ACC.15
TCT@ACC-i2 | innovation in intervention

A1591
JACC March 17, 2015
Volume 65, Issue 10S

Stable Ischemic Heart Disease

SAFETY AND EFFICACY OF LY3015014, A NEW MONOCLONAL ANTIBODY TO PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) WITH AN INHERENTLY LONGER DURATION OF ACTION, IN PATIENTS WITH PRIMARY HYPERCHOLESTEROLEMIA: A RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RANGING, PHASE 2 STUDY

Oral Contributions
Room 7B
Sunday, March 15, 2015, 11:36 a.m.-11:47 a.m.

Session Title: Highlighted Original Research: Stable Ischemic Heart Disease and the Year in Review
Abstract Category: 26. Stable Ischemic Heart Disease: Clinical
Presentation Number: 905-10

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Background: PCSK9 antibodies under development require dosing every (Q) 2 weeks (W) or large monthly doses to maintain sustained LDL-C reductions. LY3015014 (LY) is a humanized monoclonal antibody with an inherently longer duration of action. This phase 2 study assessed the LDL-C lowering effect of LY given every 4 or 8 weeks to patients with primary hypercholesterolemia, when added to standard of care lipid lowering therapy, including statins.

Methods: Patients were randomized to receive subcutaneous injections of LY 20 mg, 120 mg or 300 mg Q4W; 100 mg or 300 mg Q8W (alternating with placebo Q4W); or placebo Q4W. The primary endpoint was percentage change from baseline in LDL-C (by beta quantification) at week 16. Safety and tolerability were also assessed.

Results: 527 patients were randomized and 519 received study drug. LY demonstrated dose related decreases in LDL-C, with up to 51% reduction maintained at the end of the dosing interval (see table). There were no treatment related serious adverse events. The most common adverse event terms (≥10% of any treatment group) were nasopharyngitis, injection site pain, headache, injection site erythema and back pain. No liver or muscle safety issues emerged.

Conclusion: The PCSK9 antibody, LY, dosed every 4 or 8 weeks, resulted in robust and durable reductions in atherogenic (apo) lipoproteins, including LDL-C, non-HDL-C, ApoB and Lp(a). No clinically relevant safety issues emerged with the administration of LY.

	LY3015014					
	20 mg Q4W (n=87)	120 mg Q4W (n=86)	300 mg Q4W (n=86)	100 mg Q8W (n=86)	300 mg Q8W (n=87)	Placebo Q4W (n=87)
Percentage change from baseline to week 16, LS mean						
LDL-C[β]	-14.9 *	-40.5 *	-50.5 *	-14.9 *	-37.1 *	7.6
HDL-C[α]	4.5	7.3 #	8.8 #	4.5	8.4 #	1.6
Non HDL-C[α]	-16.1 *	-39.3 *	-48.9 *	-16.1 *	-35.8 *	4.9
TG[α]	-6.1 #	-7.2 #	-15.1 *	-7.2 #	-10.6 #	3.5
Apo B[α]	-16.6 *	-34.9 *	-46.8 *	-16.0 *	-31.9 *	4.2
Lp(a)[α,γ]	-16.6 #	-19.0 *	-37.3 *	-7.5	-21.0 *	-0.3
Serious adverse events (%)	3.4	7.0	2.3	2.3	4.6	5.7
Drug-related adverse events (%)	32.2	37.2	36.0	30.2	28.7	24.1
Discontinuation due to adverse events (%)	3.4	4.7	3.5	1.2	8.0	3.4
CK >5X ULN (%)	1.2	4.7	0	2.3	1.1	3.5
ALT or AST > 3X ULN (%)	0	1.2	0	0	1.1	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; Apo B = apolipoprotein B; CK = creatinine kinase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein a; ULN = upper limit of normal; TG = triglycerides

[α] Statistics are from mixed model repeated measures (MMRM) analysis with baseline measurement, disease classification (heterozygous familial hypercholesterolemia vs. polygenic hypercholesterolemia), statin dose, treatment, visit and treatment by visit interaction included in the model..
[β] Statistics are from analysis of covariance (ANCOVA) adjusted for disease classification (heterozygous familial hypercholesterolemia vs. polygenic hypercholesterolemia), statin dose and baseline LDL-C measuremen
[γ] LS mean change from baseline per log-transformed analysis
* p<0.001 for % change with LY3015014 group vs. placebo for efficacy endpoints
# p< 0.05 for % change with LY3015014 group vs. placebo for efficacy endpoints