ISIS-APOCIII Rx Phase 2 Study in Patients With Familial Chylomicronemia Published in the New England Journal of Medicine

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Substantial reductions of up to 86% in triglycerides observed
All patients achieved a triglyceride level <500 mg/dL during study
First study to support the role of apoC-III as a key regulator of triglyceride metabolism utilizing multiple pathways

CARLSBAD, Calif., Dec. 3, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today that data from a Phase 2 study of ISIS-APOCIII$_{Rx}$ in patients with familial chylomicronemia syndrome (FCS) were published in *The New England Journal of Medicine*. The paper, titled "Targeting ApoC-III in the Familial Chylomicronemia Syndrome" (Gaudet *et al*, *N Engl J Med* 2014: 371:23: 2200-2206), show that patients with FCS treated with ISIS-APOCIII$_{Rx}$ achieved substantial reductions in apoC-III, triglycerides, chylomicrons and apoC-III-associated very low density lipoprotein-cholesterol (VLDL-C) particles. The three FCS patients in this open-label study had baseline triglyceride levels ranging from 1,406 mg/dL to 2,083 mg/dL and all three patients achieved triglyceride levels below 500 mg/dL during the study. FCS is a rare genetic disorder characterized by severe elevated levels of triglycerides. Current treatment options do not adequately reduce triglycerides and, as a result, patients with FCS have increased risk of recurrent and potentially fatal pancreatitis and other complications.

"These data, published today in *The New England Journal of Medicine*, are a significant step in better understanding the mechanisms and treatment of a rare and very serious disorder of fat metabolism that is often associated with a number of serious health problems. Patients with FCS often have triglyceride levels that are higher than 2,000 mg/dL because they have a genetic defect affecting a key enzyme of fat management, lipoprotein lipase (LPL). FCS patients have extremely low levels of LPL activity and a significant reduction in the breakdown of triglycerides, which leads to extremely high triglyceride levels in circulation. ISIS-APOCIII$_{Rx}$ is designed to reduce apoC-III, which is known to regulate the LPL-dependent pathway. The data published today suggest, for the first time, that reducing levels of apoC-III results in marked reductions in triglycerides that are independent of LPL activity," said Daniel Gaudet, M.D., Ph.D., from the department of medicine, Universite de Montreal and scientific director of the Genome Quebec Biobank Technology Center. "Because of their genetic defect, patients with FCS have very limited therapeutic options and diet and lifestyle changes are not sufficient to significantly reduce their triglycerides. These data published today, although collected from a small number of patients, are compelling and demonstrate the potential of ISIS-APOCIII$_{Rx}$ to produce substantial triglyceride lowering in patients with FCS. They also suggest that apoC-III plays a critical role in fat management through a non-LPL dependent pathway, which would be a shift of paradigm."

The FCS patients in this study were treated with 300 mg of ISIS-APOCIII$_{Rx}$ as part of a Phase 2 open-label study that was designed to assess the safety and activity of ISIS-APOCIII$_{Rx}$ in patients with severely high triglycerides. All three FCS patients had a genetic confirmation of FCS, no detectable LPL activity and baseline triglyceride levels greater than 1,400 mg/dL.

Table 1: Substantial Reductions of Triglycerides and ApoC-III as a Single Agent Observed in a Phase 2 Study in ISIS-APOCIII$_{Rx}$- treated Patients with FCS.

	Patient 1 (485 mg/dL lowest TG)**			Patient 2 (251 mg/dL lowest TG)**			Patient 3 (234 mg/dL lowest TG)**			Mean % Change
	Baseline (mg/dL)	Primary Endpoint (mg/dL)	* % Change	Baseline (mg/dL)	Primary Endpoint (mg/dL)	*% Change	Baseline (mg/dL)	Primary Endpoint (mg/dL)	*% Change	
Triglycerides	1406	616.5	-56	2083	287.5	-86	2043	734.5	-64.0	-69
ApoC-III	18.9	5.5	-71	35.1	3.4	-90	19.8	3.5	-83	-81
VLDL-ApoC-III	12.2	4.5	-63	32.6	2.5	-92	16.8	2.3	-86	-80
HDL-C	16	24	+50	8	21	+163	14	17	+21	+78
Non-HDL-C	214	114.5	-46	327	84	-74	244	111	-55	-58

*Percent changes from baseline at primary endpoint (an average measurement of day 85 and 92)
** Lowest triglyceride level achieved during study

The safety and tolerability of ISIS-APOCIII$_{Rx}$ in patients with FCS to date supports continued development. The most common adverse event was injection site reactions, which were predominantly mild and typically resolved rapidly. There were no flu-like symptoms, no treatment-related elevations of liver enzymes greater than three times upper limit of normal, no abnormalities in renal function, no clinically meaningful changes in other laboratory values and no treatment-related serious adverse events.

"The data published today provides support for a novel mechanism by which reducing apoC-III promotes triglyceride clearance in patients with FCS and gives us a great deal of optimism as we enter Phase 3 development of ISIS-APOCIII$_{Rx}$. In our Phase 2 studies, we showed that ISIS-APOCIII$_{Rx}$ lowered triglycerides equally well in patients with high to severely high triglycerides. We also observed dramatic reductions in apoC-III and other lipid parameters and we observed an increase in HDL-cholesterol," Dr. Sotirios Tsimikas, M.D., professor of medicine and director of vascular medicine at

the University of California, San Diego and vice president of clinical development and leader of the cardiovascular franchise at Isis. "We believe that there is a significant unmet medical need for an effective triglyceride-lowering drug for patients with FCS. As such, we are encouraged with the robust results we have observed with ISIS-APOCIII$_{Rx}$ in FCS patients to date. We have initiated our registration-directed Phase 3 study of ISIS-APOCIII$_{Rx}$ in patients with FCS and plan to initiate a second Phase 3 study in patients with severely high triglycerides early next year."

FCS is a rare genetic disorder that affects approximately one to two out of a million people. The most common genetic cause of FCS is a defect in the lipoprotein lipase (LPL) gene, which results in extremely low levels of LPL activity and a significant reduction in the breakdown of triglycerides. In the study reported today, all three patients were homozygotes or compound heterozygotes for null LPL gene mutations resulting in undetectable LPL activity.

ISIS-APOCIII$_{Rx}$ is an antisense drug in development intended to treat patients with severely high triglycerides either as a single agent or in combination with other triglyceride-lowering agents. ISIS-APOCIII$_{Rx}$ is designed to target apoC-III, a protein produced in the liver that plays a central role in the regulation of serum triglycerides. Humans who do not produce apoC-III have lower levels of triglycerides and lower instances of cardiovascular disease. Humans with elevated levels of apoC-III have high triglycerides associated with multiple metabolic abnormalities, such as insulin resistance and/or metabolic syndrome. In addition, the prevalence of type 2 diabetes is increased in patients with elevated triglycerides. Humans with severely elevated levels of triglycerides are at risk of many serious health conditions, including pancreatitis, which can be life-threatening and require hospitalization.

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 34 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO®, in the United States and other countries for the treatment of patients with homozygous FH. Isis has numerous drugs in Phase 3 development in severe and rare and cardiovascular diseases. These include a ISIS-APOCIII$_{Rx}$, a drug Isis is developing to treat patients with severely high triglycerides, such as patients with familial chylomicronemia syndrome; ISIS-TTR$_{Rx}$, a drug Isis is developing with GSK to treat patients with the polyneuropathy form of TTR amyloidosis; and, ISIS-SMN$_{Rx}$, a drug Isis is developing with Biogen Idec to treat infants and children with spinal muscular atrophy, a severe and rare neuromuscular disease. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding the discovery, development, and potential of drugs for cardiovascular diseases, and the development, activity, therapeutic potential and safety of ISIS-APOCIII$_{Rx}$. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs 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, 2013, 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.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

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To view the original version on PR Newswire, visit:http://www.prnewswire.com/news-releases/isis-apociii-rx-phase-2-study-in-patients-with-familial-chylomicronemia-published-in-the-new-england-journal-of-medicine-300004522.html

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