



## **Genzyme and Isis Announce FDA Approval of KYNAMRO™ (mipomersen sodium) Injection for the Treatment of Homozygous Familial Hypercholesterolemia**

**Paris, France and Carlsbad, California, January 29, 2013** – Sanofi (EURONEXT: SAN and NYSE: SNY) and its subsidiary Genzyme, and Isis Pharmaceuticals Inc. (NASDAQ: ISIS), today announced that the U.S. Food and Drug Administration (FDA) has approved its New Drug Application (NDA) for KYNAMRO™ (mipomersen sodium) injection. KYNAMRO, given as a 200 mg weekly subcutaneous injection, has been approved as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (Apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

*“Today’s FDA approval of KYNAMRO is great news for patients with HoFH who are in need of additional treatment options for this rare, and often under-diagnosed disease,”* said Genzyme President and CEO David Meeker, M.D. *“As the leader in treatments for rare diseases, we are pleased to bring our expertise to HoFH patients living with this serious condition to better help them manage their disease.”*

HoFH is a rare inherited condition that makes the body unable to remove LDL cholesterol, often called the “bad” cholesterol, from the blood, causing abnormally high levels of circulating LDL cholesterol. In the United States, HoFH, an orphan indication, occurs in approximately one in one million individuals. For those with HoFH, heart attacks and death often occur before age 30.

*“People living with Homozygous FH do not appear to be sick, but they live with the burden of this rare disease every day,”* said Katherine Wilemon, President and Founder the FH Foundation. *“The approval of KYNAMRO gives the HoFH community hope that HoFH can be effectively managed.”*

The FDA approval triggers a \$25 million milestone payment to Isis from Genzyme.

*“KYNAMRO is the first systemic antisense drug to reach the market and is the culmination of two decades of work to create a new, more efficient drug technology platform. As evidenced by our robust pipeline, our antisense drug discovery technology is applicable to many different diseases, including the treatment of a chronic and rare disease, like HoFH,”* said Stanley T. Crooke, M.D., Ph.D., Chairman of the Board and CEO of Isis. *“We look forward to continuing to work with Genzyme toward a successful commercial launch of KYNAMRO and global expansion into other markets.”*

The FDA approval for KYNAMRO is supported by the largest clinical trial conducted to-date in the HoFH patient population. The randomized, double-blind, placebo-controlled, multi-center trial enrolled 51 patients age 12 to 53 years, including 7 patients age 12 to 16 years, who were maintaining a regimen of maximally-tolerated lipid lowering medications. Treatment with KYNAMRO further reduced LDL-C levels by an average of 113 mg/dL, or 25%, from a treated baseline of 439 mg/dL, and further reduced all measured endpoints for atherogenic particles. In March 2010, these data were published in *The Lancet* by Professor Raal, University of the Witwatersrand in South Africa.

Safety data for KYNAMRO are based on pooled results from four Phase 3, randomized, double-blind, placebo-controlled trials with a total of 390 patients of which 261 patients received a weekly subcutaneous injection of 200 mg of KYNAMRO and 129 patients received placebo for a median treatment duration of 25 weeks. Eighteen percent of patients on KYNAMRO and 2% of patients on



placebo discontinued treatment due to adverse reactions. The most common adverse reactions in patients treated with KYNAMRO that led to treatment discontinuation and occurred at a rate greater than placebo were: injection site reactions (5.0%), alanine aminotransferase (ALT) increased (3.4%), flu-like symptoms (2.7%), aspartate aminotransferase (AST) increased (2.3%), and liver function test abnormal (1.5%).

KYNAMRO is an antisense drug is metabolized without affecting the CYP450 pathways used in commonly prescribed drugs, and thus has potential for no drug-drug interactions. No clinically relevant pharmacokinetic interactions were reported between KYNAMRO and warfarin, or between KYNAMRO and simvastatin or ezetimibe.

KYNAMRO contains a Boxed Warning citing the risk of hepatic toxicity. Patients taking KYNAMRO should have liver enzyme testing before starting the drug and periodically thereafter. *See below for Important Safety Information about KYNAMRO.*

The safety and effectiveness of KYNAMRO have not been established in patients with hypercholesterolemia who do not have HoFH. The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined.

Because of the risk of hepatotoxicity, KYNAMRO is available only through a Risk Evaluation and Mitigation Strategy (REMS) called the KYNAMRO REMS. The goals of the KYNAMRO REMS are:

- To educate prescribers about the risk of hepatotoxicity associated with the use of KYNAMRO, and the need to monitor patients during treatment with KYNAMRO as per product labeling.
- To restrict access to therapy with KYNAMRO to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia (HoFH).

As part of its commitment to HoFH patients, Genzyme has developed KYNAMRO Cornerstone<sup>SM</sup>, an HoFH and KYNAMRO support program for healthcare providers, patients, and their families. KYNAMRO Cornerstone services include:

- Dedicated KYNAMRO Cornerstone Case Managers.
- Product & disease education for providers, patients, and families.
- In-person injection training, if requested.
- Reimbursement support, including out-of-pocket financial support, for patients who qualify.
- Coordination of KYNAMRO shipment and delivery.

KYNAMRO Cornerstone Case Managers are available live Monday-Friday from 9 am to 6 pm Eastern time. For more information about KYNAMRO Cornerstone, or about these support services call 1-877-KYNAMRO (877-596-2676). For additional information, please visit [www.KYNAMRO.com](http://www.KYNAMRO.com).

## Important Safety Information

### WARNING: RISK OF HEPATOTOXICITY

**KYNAMRO can cause elevations in transaminases. In the KYNAMRO clinical trial in patients with HoFH, 4 (12%) of the 34 patients treated with KYNAMRO compared with 0% of the 17 patients treated with placebo had at least one elevation in alanine aminotransferase (ALT)  $\geq 3x$  upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR) or partial thromboplastin time (PTT).**

**KYNAMRO also increases hepatic fat, with or without concomitant increases in transaminases. In the trials in patients with heterozygous familial hypercholesterolemia (HeFH) and hyperlipidemia, the median absolute increase in hepatic fat was 10% after 26 weeks of treatment,**



from 0% at baseline, measured by magnetic resonance imaging (MRI). Hepatic steatosis is a risk factor for advanced liver disease; including steatohepatitis and cirrhosis.

**Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT, AST regularly as recommended. During treatment, withhold the dose of KYNAMRO if the ALT or AST are  $\geq 3$  x ULN. Discontinue KYNAMRO for clinically significant liver toxicity.**

**Because of the risk of hepatotoxicity, KYNAMRO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYNAMRO REMS.**

## **OTHER WARNINGS AND PRECAUTIONS**

Patients are advised to read the KYNAMRO medication guide before starting treatment with KYNAMRO, and each time they receive a refill. There may be new information. This information does not take the place of talking to a doctor about a medical condition or treatment.

KYNAMRO may cause serious side effects, including liver problems. A doctor should be informed of any liver problems, including liver problems while taking other medicines, or if a patient has any of these symptoms of liver problems while taking KYNAMRO: nausea, vomiting, fever, loss of appetite, being (or feeling) more tired than usual, yellowing of eyes or skin, dark urine, itching, or stomach pain.

Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. It is recommended that patients taking KYNAMRO should consume no more than one alcoholic drink per day.

Caution should be exercised when KYNAMRO is used with other medications known to have potential for hepatotoxicity.

KYNAMRO should be used during pregnancy only if clearly needed. Females who become pregnant during KYNAMRO therapy should notify their healthcare provider.

Safety and effectiveness have not been established in pediatric patients.

KYNAMRO is not recommended in patients with severe renal impairment, clinically significant proteinuria, or on renal dialysis.

The safety and effectiveness of KYNAMRO as an adjunct to LDL apheresis have not been established; therefore, the use of KYNAMRO as an adjunct to LDL apheresis is not recommended.

## **CONTRAINDICATIONS**

KYNAMRO is contraindicated in the following conditions:

- Moderate or severe hepatic impairment (Child-Pugh B or C) or active liver disease, including unexplained persistent elevations of serum transaminases.
- Patients with a known hypersensitivity to any component of this product.

## **COMMON SIDE EFFECTS**

In clinical trials the most commonly-reported adverse reactions were injection site reactions occurring in 84% of patients receiving KYNAMRO versus 33% of placebo treated patients. The most common injection site reactions were erythema (59%), pain (56%), hematoma (32%), pruritus (29%), swelling (18%) and discoloration (17%). Injection site reactions did not occur with every injection but resulted in discontinuation of therapy in 5% of patients in pooled phase 3 trials.

Flu-like symptoms, defined as any one of the following: influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise or fatigue and occurring within 2 days of injection, have been



reported more frequently in patients receiving KYNAMRO (30%) versus placebo (16%) in the pooled Phase 3 trials. Flu-like symptoms did not occur with all injections but resulted in discontinuation of therapy in 3% of patients in pooled phase 3 trials.

**See full prescribing information for more details about Warnings & Precautions, complete list of Adverse Reactions and Boxed Warning.**

### **About KYNAMRO (mipomersen sodium) injection**

KYNAMRO is indicated as a first-in-class, oligonucleotide inhibitor, of apolipoprotein B-100 synthesis. KYNAMRO is an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH). KYNAMRO reduces LDL-C by preventing the formation of atherogenic lipoproteins, the particles that carry cholesterol through the bloodstream. KYNAMRO acts by blocking the production of apo B, the protein that provides the structural core for these atherogenic particles, including LDL.

### **About Homozygous Familial Hypercholesterolemia (HoFH)**

HoFH is a rare genetic disease characterized by extreme cholesterol levels. People with HoFH have inherited mutations that limit the body's ability to clear cholesterol. HoFH is extremely rare: it is believed to occur in only one out of every one million persons. As with other rare diseases, the true prevalence of HoFH may be underestimated because of inadequate data and under-diagnosis. Today, it is estimated that HoFH affects about 6,000 people globally. Medical literature includes different criteria for marking an HoFH diagnosis. HoFH may be diagnosed by clinical or genetic parameters, and may be considered in cases of unusually high LDL-C, such as greater than 500 mg/dL without treatment, or 300 mg/dL after taking cholesterol-lowering medication. Because HoFH is genetic, it is important that all family members of people with HoFH know their cholesterol levels, regardless of their age.

### **About Genzyme, a Sanofi Company**

Genzyme has pioneered the development and delivery of transformative therapies for patients affected by rare and debilitating diseases for over 30 years. We accomplish our goals through world-class research and with the compassion and commitment of our employees. With a focus on rare diseases and multiple sclerosis, we are dedicated to making a positive impact on the lives of the patients and families we serve. That goal guides and inspires us every day. Genzyme's portfolio of transformative therapies, which are marketed in countries around the world, represents groundbreaking and life-saving advances in medicine. As a Sanofi company, Genzyme benefits from the reach and resources of one of the world's largest pharmaceutical companies, with a shared commitment to improving the lives of patients. Learn more at [www.genzyme.com](http://www.genzyme.com).

### **About Sanofi**

Sanofi, a global and diversified 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 Isis Pharmaceuticals, Inc.**

Isis is exploiting its leadership position in antisense technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 28 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO, in the United States for the



treatment of patients with HoFH. Genzyme is also pursuing marketing approval of KYNAMRO in Europe. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com).

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Genzyme<sup>®</sup>, KYNAMRO<sup>™</sup> and KYNAMRO Cornerstone<sup>SM</sup> are registered trademarks of Genzyme Corporation. All rights reserved.

### **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, 2011. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.*

### **Isis Forward Looking Statements**

*This press release includes forward-looking statements regarding Isis' collaboration with Genzyme, a Sanofi company, and the development, activity, therapeutic benefit and safety of KYNAMRO<sup>™</sup> in treating patients with high cholesterol. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of KYNAMRO, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2011 and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.*

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