

Ionis Pharmaceuticals Reports Financial Results and Highlights for Third Quarter 2016

November 9, 2016

Conference Call Webcast Wednesday, November 9, 9:30 a.m. ET at www.ionispharma.com

CARLSBAD, Calif., Nov. 9, 2016 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today reported income from operations of \$16.1 million and a loss from operations of \$87.5 million for the three and nine months ended September 30, 2016, respectively. The Company also reported pro forma operating income of \$33.7 million and a pro forma net operating loss (NOL) of \$30.5 million, both excluding non-cash stock compensation, for the same periods. Ionis ended the third quarter with cash, cash equivalents and short term investments of \$687.8 million. The Company is on track to meet its pro forma NOL and cash guidance for the year.



"This week, we and Biogen announced positive data from an interim analysis of CHERISH, our Phase 3 study in children with later-onset (consistent with Type 2) spinal muscular atrophy (SMA). We are very encouraged with the positive SPINRAZATM data from both of our controlled Phase 3 clinical trials supporting potential benefit not only in infants, but also in children with SMA. We are pleased that our partners at Biogen are already making SPINRAZA available to patients with SMA who have no therapeutic alternatives through a broad Expanded Access Program. In about four weeks after Biogen filed for marketing approval for SPINRAZA, the FDA and the EMA each have accepted their respective application. Importantly, the FDA has granted Priority Review and the EMA has granted Accelerated Assessment, both of which can reduce the standard review time. We look forward to seeing SPINRAZA quickly and successfully advance through the regulatory review process so that it will be even more broadly available to SMA patients through commercial channels. On the basis of these positive data, we will stop the CHERISH study and afford all patients in the study the opportunity to receive SPINRAZA in the ongoing open-label study, SHINE. These data follow the positive results from ENDEAR, our Phase 3 study in infants with the most severe form of the disease, infantile-onset (consistent with Type 1) SMA, which formed the basis for the regulatory filings in the U.S. and E.U., and the filings in progress for other jurisdictions. This was followed by encouraging data from the Phase 2 NURTURE study in pre-symptomatic infants with SMA, which supports the potential beneficial effect of earlier treatment with SPINRAZA in infants with SMA. These data serve to confirm the positive data we have observed in our Phase 2 open-label studies in infants with Type 1 SMA and children with Type 2 or Type 3 SMA, in which we have patients continuing to benefit from SPINRAZA for nearly five years. We believe the totality of these results provide compelling evidence of the broad transformational potential of SPINRAZA for patients with SMA. These results further illustrate the potential of our antisense technology to target severe diseases that other therapeutic modalities are unable to adequately address," said B. Lynne Parshall, chief operating officer of Ionis Pharmaceuticals.

"In addition, last week we announced positive results from our Phase 2 study with IONIS-FXIR_x in patients with end-stage renal disease on dialysis. Results from the study demonstrated robust, statistically significant reductions in Factor XI activity in treated patients. IONIS-FXIR_x also displayed a good safety and tolerability profile. In patients treated with 200 mg or 300 mg of IONIS-FXIR_x there were no clinically meaningful platelet declines and no increase in major or clinically relevant non-major bleeding. These results provide further support for the potential benefit IONIS-FXIR_x could have for patients who need to prevent clotting but who have increased risk of bleeding," continued Ms. Parshall.

Financial Results

"We ended the third quarter of this year with net income primarily because of the \$85 million in license fees we earned, including \$75 million from Biogen for licensing SPINRAZA. Through the first nine months of 2016, we have earned more than \$186 million in revenue from license fees and milestone and other payments from our partnered programs. We have the opportunity to add to our strong base of revenue from partnerships with commercial revenue from SPINRAZA," said Elizabeth L. Hougen, chief financial officer of Ionis Pharmaceuticals.

"Through the first nine months of 2016, we have continued to advance our Phase 3 programs and Akcea is preparing to commercialize volanesorsen while we have prudently managed our expenses. As a result, we finished the first nine months of 2016 with a GAAP loss from operations of \$87.5 million, which included nearly \$57 million in non-cash compensation expense related to equity awards, that when excluded, resulted in a pro forma net operating loss of \$30.5 million. We also ended the first nine months of this year with more than \$685 million in cash. We are on track to meet our guidance of a pro forma NOL in the low \$60 million range and a year-end cash balance in excess of \$600 million," concluded Ms. Hougen.

All pro forma amounts referred to in this press release exclude non-cash compensation expense related to equity awards. Please refer to the reconciliation of GAAP to pro forma measures, which is provided later in this release.

Revenue

Ionis' revenue for the three and nine months ended September 30, 2016 was \$110.9 million and \$186.3 million, compared to \$49.1 million and \$232.1 million for the same periods in 2015. Ionis' revenue in the first nine months of 2016 consisted of the following:

- \$96.9 million from Biogen for licensing and advancing the Phase 3 program for SPINRAZA and advancing IONIS-BIIB4_{Rx};
- \$15 million from Kastle Therapeutics for acquiring Kynamro;
- \$10 million from Janssen for licensing IONIS-JBI1-2.5_{Rx};
- \$1.5 million from GSK for advancing IONIS-HBV-L_{Rx}; and
- \$62.9 million primarily from the amortization of upfront fees and manufacturing services Ionis performed for its partners.

Ionis' revenue in the first nine months of 2015 included \$91.2 million in connection with the exclusive license agreement with Bayer, \$89.8 million in milestone payments from partnered programs and \$51.1 million, primarily from the amortization of upfront fees and manufacturing services Ionis performed for its partners.

Ionis' revenue fluctuates based on the nature and timing of payments under agreements with its partners and consists primarily of revenue from the amortization of upfront fees, milestone payments and license fees.

Operating Expenses

Ionis' operating expenses included costs to support the Company's five ongoing Phase 3 studies and three open-label extension studies related to its Phase 3 programs for SPINRAZA, IONIS-TTR_{Rx} and volanesorsen. In addition, Akcea continued to build a global organization and prepare for the commercial launch of volanesorsen. As such, Ionis' operating expenses on a GAAP basis for the three and nine months ended September 30, 2016 were \$94.8 million and \$273.7 million, respectively, and on a pro forma basis, were \$77.2 million and \$216.8 million, respectively. This is compared to GAAP operating expenses of \$97.3 million and \$245.0 million and pro forma operating expenses of \$82.3 million and \$203.0 million for the same periods in 2015. In addition, Ionis' operating expenses for the first nine months of 2016 on a GAAP basis increased due to an increase in non-cash compensation expense that resulted from an increase in the exercise price of the stock options the Company has granted over the past several years.

Net Income (Loss)

Ionis reported net income of \$7.4 million and a net loss of \$112.4 million for the three and nine months ended September 30, 2016, respectively, compared to a net loss of \$35.8 million and \$16.8 million for the same periods in 2015. Basic and diluted net income per share for the three months ended September 30, 2016 was \$0.06. Basic and diluted net loss per share for the nine months ended September 30, 2016 was \$0.93. This is compared to a basic and diluted net loss of \$0.30 and \$0.14 for the three and nine months ended September 30, 2015, respectively.

Balance Sheet

As of September 30, 2016, Ionis had cash, cash equivalents and short-term investments of \$687.8 million compared to \$779.2 million at December 31, 2015. Ionis' cash balance decreased in the first nine months of 2016 primarily due to spending to support the Company's ongoing Phase 3 programs for SPINRAZA, IONIS-TTR_{Rx} and volanesorsen. Ionis' working capital was \$623.4 million at September 30, 2016 compared to \$688.1 million at December 31, 2015. The decline in Ionis' working capital was a result of the cash used in operations and a decline in the Company's investment in Regulus Therapeutics resulting from a decline in Regulus' share price.

Conference Call

At 9:30 a.m. Eastern Time today, November 9, 2016, Ionis will conduct a live webcast conference call to discuss this earnings release and related activities. Interested parties may listen to the call by dialing 877-443-5662 or access the webcast at www.ionispharma.com. 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 a dozen drugs in mid- to late-stage development. 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; IONIS-TTR_{Rx}, a drug Ionis is developing with GSK to treat patients with all forms of TTR amyloidosis; and SPINRAZA (nusinersen), a drug Ionis is developing with Biogen to treat infants and children with spinal muscular atrophy. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Ionis Pharmaceuticals' financial position and outlook, Ionis' business, the business of Akcea Therapeutics, Inc., a subsidiary of Ionis Pharmaceuticals, and the therapeutic and commercial potential of Ionis' technologies and products in development, including SPINRAZA (nusinersen), IONIS-TTR_{Rx} and volanesorsen. 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 release, 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 trademark of Ionis Pharmaceuticals, Inc. SPINRAZA™ is a trademark of Biogen. KYNAMRO® is the registered trademark of Kastle Therapeutics.

Ionis Pharmaceuticals' Corporate and Drug Development Highlights (Q3 2016 and subsequent activities)

Recent SPINRAZA (formerly nusinersen) Accomplishments:

- The FDA accepted the NDA filing and granted Priority Review in the U.S. for SPINRAZA for the treatment of patients with SMA.
- The EMA validated the MAA and granted Accelerated Assessment in the E.U. for SPINRAZA for the treatment of patients with SMA.

- Biogen and Ionis reported positive data from an interim analysis of the Phase 3 CHERISH study in patients with later-onset (consistent with Type 2) SMA.
- Biogen and Ionis presented new positive clinical data with SPINRAZA at the World Muscle Society Congress supporting the companies' efforts to rapidly make SPINRAZA available to patients with SMA, including:
 - Safety results from the interim analysis of the Phase 3 ENDEAR study in patients with infantile-onset (consistent with Type 1) SMA;
 - Encouraging preliminary results from NURTURE, a Phase 2 open-label study in pre-symptomatic infants; and
 - A recent analysis of the ongoing Phase 2 open-label study in patients with later-onset SMA.
- Ionis reported positive data from an interim analysis of the ENDEAR Phase 3 study in patients with infantile-onset (consistent with Type 1) SMA. Biogen paid Ionis \$75 million to license SPINRAZA.

Recent Progress across Ionis' Pipeline:

- Ionis and Dr. Merrill Benson reported positive data from the IONIS-TTR_{Rx} program at the International Symposium on Amyloidosis (ISA) meeting. In line with previously reported data from his investigator-initiated study, Dr. Benson observed continued evidence of cardiac disease stabilization in eight TTR cardiomyopathy patients treated for 12 months with IONIS-TTR_{Rx}.
- Akcea and Ionis received Orphan Designation in the E.U. for volanesorsen for the treatment of patients with Familial Partial Lipodystrophy (FPL).
- Ionis reported positive, top-line Phase 2 data with IONIS-FXI_{Rx} demonstrating robust, statistically significant reductions in Factor XI activity in patients with ESRD receiving chronic hemodialysis. IONIS-FXI_{Rx} was safe and well tolerated in treated patients with no clinically meaningful platelet declines and no increase in major or clinically relevant non-major bleeding.
- Ionis reported positive interim data from a Phase 2 dose-optimization study of IONIS-GCGR_{Rx} in patients with type 2 diabetes demonstrating that doses of 75 mg and 50 mg could produce reductions in HbA1c of greater than two percent and one percent, respectively, with minimal to no effects on liver enzyme elevations.
- Ionis reported positive data from a Phase 2 study of IONIS-AR-2.5_{Rx} in patients with prostate cancer showing durable prostate-specific antigen (PSA) responses with prolonged stable disease in heavily pre-treated castrate-resistant prostate cancer patients.
- Akcea and Ionis published clinical results with Lp(a)-lowering drugs, IONIS-APO(a)_{Rx} and IONIS-APO(a)-L_{Rx}, in *The Lancet* demonstrating robust reductions in Lp(a) levels, regardless of a patient's starting Lp(a) level.
- Ionis reported positive results from studies in normal volunteers with IONIS-ANGPTL3-L_{Rx} and IONIS-GSK4-L_{Rx} that demonstrated these drugs had similar potency to IONIS-APO(a)-L_{Rx}, confirming the high potency of the LICA platform.
- Ionis added to its pipeline its first oral antisense drug acting locally in the GI tract for which Ionis earned a \$10 million license fee from Janssen.

Recent Corporate Highlights:

- Ionis' CEO, Dr. Stanley Crooke, received two awards, the E. B. Hershberg Award from the American Chemical Society and the Lifetime Achievement Award from the Oligonucleotide Therapeutics Society recognizing his achievements in the field of oligonucleotide therapeutics.
- Ionis published a paper in Nature Biotechnology on the novel mechanism of action for antisense drugs that significantly expands therapeutic opportunities for the technology.

IONIS PHARMACEUTICALS, INC.
SELECTED FINANCIAL INFORMATION
Condensed Consolidated Statements of Operations
(In Thousands, Except Per Share Data)

| | Three months ended, September 30, 2016 | | Nine months ended, September 30, 2015 | |
|---|--|----------|---------------------------------------|-----------|
| | (unaudited) | | (unaudited) | |
| Revenue: | | | | |
| Research and development revenue under collaborative agreements | \$108,913 | \$48,918 | \$166,583 | \$230,469 |
| Licensing and royalty revenue | 2,014 | 203 | 19,689 | 1,664 |
| Total revenue | 110,927 | 49,121 | 186,272 | 232,133 |
| Expenses: | | | | |

| | | | | |
|--|---------|------------|-------------|------------|
| Research, development and patent expenses | 84,631 | 88,508 | 243,169 | 220,962 |
| General and administrative | 10,188 | 8,751 | 30,574 | 23,992 |
| Total operating expenses | 94,819 | 97,259 | 273,743 | 244,954 |
| Income (loss) from operations | 16,108 | (48,138) | (87,471) | (12,821) |
| Other income (expense): | | | | |
| Investment income | 989 | 1,384 | 3,912 | 3,146 |
| Interest expense | (9,746) | (9,233) | (28,861) | (27,381) |
| Gain on investment in Regulus Therapeutics, Inc. | - | 20,211 | - | 20,211 |
| Income (loss) before income tax expense | 7,351 | (35,776) | (112,420) | (16,845) |
| Income tax expense | - | - | (1) | - |
| Net income (loss) | \$7,351 | \$(35,776) | \$(112,421) | \$(16,845) |
| Basic net income (loss) per share | \$0.06 | \$(0.30) | \$(0.93) | \$(0.14) |
| Diluted net income (loss) per share | \$0.06 | \$(0.30) | \$(0.93) | \$(0.14) |
| Shares used in computing basic net income (loss) per share | 120,989 | 119,979 | 120,795 | 119,560 |
| Shares used in computing diluted net income (loss) per share | 123,378 | 119,979 | 120,795 | 119,560 |

Ionis Pharmaceuticals, Inc.

Reconciliation of GAAP to Pro Forma Basis:

Condensed Consolidated Operating Expenses, Income (Loss) From Operations, and Net Income (Loss)
(In Thousands)

| | Three months ended, September 30, 2016 | | Nine months ended, September 30, 2015 | |
|--|--|-------------------|---|------------------|
| | (unaudited) | | (unaudited) | |
| As reported operating expenses according to GAAP | \$94,819 | \$97,259 | \$273,743 | \$244,954 |
| Excluding compensation expense related to equity awards | (17,586) | (14,997) | (56,950) | (41,907) |
| Pro forma operating expenses | <u>\$77,233</u> | <u>\$82,262</u> | <u>\$216,793</u> | <u>\$203,047</u> |
| As reported income (loss) from operations according to GAAP | \$16,108 | \$(48,138) | \$(87,471) | \$(12,821) |
| Excluding compensation expense related to equity awards | (17,586) | (14,997) | (56,950) | (41,907) |
| Pro forma income (loss) from operations | <u>\$33,694</u> | <u>\$(33,141)</u> | <u>\$(30,521)</u> | <u>\$29,086</u> |
| As reported net income (loss) according to GAAP | \$7,351 | \$(35,776) | \$(112,421) | \$(16,845) |
| Excluding compensation expense related to equity awards | (17,586) | (14,997) | (56,950) | (41,907) |
| Pro forma net income (loss) | <u>\$24,937</u> | <u>\$(20,779)</u> | <u>\$(55,471)</u> | <u>\$25,062</u> |

Reconciliation of GAAP to Pro Forma Basis

As illustrated in the Selected Financial Information in this press release, pro forma operating expenses, pro forma income (loss) from operations, and pro forma net income (loss) were adjusted from GAAP to exclude compensation expense related to equity awards, which are non-cash. Ionis has regularly reported non-GAAP measures for operating results as pro forma results. These measures are provided as supplementary information and are not a substitute for financial measures calculated in accordance with GAAP. Ionis reports these pro forma results to better enable financial statement users to assess and compare its historical performance and project its future operating results and cash flows. Further, the presentation of Ionis' pro forma results is consistent with how Ionis' management internally evaluates the performance of its operations.

Ionis Pharmaceuticals, Inc.

Condensed Consolidated Balance Sheets
(In Thousands)

| | September 30, 2016 | December 31, 2015 |
|---|--------------------|-------------------|
| | (unaudited) | |
| Assets: | | |
| Cash, cash equivalents and short-term investments | \$687,848 | \$779,183 |
| Investment in Regulus Therapeutics Inc. | 9,382 | 24,792 |
| Other current assets | 33,099 | 33,028 |
| Property, plant and equipment, net | 90,970 | 90,233 |
| Other assets | 22,287 | 20,664 |
| Total assets | <u>\$843,586</u> | <u>\$947,900</u> |
| Liabilities and stockholders' equity: | | |
| Other current liabilities | \$50,353 | \$81,554 |
| Current portion of deferred contract revenue | 56,539 | 67,322 |
| 1% convertible senior notes | 356,440 | 339,847 |
| 2 3/4% convertible senior notes | 51,570 | 49,523 |
| Long-term obligations, less current portion | 87,214 | 74,558 |
| Long-term deferred contract revenue | 101,831 | 134,306 |
| Stockholders' equity | <u>139,639</u> | <u>200,790</u> |
| Total liabilities and stockholders' equity | <u>\$843,586</u> | <u>\$947,900</u> |

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