Ionis highlights achievements, commercial strategy and technology advancements at Investor Day

December 9, 2020

- Prioritizing and preparing its growing Ionis-owned pipeline for commercialization
- Potential to launch 6+ new products in next five years
- Positioned for a strong 2021 and beyond

CARLSBAD, Calif., Dec. 8, 2020 /PRNewswire/ -- At its Investor Day yesterday, Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) highlighted the company's significant achievements in 2020 and outlined its strategy to realize the substantial opportunity of its pipeline.

Ionis has been preparing and prioritizing its growing wholly owned pipeline for commercialization in line with its commercial strategy. The company's commercial priorities are three-fold: (1) Initially focusing its commercial efforts on rare diseases within its prolific neurology and cardiology franchises (2) pioneer new markets where there are no available treatments (3) create new standards of care where there has been a lack of innovation to optimize patient care.

Delivering on these three priorities will have meaningful impact to patients, their families, and healthcare providers all while reducing the burden on healthcare systems and driving value for all Ionis' stakeholders including patients and shareholders.

Ionis also has plans to expand opportunistically to new products in additional treatment areas such as hematology, endocrinology and pulmonology.

Ionis projects having the opportunity to launch six or more new products through 2026, with each being ready for launch in a close window, ranging from 18 to 24 months between each new product launch. The expectation is that the implementation of this strategy will drive double-digit revenue growth and substantial earnings growth.

Brett P. Monia, Ph.D., chief executive officer at Ionis, said, "In 2020, we pursued an aggressive agenda focused on building our commercial plans and capabilities, progressing the Ionis-owned pipeline, advancing our technology and growing our leadership position in RNA-targeted therapeutics. We are pleased to say that we delivered against all these objectives. We invested in building our commercial plans and capabilities and began implementation. These actions were accelerated through the acquisition of our commercial affiliate Akcea. We have also progressed and substantially expanded the Ionis-owned pipeline. In addition, we have six Phase 3 trials underway, initiated 13 Phase 2 trials, achieved multiple, positive clinical proof-of-concept readouts, and advanced new delivery platforms."

Dr. Monia continued, "For years we have been recognized for our excellence in research, early drug development and scientific innovation. We will now add to this by building a strong and efficient commercial organization of equal excellence. All of which will provide substantial benefit to patients and shareholders for years to come."

Highlights of Investor Day

- **Ionis estimates the total market opportunity for the indications targeted by its pipeline is well in excess of $15 billion, with a significant portion from its wholly owned medicines.**
- **Ionis' cardiovascular franchise includes many potential first-in-class and/or best-in-class medicines targeting a full spectrum of cardiovascular disease risk factors**. **The company is positioned to potentially launch multiple Ionis-owned cardiovascular medicines through 2026, including:**
    - **AKCEA-APOCIII-L_{Rx}**: One product with the potential for addressing multiple indications targeting elevated triglycerides and the opportunity to set a new standard of care for triglyceride management
        - 91% of patients achieved normal serum triglycerides levels with favorable safety and tolerability in Phase 2
        - As announced on Dec. 1, 2020, a Phase 3 study in patients with familial chylomicronemia syndrome (FCS) is now underway
        - Evaluating additional indications with plans to initiate an additional Phase 3 study in 2021
    - **AKCEA-TTR-L_{Rx}**: Opportunity to significantly expand ATTR franchise
        - Robust target reductions of more than 90% and favorable safety and tolerability demonstrated in Phase 1
        - Flexibility of at-home monthly self-administration
        - Two Phase 3 studies underway – CARDIO-TTRansform for patients with hereditary or wild type TTR cardiomyopathy and NEURO-TTRansform for patients with hereditary TTR polyneuropathy.
    - **IONIS-AGT-L_{Rx}:** Large unmet need in patients with treatment-resistant hypertension (RHTN)
        - Two Phase 2 clinical studies: Patients with mild HTN and patients with uncontrolled HTN who are on two (65%) or three (35%) antihypertensive medications
        - Positive Phase 2 study in patients in uncontrolled HTN: patients achieved mean reductions of 12 mmHg and 6 mmHg in systolic and diastolic blood pressure from their own baseline, respectively, after eight weeks of once-weekly 80 mg IONIS-AGT-L_{Rx}
        - IONIS-AGT-L_{Rx} has demonstrated a favorable safety and tolerability profile in clinical trials to date
        - More detailed results to be presented at an upcoming medical conference
- **Ionis' neurology franchise has the potential to establish the standard of care for millions of patients and generate**

substantial value as it advances its first-in-class medicines to the market. The neurological disease market is a nascent market poised for substantial growth. Ionis believes it can be the catalyst for this growth as it is positioned to launch multiple Ionis-owned medicines through 2026, including:

- **ION363**: First medicine in development to specifically target FUS-ALS, a rare, rapidly progressing form of ALS
  - Pivotal study on track for initiation in 2021
  - Potential for a rapid path to the market
- **ION716**: Potential to be first approved treatment for prion diseases
  - Designed to reduce production of prion protein, root cause of prion disease
  - Pursuing pre-symptomatic (genetic carriers) and symptomatic (genetic and sporadic) indications
  - Pivotal study planned for 2021, design should provide a rapid path to market

Akcea Integration Update

The recently completed acquisition of Akcea has created a stronger, more efficient company, further bolstering Ionis' financial strength. The integration of Akcea is ahead of schedule, delivering cost synergies and efficiencies. It was also announced that Akcea is going to commercialize TEGSEDI and WAYLIVRA in Europe through a distribution agreement with Swedish Orphan Biovitrum AB ("Sobi"), an international biopharmaceutical company that focuses on rare diseases. Under the terms of this agreement, Akcea retains the marketing authorization ("MAH") for both medicines in Europe. Additionally, Akcea will continue to maintain limited European operations including regulatory, manufacturing, and the management of relationships with key opinion leaders. Akcea will continue to lead the TEGSEDI and WAYLIVRA global commercial strategy. The agreement provides Ionis the flexibility to reinvest resources to support its other commercial plans.

Oral Delivery Development Update

Ionis and AstraZeneca are committed to bringing the best possible PCSK9 antisense treatments to patients and have been collaborating on both the subcutaneous and oral formulations. The subcutaneous formulation of ION449 has a potential best-in-class profile and is advancing rapidly toward Phase 3 development.

Preclinical and early clinical data give Ionis and AstraZeneca confidence that they can achieve effective oral delivery of ION449 and other ASOs. Based on ongoing research and experience to date, both companies believe they can improve upon the current oral formulation. Therefore, Ionis and AstraZeneca have decided to terminate the Phase 1 PCSK9 oral study. Ionis and AstraZeneca will continue to broadly work together to further optimize the oral delivery of ASOs, including ION449.

Ionis is expanding its oral delivery to include medicines from its pipeline and has increased its internal investment in oral delivery research. The company plans on initiating one or more programs from its pipeline within the next year or two. Candidates for consideration include IONIS-TTR-L_{Rx}, IONIS-PKK-L_{Rx}, ION994 (AGT), and ION547. Success would further enhance the commercial value of Ionis-owned programs.

Webcast

Additional details are available in the replay of the webcast. It is available here for a limited time.

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 potentially treat a broad range of diseases, including neurological, cardio-renal, metabolic, infectious, and pulmonary diseases.

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

Forward-looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen), TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen) and Ionis' technologies and products in development, including the business of Akcea Therapeutics, Inc., Ionis' wholly owned subsidiary. 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 those related to the impact COVID-19 could have on our business, and 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. 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, 2019 and our most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of this and other documents are available at www.ionispharma.com. In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries. Ionis Pharmaceuticals™ is a trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics® is a registered trademark of Akcea Therapeutics, Inc. TEGSEDI® is a trademark of Akcea Therapeutics, Inc. WAYLIVRA® is a registered trademark of Akcea Therapeutics, Inc. SPINRAZA® is a registered trademark of Biogen.

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