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Regeneron and Sanofi Announce New Results from Six Phase 3 Trials Showing that Alirocumab Significantly Reduced LDL Cholesterol

All six trials met primary efficacy endpoint Data presented at AHA Scientific Sessions 2014

TARRYTOWN, N.Y. and PARIS, Nov. 19, 2014 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) and Sanofi today announced new detailed positive results from six Phase 3 ODYSSEY trials that showed alirocumab significantly reduced low-density lipoprotein cholesterol (LDL-C, or "bad" cholesterol). Alirocumab is an investigational fully human monoclonal antibody targeting the protein PCSK9 (proprotein convertase subtilisin/kexin type 9) that is being evaluated for its ability to lower LDL-C.

All six trials, ODYSSEY LONG TERM, COMBO I, ALTERNATIVE, OPTIONS I, OPTIONS II, and HIGH FH, met their primary efficacy endpoint of a greater reduction in LDL-C at 24 weeks, versus either active comparator or placebo, which included standard-of-care therapy. Detailed results from these trials were presented as part of a special session on the ODYSSEY program today, and on November 17 during a late-breaker presentation at the American Heart Association (AHA) Scientific Sessions in Chicago, IL. The companies had announced in July that all six studies met their primary efficacy endpoints.

"In these trials patients treated with alirocumab achieved significant and robust LDL-C reductions compared to baseline," said Jennifer Robinson, M.D., M.P.H., Director of the Prevention Intervention Center, Professor, Departments of Epidemiology & Medicine, College of Public Health at the University of Iowa. "New interim results from ODYSSEY LONG TERM provide further support for alirocumab's consistent safety profile, including in more than 500 patients who achieved LDL-C levels lower than 25 mg/dL."

The trials assessed alirocumab in hypercholesterolemic patients who were at high cardiovascular (CV) risk, had an inherited form of high cholesterol known as heterozygous familial hypercholesterolemia (HeFH), and/or a history of intolerance to two or more statins, including one at the lowest dose. All patients received alirocumab in addition to standard-of-care lipid-lowering therapy, with the exception of some patients in ODYSSEY ALTERNATIVE.

Table 1: Summary of Primary Efficacy Endpoint and Most Common Adverse Events (AEs)

Study	Patient group	Primary efficacy endpoint (percent change from baseline in LDL-C at 24 weeks)		Most common AEs ^a
		Alirocumab	Comparator	
LONG TERM Alirocumab (n=1,553) vs. placebo (n=788) 150 mg dose	All patients (high CV risk) ^b (total n=2,341)	61 percent reduction	1 percent increase (placebo) ^c	Nasopharyngitis, upper respiratory tract infection, injection site reactions, influenza, diarrhea, urinary tract infection, bronchitis, myalgia, headache, back pain, arthralgia
	HeFH subgroup (n= 416)	56 percent reduction	7 percent increase (placebo) ^d	
	Non-HeFH subgroup (n= 1,894)	62 percent reduction	0.5 percent reduction (placebo) ^e	
COMBO I Alirocumab (n=209) vs. placebo (n=107) 75 mg / 150 mg dose	High CV risk	48 percent reduction	2 percent reduction (placebo) ^c	Upper respiratory tract infection, nasopharyngitis, urinary tract infection, dizziness, sinusitis, injection-site reaction
OPTIONS I [Baseline statin = atorvastatin 20/40 mg] Alirocumab (n=104) vs. ezetimibe (n=102) or double atorvastatin (n=104) or switch to rosuvastatin ^f (n=45)	High CV risk	44-54 percent reduction	- 20.5-23 percent reduction (ezetimibe)g - 5 percent reduction (double statin dose)c - 21 percent reduction (statin switch)c	Nasopharyngitis, upper respiratory tract infection, hypertension, back pain

75 mg / 150 mg dose				
OPTIONS II [Baseline statin = rosuvastatin 10/20 mg] Alirocumab (n=103) vs. ezetimibe (n=101) or double rosuvastatin (n=101)	High CV risk	36-51 percent reduction	- 11-14 percent reduction (ezetimibe) ^h - 16 percent reduction (double statin dose) ^h	Nasopharyngitis, upper respiratory tract infection, hypertension, back pain
75 mg / 150 mg dose				
ALTERNATIVE Alirocumab (n=126) vs. ezetimibe (n=125) [Validation arm = atorvastatin 20 mg (n=63)]	High CV risk and history of intolerance to two or more statins	45 percent reduction	15 percent reduction (ezetimibe) ^c	Myalgia, nasopharyngitis, arthralgia, upper respiratory tract infection, headache, fatigue
75 mg / 150 mg dose				
HIGH FH Alirocumab (n=72) vs. placebo (n=35) 150 mg dose	HeFH	46 percent reduction	7 percent reduction (placebo) ^c	Nasopharyngitis, injection-site reaction, diarrhea, sinusitis, bronchitis, headache, fatigue

- Occurred in at least 5 percent of alirocumab-treated patients
- Previously reported in August 2014
- P less than 0.0001
- 95 percent confidence interval of the LS mean difference vs. placebo: 57.5-69 percent reduction
- 95 percent confidence interval of the LS mean difference vs. placebo: 59-64 percent reduction
- 45 patients on atorvastatin 40 mg starting dose switched to rosuvastatin 40 mg
- For patients on atorvastatin 20 mg starting dose p=0.0004; for patients on atorvastatin 40 mg starting dose p less than 0.0001
- For patients on rosuvastatin 10 mg starting dose p less than 0.0001; patients on rosuvastatin 20 mg starting dose did not reach statistical significance

In a pre-specified interim analysis of the ongoing, 78-week ODYSSEY LONG TERM safety, tolerability and efficacy trial, a generally comparable rate of AEs was observed among the 37 percent (n=562) of alirocumab-treated patients who achieved two consecutive LDL-C values of less than 25 mg/dL, as compared to the overall alirocumab patient population in this trial.

ODYSSEY ALTERNATIVE is the first trial of a PCSK9 inhibitor to reassess statin intolerance, as measured by skeletal muscle AEs, by including a validation arm (atorvastatin 20 mg). In clinical practice, 10 to 25 percent of patients report intolerance to statins, and many have poorly-controlled LDL-C, which puts them at greater risk of CV events.^{1,2} In this trial, there were fewer skeletal muscle AEs in the alirocumab group compared to patients treated with atorvastatin (32.5 percent versus 46 percent, hazard ratio = 0.61; nominal p value = 0.042), and there was no significant difference when compared to the ezetimibe group (41 percent). In addition, there were numerically fewer discontinuations for skeletal muscle AEs in the alirocumab group, but this did not reach statistical significance (alirocumab 16 percent, ezetimibe 20 percent, atorvastatin 22 percent). In comparison, the overall rate of discontinuations for skeletal muscle AEs across the Phase 2 and 3 alirocumab placebo-controlled studies, where the majority of patients were also on statins, was 0.4 percent for alirocumab (n=2,476) and 0.5 percent for placebo (n=1,276).

Patients in all six randomized, double-blind, Phase 3 ODYSSEY trials received alirocumab via a single, self-administered 1-milliliter (mL) subcutaneous injection, every two weeks. Alirocumab-treated patients received the 150 milligram (mg) dose in ODYSSEY LONG TERM and HIGH FH, and the 75 mg dose (increasing to 150 mg if needed to reach pre-specified LDL-C levels) in ODYSSEY ALTERNATIVE, OPTIONS I, OPTIONS II, and COMBO I. In the trials that used an individualized approach with 75 mg and 150 mg doses, the majority of patients reached their LDL-C goal while remaining on the 75 mg dose. Average baseline LDL-C levels in all six trials were between approximately 100-120 mg/dL, with the exception of ODYSSEY ALTERNATIVE and HIGH FH where baseline LDL-C levels were greater than 190 mg/dL.

The six ODYSSEY trials reported at AHA Scientific Sessions 2014, along with results from four other Phase 3 studies, encompass more than 5,000 patients studied in double-blind trials for 24-104 weeks. Regulatory submissions are planned in the U.S. and EU before the end of this year.

The ODYSSEY clinical trial program is ongoing. Click [here](#) for more information on alirocumab, LDL-C, and the ODYSSEY studies presented at the AHA Scientific Sessions 2014. Alirocumab is currently under clinical development and its safety and efficacy have not been evaluated by any regulatory authority.

About Sanofi

Sanofi, an integrated global healthcare leader, discovers, develops and distributes therapeutic solutions focused on patients' needs. Sanofi has core strengths in the field of healthcare with seven growth platforms: diabetes solutions, human vaccines, innovative drugs, consumer healthcare, emerging markets, animal health and the new Genzyme. Sanofi is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY).

About Regeneron Pharmaceuticals, Inc.

Regeneron is a leading science-based biopharmaceutical company based in Tarrytown, New York that discovers, invents, develops, manufactures, and commercializes medicines for the treatment of serious medical conditions. Regeneron commercializes medicines for eye diseases, colorectal cancer, and a rare inflammatory condition and has product candidates in development in other areas of high unmet medical need, including hypercholesterolemia, oncology, rheumatoid arthritis, asthma, and atopic dermatitis. Several Regeneron programs are based on human genetics findings. For additional information about the company, please visit www.regeneron.com.

References:

1. Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients —the PRIMO study. *Cardiovasc Drugs Ther.* 2005;19:403-414.
2. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding statin use in America and gaps in patient education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol.* 2012 May-Jun;6(3):208-15.

Sanofi Forward-Looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions and expectations with respect to future financial results, events, operations, services, product development and potential, and statements regarding future performance. Forward-looking statements are generally identified by the words "expects", "anticipates", "believes", "intends", "estimates", "plans" and similar expressions. Although Sanofi's management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Sanofi, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post marketing, decisions by regulatory authorities, such as the FDA or the EMA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labelling and other matters that could affect the availability or commercial potential of such product candidates, the absence of guarantee that the product candidates if approved will be commercially successful, the future approval and commercial success of therapeutic alternatives, the Group's ability to benefit from external growth opportunities, trends in exchange rates and prevailing interest rates, the impact of cost containment policies and subsequent changes thereto, the average number of shares outstanding as well as those discussed or identified in the public filings with the SEC and the AMF made by Sanofi, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in Sanofi's annual report on Form 20-F for the year ended December 31, 2013. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.

Regeneron Forward-Looking Statements

This news release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron Pharmaceuticals, Inc. ("Regeneron"), and actual events or results may differ materially from these forward-looking statements. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," variations of such words, and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications of Regeneron's products, product candidates, and research and clinical programs now underway or planned, including without limitation alirocumab; unforeseen safety issues resulting from the administration of products and product candidates in patients, including serious complications or side effects in connection with the use of Regeneron's product candidates in clinical trials, such as the ODYSSEY global trial program evaluating alirocumab; the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates, including without limitation alirocumab; ongoing regulatory obligations and oversight impacting Regeneron's research and clinical programs and business, including those relating to patient privacy; determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize Regeneron's products and product candidates; competing drugs and product candidates that may be superior to Regeneron's products and product candidates; uncertainty of market acceptance and commercial success of Regeneron's products and product candidates; the ability of Regeneron to manufacture and manage supply chains for multiple products and product candidates; coverage and reimbursement determinations by third-party payers, including Medicare and Medicaid; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its sales or other financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license or collaboration agreement, including Regeneron's agreements with Sanofi and Bayer HealthCare LLC, to be cancelled or terminated without any further product success; and risks associated with intellectual property of other parties and pending or future litigation relating thereto. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2013 and its Form 10-Q for the quarter ended September 30, 2014. The reader is cautioned not to rely on any forward-looking statements made by Regeneron. Regeneron does not undertake any obligation to update publicly any forward-looking statement, including without limitation any financial projection or guidance, whether as a result of new information, future events, or otherwise.

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