Ionis Pharmaceuticals Reports Positive Data from Phase 2 Study of IONIS-GCGR$_{Rx}$ in Patients with Type 2 Diabetes

Company to present top-line results at Pipeline Update Webcast on January 5

Carlsbad, Calif., January 4, 2017 – Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), today announced positive data from a Phase 2 study of IONIS-GCGR$_{Rx}$ in 79 patients with type 2 diabetes. In this study, patients with type 2 diabetes uncontrolled on stable, maximal metformin therapy treated with IONIS-GCGR$_{Rx}$ achieved robust and sustained, statistically significant improvements in hemoglobin A1c (HbA1c) and other measures of glucose control after 26 weeks of treatment.

- Patients treated with 50 mg and 75 mg weekly doses achieved mean reductions in HbA1c of 0.7 percentage points ($p < 0.05$) and 1.4 percentage points ($p < 0.001$) from baseline, respectively, compared to a reduction of 0.1 percentage points for placebo-treated patients, in an intent to treat (ITT) analysis. A per protocol analysis showed additional improvements in HbA1c in both treatment groups compared to placebo. At baseline, mean HbA1c levels were approximately 8.8% for all cohorts.
- A substantial number of IONIS-GCGR$_{Rx}$-treated patients achieved HbA1c reductions of equal to or greater than 1 percentage point, including 42% of 50 mg-treated patients and 64% of 75 mg-treated patients, compared to 8% of the placebo-treated patients.
- IONIS-GCGR$_{Rx}$-treated patients experienced a mean increase in total GLP-1 from baseline compared to a decline in placebo-treated patients.

IONIS-GCGR$_{Rx}$ is a Generation 2+ antisense drug designed to reduce the production of the glucagon receptor, or GCGR. Glucagon is a hormone that opposes the action of insulin and stimulates the liver to produce glucose, particularly in type 2 diabetes.

The primary goal of the Phase 2 study was to identify a dose that produced robust HbA1c reductions without triggering previously observed on-target liver enzyme elevations or other off-target side effects observed with small molecule inhibitors of GCGR, such as increases in LDL-cholesterol and blood pressure. This goal was achieved with the 50 mg dose cohort, in which there were no clinically meaningful (>3x upper limit of normal [ULN]) increases in liver enzymes observed. In the 75 mg cohort, three patients experienced alanine aminotransferase (ALT) elevations >3x ULN that resolved with dose reduction. In the study, IONIS-GCGR$_{Rx}$ was generally safe and well tolerated. In both cohorts, there were no clinically meaningful changes in lipids, blood pressure, bodyweight, gastrointestinal symptoms or cases of hypoglycemia. There were no flu-like symptoms, abnormalities in renal function, or clinically meaningful platelet events observed. The majority of adverse events (AEs) reported were mild. The most common AE reported was a low incidence of injection site reactions (4.4% of injections).

"Developing a safe and effective glucagon receptor-targeted drug that can be combined with available antidiabetic agents would represent a major advance in the treatment of type 2 diabetes. As type 2 diabetes progresses, the contribution of glucagon in worsening glucose control becomes even more significant," said Robert Henry, M.D., professor of medicine, division of endocrinology and metabolism, University of California, San Diego School of Medicine; chief, section of endocrinology and metabolism and director, center for metabolic research, VA; and past-president medicine and science, American Diabetes Association. "The HbA1c reduction observed from this trial in patients on

stable, maximal doses of metformin is quite remarkable, especially with none of the side effects previously seen with alternative approaches to targeting the glucagon receptor."

"More than half of patients with type 2 diabetes today are not meeting their HbA1c treatment goals, despite available treatments including insulin. We are developing IONIS-GCGR$_{Rx}$ to provide additional therapeutic benefit to these patients with severe and uncontrolled Type 2 diabetes. The substantial improvement in glucose control, despite stable, maximal doses of metformin, is evidence of the potential benefit IONIS-GCGR$_{Rx}$ may provide to patients with severe, uncontrolled type 2 diabetes," said Richard Geary, Ph.D., senior vice president of clinical development at Ionis. "Based on the profile we observed in this study, including substantial HbA1c lowering and favorable safety, we have identified an optimal dose to advance to a large pivotal program. We are now evaluating partnership opportunities for IONIS-GCGR$_{Rx}$ and are excited with the prospect of moving this potential novel treatment forward."

Pipeline Update Webcast
Ionis will host a webcast to discuss its pipeline progress on Thursday, January 5 at 9:30 a.m. Eastern Time. Interested parties may access the webcast at www.ionispharma.com or listen by phone by dialing 877-443-5662. A webcast replay will be available for a limited time at the same address.

ABOUT IONIS PHARMACEUTICALS, INC.
Ionis is the leading company in RNA-targeted drug discovery and development focused on developing drugs for patients who have the highest unmet medical needs, such as those patients with severe and rare diseases. Using its proprietary antisense technology, Ionis has created a large pipeline of first-in-class or best-in-class drugs, with over three dozen drugs in development. SPINRAZA™ (nusinersen) is a drug that has been approved in the U.S. for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. Biogen is responsible for commercialization of SPINRAZA. Drugs currently in Phase 3 development include volanesorsen, a drug Ionis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy; and IONIS-TTR$_{Rx}$, a drug Ionis is developing with GSK to treat patients with TTR amyloidosis. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

IONIS' FORWARD-LOOKING STATEMENT
This press release includes forward-looking statements regarding the development, activity, therapeutic and commercial potential and safety of IONIS-GCGR$_{Rx}$. Any statement describing Ionis' 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. 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 Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2015, 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, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

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