NMR but dose-dependent with GGE. The table shows the % change from baseline to 12 wk in the middle-dose group for selected HDL efficacy parameters. After precipitation, ApoE increased in the HDL fraction (unchanged in total plasma) and cholesterol free/ester ratio did not change.

Secondary Efficacy Parameter	% Change, Baseline - Week 12, 600 mg dalcetrapib	
	NMR	Electrophoresis
HDL particles (total)	+10.9	----
HDL large	+171.3	----
HDL medium	+69.6	----
HDL small	+2.4	----
HDL 2a	----	+10.1
HDL 2b	----	+30.1
HDL 3a	----	-6.7
HDL 3b	----	-13.9
HDL 3c	----	-14.6

Conclusions: Adding dalcetrapib to pravastatin beneficially modified the atherogenic lipoprotein profile in dyslipidemic patients. ApoE is redistributed from very low density lipoprotein/LDL to HDL particles, which may facilitate cholesterol delivery to the liver.