New England Journal of Medicine publishes results from pivotal study of WAYLIVRA® (volanesorsen) in patients with familial chylomicronemia syndrome

August 7, 2019

Mean triglyceride levels decreased 77% in volanesorsen-treated patients versus an 18% increase in patients in placebo group

Akcea launching WAYLIVRA in the European Union

BOSTON and CARLSBAD, Calif, Aug. 07, 2019 (GLOBE NEWSWIRE) -- Akcea Therapeutics, Inc. (NASDAQ: AKCA), an affiliate of Ionis Pharmaceuticals, Inc., and Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), announced today that the final study results from the Phase 3 APPROACH study evaluating WAYLIVRA® (volanesorsen) in patients with familial chylomicronemia syndrome (FCS) were published in the August 8th issue of *The New England Journal of Medicine* (*NEJM*). The manuscript is titled "Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome."

Ionis Logo

FCS is an ultra-rare debilitating disease that can be life-altering. It is caused by impaired production or function of the enzyme, lipoprotein lipase (LPL), responsible for breaking down chylomicrons, lipoproteins rich in triglycerides. This results in extremely high triglyceride levels that lead to significant risk and disease burden, including unpredictable and potentially fatal acute pancreatitis as well as chronic complications due to permanent organ damage. It is estimated that there are between 3,000 to 5,000 people living with FCS worldwide. WAYLIVRA is designed to reduce the production of apolipoprotein C-III (apoC-III), a protein produced in the liver that plays a central role in the regulation of plasma triglycerides.

"Results from the APPROACH study indicate that WAYLIVRA lowers triglyceride levels below the threshold for risk of triglyceride-induced acute pancreatitis in the majority of patients," said Dr. Marcello Arca, head of the lipid and atherosclerosis unit of the University Hospital Policlinico Umberto I. "Acute pancreatitis is one of the most severe consequences of FCS, causing hospitalization, missed work or school, reduced time with family in addition to the potential for permanent organ damage or death. WAYLIVRA is a promising treatment that could significantly reduce the burden of FCS for patients and their families."

APPROACH was a Phase 3, double-blind, randomized, placebo-controlled clinical trial designed to evaluate the safety and efficacy of WAYLIVRA in FCS patients. It is the largest study ever conducted in FCS to-date, involving 66 patients from 40 different treatment centers in 12 countries. Results from the APPROACH trial show that FCS patients treated with WAYLIVRA achieved a statistically significant mean reduction in triglycerides of 77 percent from baseline (mean reduction of 94 percent when compared to placebo) at three months. The levels of apoC-III also decreased by an average of 84 percent from baseline at three months ($P<0.001$) following treatment with WAYLIVRA. The most common adverse events were injection site reactions and platelet declines. For the full text of this publication, please visit: https://www.nejm.org/doi/full/10.1056/NEJMoa1715944?query=featured_home.

"We are very pleased that *The New England Journal of Medicine* recognizes the significance of the APPROACH data and the potential of WAYLIVRA to address an area of significant unmet need in the treatment of FCS," said Louis O'Dea, chief medical officer of Akcea Therapeutics. "WAYLIVRA is the only treatment approved for FCS. We are currently preparing to make WAYLIVRA available to patients in Europe beginning in Germany this month. Our hope is that we will be able to deliver WAYLIVRA to patients with FCS in other geographies who desperately need an approved treatment."

"This publication of the APPROACH study results and the recent EU approval of WAYLIVRA, clearly demonstrate WAYLIVRA's safety and efficacy profile for patients with FCS. We and Akcea are focusing on delivering this much needed medicine to those patients living with this severe disease who are waiting to have WAYLIVRA as a treatment option," said Brett P. Monia, Ph.D., chief operating officer of Ionis Pharmaceuticals.

About WAYLIVRA® (volanesorsen)
With conditional marketing authorization from the European Commission (EC) as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate, WAYLIVRA is now the only therapy indicated for people with familial chylomicronemia syndrome (FCS). Akcea is working to confirm a path forward for WAYLIVRA in the U.S. and Canada.

WAYLIVRA, a product of Ionis' proprietary antisense technology, is designed to reduce the production of apoC-III, a protein that regulates plasma

triglycerides and may also affect other metabolic parameters.

The European Commission's marketing authorization of WAYLIVRA is based on results from the Phase 3 APPROACH study and the ongoing APPROACH Open Label Extension (OLE) study and is supported by results from the Phase 3 COMPASS study. Results from the Phase 3 APPROACH trial, the largest study ever conducted in patients with FCS, show that in comparison to placebo, treatment with WAYLIVRA reduced triglycerides 77% (-94% when compared to placebo). All patients in the trial maintained a low-fat diet.

WAYLIVRA is associated with risk of thrombocytopenia. Enhanced monitoring is required to support early detection and management of thrombocytopenia. The most frequently observed adverse reactions (more than 10%) during treatment with WAYLIVRA were events associated with injection site reactions, immunogenicity and reduction in platelet levels.

The WAYLIVRA Early Access Program (EAP) has been initiated in Europe, the U.S. and Canada and is currently enrolling eligible patients. Click here for more information on the WAYLIVRA EAP. For more information on WAYLIVRA, please visit www.WAYLIVRA.eu.

In August 2019 Akcea and Ionis announced positive top-line results for the BROADEN study of WAYLIVRA for the treatment of patients with familial partial lipodystrophy, or FPL. To view the release, click here.

About FCS

FCS is an ultra-rare disease caused by impaired function of the enzyme lipoprotein lipase (LPL) and characterized by severe hypertriglyceridemia (>880mg/dL or 10mmol/L) and a risk of unpredictable and potentially fatal acute pancreatitis. Because of limited LPL production or function, people with FCS cannot breakdown chylomicrons, lipoprotein particles that are 90% triglycerides. In addition to pancreatitis, FCS patients are at risk of chronic complications due to permanent organ damage, including chronic pancreatitis and pancreatogenic (type 3c) diabetes. They can experience daily symptoms including abdominal pain, generalized fatigue and impaired cognition that affect their ability to work. People with FCS also report major emotional and psychosocial effects including anxiety, social withdrawal, depression and brain fog. Additional information on FCS is available at www.fcsfocus.com, through the LPLD Alliance at www.lpldalliance.org and through The FCS Foundation at http://www.livingwithfcs.org. For a full list of organizations supporting the FCS community worldwide, please click here.

ABOUT IONIS PHARMACEUTICALS, INC.

As the leader in RNA-targeted drug discovery and development, Ionis has created an efficient, broadly applicable, drug discovery platform called antisense technology that can treat diseases where no other therapeutic approaches have proven effective. Our drug discovery platform has served as a springboard for actionable promise and realized hope for patients with unmet needs. We created the first and only approved treatment for children and adults with spinal muscular atrophy as well as the world's first RNA-targeted therapeutic approved for the treatment of polyneuropathy in adults with hereditary transthyretin amyloidosis. Our sights are set on all the patients we have yet to reach with a pipeline of more than 40 novel medicines designed to treat a broad range of diseases including cardiovascular diseases, neurological diseases, infectious diseases, pulmonary diseases and cancer.

To learn more about Ionis follow us on twitter @ionispharma or visit www.ionispharma.com.

ABOUT AKCEA THERAPEUTICS, INC.

Akcea Therapeutics, Inc., an affiliate of Ionis Pharmaceuticals, Inc., is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious and rare diseases. Akcea is commercializing TEGSEDI® (inotersen) and advancing a mature pipeline of novel drugs, including WAYLIVRA® (volanesorsen), AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx}, and AKCEA-TTR-L_{Rx}, with the potential to treat multiple diseases. All six drugs were discovered by Ionis, a leader in antisense therapeutics, and are based on Ionis' proprietary antisense technology. TEGSEDI is approved in the U.S., E.U. and Canada. WAYLIVRA is approved in the E.U. and is currently in Phase 3 clinical development for the treatment of people with familial partial lipodystrophy, or FPL. Akcea is building the infrastructure to commercialize its drugs globally. Akcea is a global company headquartered in Boston, Massachusetts. Additional information about Akcea is available at www.akceatx.com and you can follow us on twitter at @akceatx.

AKCEA'S AND IONIS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding the business of Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc. and the therapeutic and commercial potential of WAYLIVRA® (volanesorsen) and other products in development. Any statement describing Akcea's or Ionis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of WAYLIVRA or other of Akcea's or Ionis' drugs in development 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. Akcea's and Ionis' 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 Akcea's and Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Akcea and Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Akcea's and Ionis' programs are described in additional detail in Akcea's and Ionis' quarterly reports on Form 10-Q and annual reports on Form 10-K, which are on file with the SEC. Copies of these and other documents are available from each company.

In this press release, unless the context requires otherwise, "Ionis", "Akcea," "Company," "Companies" "we," "our," and "us" refers to Ionis Pharmaceuticals and/or Akcea Therapeutics.

Therapeutics, Inc.

Akcea Investor Contact:
Kathleen Gallagher
Vice President, Corporate Communications and Investor Relations
(617)-207-8509
kgallagher@akceatx.com

Bill Berry
Berry & Company
T: 212 253-8881
bberry@berrypr.com

Lynn Granito
Berry & Company
T: 212 253-8881
lgranito@berrypr.com

Ionis Investor Contact:
D. Wade Walke, Ph.D.
Vice President, Investor Relations
760-603-2741
wwalke@ionisph.com

Ionis Media Contact:
Roslyn Patterson
Vice President, Corporate Communications
760-603-2681
rpatterson@ionisph.com

Source: Akcea Therapeutics, Inc.

Source: Ionis Pharmaceuticals