ODYSSEY HIGH FH: Efficacy and Safety of Alirocumab in Patients With Severe Heterozygous Familial Hypercholesterolemia

Henry N Ginsberg, Columbia Univ Coll of Physicians and Surgeons, New York, NY; Daniel J Rader, Perelman Sch of Med, Univ of Pennsylvania, Smilow Ctr for Translational Res, Philadelphia, PA; Frederick J Raal, Univ of the Witwatersrand, Johannesburg, South Africa; John R Guyton, Duke Univ Medical Ctr, Durham, NC; Christelle Lorenzato, Sanofi, Chilly Mazarin, France; Robert Pordy, Regeneron Pharmaceuticals, Inc, Tarrytown, NY; Marie T Baccara-Dinet, Sanofi, Paris, France; Eric SG Stroes, Academic Medical Ctr, Amsterdam, Netherlands

Background: Patients with heterozygous familial hypercholesterolemia (heFH) typically have very high untreated levels of low-density lipoprotein cholesterol (LDL -C). Even with existing lipid-lowering therapies (LLTs), many patients continue to have elevated LDL-C levels and remain at increased risk for premature cardiovascular disease. The ODYSSEY HIGH FH study (NCT01617655) compared the LDL-C-lowering efficacy and safety of alirocumab (ALI), a fully human PCSK9 monoclonal antibody, to placebo (PBO) in heFH patients with LDL-C =160 mg/dL despite maximally tolerated statin ± other LLT.

Methods: In this Phase 3, randomized, double-blind, PBO-controlled study, patients were randomized in a 2:1 ratio to ALI 150 mg every 2 weeks (Q2W) or PBO, both self-administered subcutaneously via 1-mL pre -filled pen, for 78 weeks (W). The primary endpoint was the percent change in LDL-C from baseline to W24 in the intention-to-treat population. The pre -specified safety analysis includes all data from baseline to W78 (up to W52 for all patients). During the trial, 2 sites were found to have significant Good Clinical Practice (GCP) issues and a sensitivity analysis was performed excluding the patients from these sites.

Results: Significant reductions in LDL-C from baseline to W24 were observed with ALI vs. PBO (Table), which were maintained to W52. Absolute LS mean (SE) LDL-C levels were reduced by 90.8 (6.7) mg/dL with ALI at W24. Excluding the 2 sites with significant GCP issues, the LS mean (SE) difference vs PBO in % change from baseline to W24 was -48.0 (5.8)% (Table). Treatment-emergent adverse events (TEAEs) were generally comparable between groups (Table).

Conclusions: ALI demonstrated significant reductions in LDL-C vs. PBO after 24W of treatment in this population of patients with severe heFH and very high baseline levels of LDL-C despite maximally tolerated statin ± other LLT. ALI was generally well-tolerated and TEAEs were generally comparable between groups.

Table. Effects of alirocumab on LDL-C in patients with heFH and baseline LDL-C ≥160 mg/dL despite maximally tolerated statin ± other LLT		
Randomized pts	**ALI (N=72)**	**PBO (N=35)**
ITT population, N	71	35
Baseline LDL-C (ITT), mean (SD), mg/dL	196.3 (57.9)	201.0 (43.4)
LDL-C at W24, LS mean (SE), mg/dL	107.0 (6.7)	182.3 (9.5)
Absolute change from baseline to W24, LS mean (SE), mg/dL	-90.8 (6.7)	-15.5 (9.5)
Change from baseline to W24, LS mean (SE), %	-45.7 (3.5)	-6.6 (4.9)
Difference vs. PBO, LS mean (SE), %	-39.1 (6.0)	
P value	<0.0001	
Patients reaching LDL-C goal at W24,† %	41.0	5.7
P value	0.0016	
Sensitivity analysis of primary endpoint (excluding two sites with serious GCP non-compliance)		
Sensitivity analysis population, N	62	31
Change from baseline to W24, LS mean (SE), %	-50.3 (3.3)	-2.3 (4.7)
Difference vs. PBO, LS mean (SE), %	-48.0 (5.8)	
P value	<0.0001	
Safety summary (N)	72	35
TEAEs overall, % pts (n)	61.1% (44)	71.4% (25)
TEAEs leading to discontinuation, % pts (n)	4.2% (3)	2.9% (1)
Most common TEAEs, % pts (n)		
Nasopharyngitis	11.1% (8)	11.4% (4)
Influenza	11.1% (8)	2.9% (1)
Diarrhea	5.6% (4)	8.6% (3)
Myalgia	4.2% (3)	8.6% (3)
†Very high-risk <70 mg/dL; Very high CV risk defined as patients with coronary heart disease (CHD) or CHD risk equivalents. High CV risk (all other patients): <100 mg/dL.		

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