Ionis enters new chapter in 2025 as commercial-stage biotech with multiple independent product launches anticipated and continued late-stage pipeline momentum

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– Accelerating value creation with numerous commercial, regulatory and pipeline milestones –

– Ionis outlines clear path to sustained positive cash flow –

CARLSBAD, Calif., Jan. 13, 2025 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced highlights from the Company's 2024 achievements and previewed important milestones expected in 2025. Ionis will provide a business update at the 42nd Annual J.P. Morgan Healthcare Conference on Wednesday, January 15 at 10:30am PT; the presentation is available today on the Ionis website.

"With last month's U.S. approval and launch of TRYNGOLZA™ (olezarsen) as the first-ever therapy for familial chylomicronemia syndrome and the potential approval of donidalorsen in hereditary angioedema later this year, Ionis has entered a new chapter as a fully integrated commercial-stage biotechnology company that independently brings our innovative medicines to patients," said Brett P. Monia, Ph.D., chief executive officer, Ionis. "TRYNGOLZA is the first of four independent Ionis product launches anticipated over the next three years. We also expect four key launches from important partnered programs within this timeframe. Collectively, these medicines stand to help millions of patients with serious diseases and create substantial value for all our stakeholders. To that end, we expect increasing product and royalty revenue to enable Ionis to achieve our goal of being cash flow positive."

2025 Anticipated Highlights Include:

- **Launch TRYNGOLZA, Ionis' first independent product and the first-ever therapy for U.S. patients with familial chylomicronemia syndrome (FCS):**
  - U.S. Food and Drug Administration (FDA) Approval for FCS on December 19, 2024
  - Potential European Medicines Agency (EMA) approval for FCS
- **Phase 3 results and U.S. regulatory submission for olezarsen in severe hypertriglyceridemia, a large patient population with high unmet need**
  - Phase 3 topline data for CORE, CORE 2 and ESSENCE Phase 3 trials expected in second half of 2025
- **Potential approval of donidalorsen, a first-in-class RNA-targeted medicine for hereditary angioedema and Ionis' second anticipated independent launch:**
  - U.S. FDA action date of August 21, 2025
  - U.S. commercial field team scale-up and launch
- **Continue progress with WAINUA ™(eplontersen), Ionis' first U.S. co-commercialized medicine in collaboration with AstraZeneca:**
  - Continued positive performance in U.S. launch for polyneuropathy of hereditary transthyretin-mediated amyloidosis (ATTRv-PN)
  - OUS approvals for ATTRv-PN
  - Continuing the fully enrolled, landmark CARDIO-TTRansform trial in ATTR cardiomyopathy, with data expected in the second half of 2026

- **Advance the next wave of wholly owned medicines for serious neurological diseases, including seven clinical-stage therapies:**
  - Phase 3 trial start in first half of 2025 for ION582 for Angelman syndrome
  - Phase 3 data for zilganersen in Alexander disease, a rare leukodystrophy with no approved disease-modifying therapies
  - Phase 2 data for ION464 (SNCA) in multiple system atrophy

- **Continue momentum with key partnered programs, including:**
  - Phase 3 data for pelacarsen, a potentially groundbreaking medicine for Lp(a)-driven cardiovascular disease (Novartis)

- **Continue advancing next-generation technologies for RNA-targeted medicines**
  - Achieve clinical proof of concept for Mesyl Phosphoramidate (MsPA) backbone and siRNA platforms
  - Advance first Bicycle-siRNA into clinical development
  - Select first clinical candidate engineered to cross the blood brain barrier

INDICATION for TRYNGOLZA™ (olezarsen)
TRYNGOLZA™ (olezarsen) was approved by the U.S. Food and Drug Administration as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
TRYNGOLZA is contraindicated in patients with a history of serious hypersensitivity to TRYNGOLZA or any of the excipients in TRYNGOLZA. Hypersensitivity reactions requiring medical treatment have occurred.

WARNINGS AND PRECAUTIONS
Hypersensitivity Reactions
Hypersensitivity reactions (including symptoms of bronchospasm, diffuse erythema, facial swelling, urticaria, chills and myalgias) have been reported in patients treated with TRYNGOLZA. Advise patients on the signs and symptoms of hypersensitivity reactions and instruct patients to promptly seek medical attention and discontinue use of TRYNGOLZA if hypersensitivity reactions occur.

ADVERSE REACTIONS
The most common adverse reactions (incidence >5% of TRYNGOLZA-treated patients and >3% higher frequency than placebo) were injection site reactions, decreased platelet count and arthralgia.

Please see full Prescribing Information for TRYNGOLZA.

INDICATION for WAINUA™ (eplontersen)
WAINUA injection, for subcutaneous use, 45 mg is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

IMPORTANT SAFETY INFORMATION for WAINUA™ (eplontersen)

WARNINGS AND PRECAUTIONS
Reduced Serum Vitamin A Levels and Recommended Supplementation WAINUA leads to a decrease in serum vitamin A levels. Supplement with recommended daily allowance of vitamin A. Refer patient to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.

ADVERSE REACTIONS
Most common adverse reactions (≥9% in WAINUA-treated patients) were vitamin A decreased (15%) and vomiting (9%).

Please see U.S. Full Prescribing Information for WAINUA.

About Ionis Pharmaceuticals, Inc.
For three decades, Ionis has invented medicines that bring better futures to people with serious diseases. Ionis currently has six marketed medicines and a leading pipeline in neurology, cardiology, and other areas of high patient need. As the pioneer in RNA-targeted medicines, Ionis continues to drive innovation in RNA therapies in addition to advancing new approaches in gene editing. A deep understanding of disease biology and industry-leading technology propels our work, coupled with a passion and urgency to deliver life-changing advances for patients. To learn more about Ionis, visit Ionis.com and follow us on X (Twitter), LinkedIn and Instagram.

Ionis Forward-Looking Statements
This press release includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of TRYNGOLZA, Ionis' technologies and other products in development. 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, including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business

around such medicines. 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. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. 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 Dec. 31, 2023, and most recent Form 10-Q, which are on file with the SEC. Copies of these and other documents are available at www.Ionis.com.

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