Unprecedented Productivity in Neurological Diseases

April 21st, 2016
Participants

Dr. Stan Crooke
CEO and Chairman
Ionis Pharmaceuticals

Dr. Richard Finkel
Chief, Division of Neurology
Department of Pediatrics,
Nemours Children’s Hospital
Orlando, FL

Sarah Boyce
CBO
Ionis Pharmaceuticals

Dr. Frank Bennett
SVP Research
Ionis Pharmaceuticals

Dr. Eugene Schneider
VP Clinical Development
Ionis Pharmaceuticals

Dr. Wade Walke
VP Corporate Communications
Ionis Pharmaceuticals

Dr. Richard Finkel
Chief, Division of Neurology
Department of Pediatrics,
Nemours Children’s Hospital
Orlando, FL
Forward Looking Language Statement

This presentation includes forward-looking statements regarding Ionis’ business, the business of Ionis’ Pharmaceuticals, Ionis’ collaborations with Biogen, GSK and Roche, the discovery, development, activity, therapeutic and commercial potential and safety of nusinersen for the treatment of spinal muscular atrophy and the discovery, development, activity, therapeutic potential, safety and commercialization of drugs in Ionis’ neurological disease franchise, including IONIS-TTR\textsubscript{Rx}, IONIS-HTT\textsubscript{Rx}, IONIS-SOD1\textsubscript{Rx} and IONIS-DMPK-2.5\textsubscript{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, which is on file with the SEC. Copies of this and other documents are available from the Company.

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 trademark of Ionis Pharmaceuticals, Inc.
Agenda

- **Welcome and Introductions**
  - Dr. Stanley Crooke, Chairman of the Board & Chief Executive Officer at Ionis Pharmaceuticals

- **Nusinersen Phase 2 Open Label Study in Infants with Type 1 SMA Update**
  - Dr. Richard Finkel, Chief, Division of Neurology, Department of Pediatrics, Nemours Children’s Hospital in Orlando, Florida

- **Nusinersen Program Update**
  - Dr. Eugene Schneider, VP Clinical Development at Ionis Pharmaceuticals

- **Ionis’ Large and Growing Neurological Disease Pipeline**
  - Dr. Eugene Schneider, VP Clinical Development at Ionis Pharmaceuticals

- **Addressing a Broad Spectrum of Neurological Diseases with Antisense**
  - Dr. Frank Bennett, SVP Research at Ionis Pharmaceuticals

- **Closing Remarks and Q&A**
  - Dr. Stanley Crooke, Chairman of the Board & Chief Executive Officer at Ionis Pharmaceuticals
Significant Growth in Understanding CNS Distribution and Mechanisms of Action of Antisense Drugs

- Spinal Cord Focused
- RNase H1-Reduction
- Nuclear retained and toxic RNA's
- Alternative Splicing
- Expand to Muscle and Cortical Brain Structures
- Broad Distribution Throughout the CNS

Timeline:
- 2010
- 2012
- 2016 - Today
Significant Growth in Understanding CNS Distribution and Mechanisms of Action of Antisense Drugs

RNase H1- Reduction

Alternative Splicing

Nuclear retained and toxic RNA’s

Expanding to Muscle and Cortical Brain Structures

Spinal Cord Focused

2010

2012

2016 - Today

CNS Tissues and Mechanisms

Broad Distribution Throughout the CNS
Significant Growth in Understanding CNS Distribution and Mechanisms of Action of Antisense Drugs

- Spinal Cord Focused
- Expand to Muscle and Cortical Brain Structures
- Broad Distribution Throughout the CNS

- RNase H1-Reduction
- Alternative Splicing
- Nuclear Retained and Toxic RNA’s

2010     2012     2016 - Today
Exponential Expansion of Neurological Disease Pipeline Enabled by the Efficiency of Antisense Technology

First Antisense Neurological Disease Program

Nusinersen Enters Clinic
- 1 other drug in the clinic
- 3 in preclinical and research

>25 Programs
- 2 drugs in Phase 3
- 3 drugs in Phase 2
- >20 others in preclinical and research

Neurological Disease Programs

2010  2012  2016 - Today
Exponential Expansion of Neurological Disease Pipeline Enabled by the Efficiency of Antisense Technology

Nusinersen Enters Clinic
- 1 other drug in the clinic
- 3 in preclinical and research

First Antisense Neurological Disease Program
- >25 Programs
  - 2 drugs in Phase 3
  - 3 drugs in Phase 2
  - >20 others in preclinical and research

2010     2012     2016 - Today
Exponential Expansion of Neurological Disease Pipeline Enabled by the Efficiency of Antisense Technology

>25 Programs
- 2 drugs in Phase 3
- 3 drugs in Phase 2
- >20 others in preclinical and research

Nusinersen Enters Clinic
- 1 other drug in the clinic
- 3 in preclinical and research

First Antisense Neurological Disease Program
- 1

2010  2012  2016 - Today
Multiple Partnerships Demonstrate Value and Enhance Growth of Neurological Disease Pipeline
Advances in Knowledge Support Expanding Antisense Drugs to Large Market Opportunities

Potential Patient Populations

- Huntington’s Disease ~51k
- Alzheimer’s Disease ~15.5M
- Spinal Muscular Atrophy ~35k
- Parkinson’s Disease ~1.4M
- Spinocerebellar Ataxia’s ~76k
- Amyotrophic Lateral Sclerosis ~55k
- TTR FAP ~10k
- Myotonic Dystrophy Type 1 ~120k
- Amyotrophic Lateral Sclerosis ~55k
- Spinocerebellar Ataxia’s ~76k
- Parkinson’s Disease ~1.4M
- TTR FAP ~10k
- Spinal Muscular Atrophy ~35k
- Alzheimer’s Disease ~15.5M
- Huntington’s Disease ~51k
- Myotonic Dystrophy Type 1 ~120k
Ionis’ Neurological Disease Pipeline: Large Near-Term Value, Even Greater Potential Long-Term Value

- Two Phase 3 drugs close to commercialization for patients with neurological diseases
- Antisense is uniquely suited to address previously untreatable neurological diseases
- Expanding opportunities to new targets, new diseases and new regions in the CNS
- Rapid growth in Ionis’ neurological disease pipeline enabled by the efficiency of antisense
Data suggests that nusinersen treatment could provide benefit to infants with Type 1 SMA

- No new events\(^1\) since Dec 2014
- Muscle function scores continue to increase
- Treated infants continue to achieve new developmental milestones
- Safety and tolerability profile support continued development

Ongoing, productive conversations with regulatory agencies focused on the fastest path to approval

- Ionis and Biogen are actively preparing for potential filing and commercial launch

\(^1\)An event is defined as death or permanent ventilation (>16 hours/day ventilation continuously for ≥2 weeks, in the absence of an acute reversible illness)
# Agenda

- **Welcome and Introductions**
  - Dr. Stanley Crooke, Chairman of the Board & Chief Executive Officer at Ionis Pharmaceuticals

- **Nusinersen Phase 2 Open Label Study in Infants with Type 1 SMA Update**
  - Dr. Richard Finkel, Chief, Division of Neurology, Department of Pediatrics, Nemours Children’s Hospital in Orlando, Florida

- **Nusinersen Program Update**
  - Dr. Eugene Schneider, VP Clinical Development at Ionis Pharmaceuticals

- **Ionis’ Large and Growing Neurological Disease Pipeline**
  - Dr. Eugene Schneider, VP Clinical Development at Ionis Pharmaceuticals

- **Addressing a Broad Spectrum of Neurological Diseases with Antisense**
  - Dr. Frank Bennett, SVP Research at Ionis Pharmaceuticals

- **Closing Remarks and Q&A**
  - Dr. Stanley Crooke, Chairman of the Board & Chief Executive Officer at Ionis Pharmaceuticals
Spinal Muscular Atrophy (SMA)
Progressive Muscle Atrophy Caused by Genetic Defects in the SMN1 Gene

Rare, severe genetic neuromuscular disease characterized by progressive muscle atrophy and loss of motor function

- Caused by genetic defects in the SMN1 gene that result in a lack of functional SMN protein
- Number one genetic cause of death in infants
- ~30-35k patients worldwide for all forms of SMA
- No currently approved therapies
SMA: Broad Spectrum of Disease Severity Correlates with Copy Number of SMN2 Gene

**Type 1 Infant Onset**
- Most severe form of SMA
- Age of symptom onset <6 months
- Very short life expectancy
- Recent natural history studies show the median event-free survival is 6.1*-10.5 months**
- Never able to sit
- Most have 2 copies of SMN2 gene

**Type 2 Childhood Onset**
- Age of symptom onset >6 months
- Shortened life expectancy
- Able to sit or stand, but not walk
- Muscle weakness/skeletal deformities
- Most have 3 copies of SMN2 gene

**Type 3 Childhood Onset**
- Age of symptom onset >6 months
- Close to normal life expectancy
- Ability to walk declines over time to a non-ambulatory state
- Muscle weakness/skeletal deformities
- Most have 3-4 copies of SMN2 gene

The Majority of Patients with SMA are Born with the Most Severe Form of the Disease

**Incidence of SMA Types**
- Type 2: 29%
- Type 3: 13%
- Type 4: <1%
- Type 1: 58%

**Prevalence of SMA Types**
- Type 3: 36%
- Type 2: 52%
- Type 1: 12%
- Type 4: <1%

SMA: Broad Spectrum of Disease Severity Correlates with Copy Number of SMN2 Gene

**Type 1 Infant Onset**
- Most severe form of SMA
- Age of symptom onset <6 months
- Very short life expectancy
- Recent natural history studies show the median event-free survival is 6.1*-10.5 months**
- Never able to sit
- Most have 2 copies of SMN2 gene

**Type 2 Childhood Onset**
- Age of symptom onset >6 months
- Shortened life expectancy
- Able to sit or stand, but not walk
- Muscle weakness/skeletal deformities
- Most have 3 copies of SMN2 gene

**Type 3 Childhood Onset**
- Age of symptom onset >6 months
- Close to normal life expectancy
- Ability to walk declines over time to a non-ambulatory state
- Muscle weakness/skeletal deformities
- Most have 3-4 copies of SMN2 gene

PNCR Natural History Data Illustrate that Type 1 SMA is an Aggressive, Fatal Disease

Median time to death or permanent ventilation is 10.5 months

Average decline of 1.27 points/year in CHOP-INTEND scores

80% of infants with two copies of SMN2 gene have an event by 18 months

CHOP INTEND (SMA infant motor function test) scores gradually decline over time

Natural History Shows Objective Measures of Electrophysiology (CMAP) Decline Sharply and Do Not Improve Over Time

CMAP amplitude decline precedes Symptoms in Type I SMA patients

CMAP amplitude values in Type I SMA are very low (<1 mV)

From KJ Swoboda et al, Ann Neurol 2005
Interim Results of a Phase 2 Clinical Study of Nusinersen in Patients with Infantile-Onset Spinal Muscular Atrophy

Finkel, R.1; Chiriboga, C.A.2; Vajsar, J.3; Day, J.4; Montes, J.2; De Vivo, D. C.2; Yamashita, M.5; Hung, G.5; Schneider, E.5; Rigo, F.5; Norris, D. A.5; Xia, S.5; Bennett, C. F.5; Bishop, K.M.5

1Nemours Children’s Hospital, Orlando, FL, USA
2Columbia University Medical Center, New York, NY, USA
3University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada
4Stanford University School of Medicine, Stanford, CA, USA
5Ionis Pharmaceuticals, Inc., Carlsbad, CA, USA

Presented at 68th Annual Meeting of the American Academy of Neurology
Session 205 Neuromuscular and Clinical Neurophysiology Poster Discussion Session
Poster #004 and Datablitz Presentation
Phase 2 Open-Label Study of Nusinersen in Patients with Infantile-onset (Type 1) SMA

- Multiple doses given intrathecally in infants with SMA ≤7 months of age
  - Study is being conducted at 4 sites in North America
- Clinical efficacy endpoints
  - Survival and time to permanent ventilation\(^1\)
  - Motor function: Motor milestones and CHOP INTEND
  - Electrophysiology: Ulnar and Peroneal nerve Compound Muscle Action Potential (CMAP)

<table>
<thead>
<tr>
<th>Dose Cohort</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mg equivalent</td>
<td>4</td>
</tr>
<tr>
<td>12 mg equivalent</td>
<td>16</td>
</tr>
</tbody>
</table>

**Subject demographics**

<table>
<thead>
<tr>
<th></th>
<th>6 mg Cohort (n=4)</th>
<th>12 mg Cohort (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: Female</td>
<td>3:1</td>
<td>9:7</td>
</tr>
<tr>
<td>Mean age at symptom onset (range)</td>
<td>7 weeks (4 to 10)</td>
<td>9 weeks (3 to 22)</td>
</tr>
<tr>
<td>Mean age at enrollment (range)</td>
<td>21 weeks (10 to 30)</td>
<td>20 weeks (5 to 30)</td>
</tr>
<tr>
<td>SMN2 gene #</td>
<td>2 SMN2 copies = 4</td>
<td>2 SMN2 copies = 13; 3 SMN2 copies = 2; unknown = 1</td>
</tr>
</tbody>
</table>

\(^1\)≥16 hours/day of ventilation continuously for ≥2 weeks, in the absence of an acute reversible illness
Increased Event-Free Survival in Nusinersen-treated Infants with SMA Compared to Natural History (PNCR)
As of January 26th, 2016

- No events since Dec 2014
- All infants continuing in study are older than 2 years of age
- Median event-free age has not been reached in the Phase 2 nusinersen study
Increased Muscle Function Scores in Nusinersen-treated Infants with SMA Compared to Natural History (PNCR)
As of January 26th, 2016

Individual CHOP INTEND Change Scores: 12 mg Cohort (N=15)

- Infants continue to demonstrate increases in motor function scores with a mean increase of 22.2 points at 26 months

*Mean value calculated based on patient values at each time point.
Increases in Ulnar CMAP Amplitude Diverge Significantly from Natural History
As of January 26th, 2016

• Increases in ulnar CMAP amplitudes are consistent with increases in muscle function scores in nusinersen-treated Type 1 SMA infants

* KJ Swoboda et al, Ann Neurol 2005
# Achievement of New Motor Milestones Observed in Nusinersen-treated Infants

## Baseline Milestones

<table>
<thead>
<tr>
<th>Voluntary Grasp</th>
<th>No Grasp</th>
<th>Uses Whole Hand</th>
<th>Index finger and thumb but immature grasp</th>
<th>Pincer grasp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to Kick (in supine)</td>
<td>No Kicking</td>
<td>Kick horizontal, legs do not lift</td>
<td>Upward (vertical)</td>
<td>Touches leg</td>
</tr>
<tr>
<td>Head Control</td>
<td>Unable to maintain upright</td>
<td>Wobbles</td>
<td>All the time upright</td>
<td></td>
</tr>
<tr>
<td>Rolling</td>
<td>No rolling</td>
<td>Rolling to side</td>
<td>Prone to supine</td>
<td>Supine to prone</td>
</tr>
<tr>
<td>Sitting</td>
<td>Cannot sit</td>
<td>Sit with support at hips</td>
<td>Props</td>
<td>Stable sit</td>
</tr>
<tr>
<td>Crawling</td>
<td>Does not lift head</td>
<td>On elbow</td>
<td>On outstretched hand</td>
<td>Crawling flat on abdomen</td>
</tr>
<tr>
<td>Standing</td>
<td>Does not support weight</td>
<td>Supports weight</td>
<td>Stands with support</td>
<td>Stands unaided</td>
</tr>
<tr>
<td>Walking</td>
<td>No walking</td>
<td>Bouncing</td>
<td>Cruising (holding on)</td>
<td>Walking independently</td>
</tr>
</tbody>
</table>
Achievement of New Motor Milestones Observed in Nusinersen-treated Infants

As of January 26th, 2016  **Blue—6 mg, Red—12 mg**

<table>
<thead>
<tr>
<th>Voluntary Grasp</th>
<th>No Grasp</th>
<th>Uses Whole Hand</th>
<th>Index finger and thumb but immature grasp</th>
<th>Pincer grasp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to Kick (in supine)</td>
<td>No Kicking</td>
<td>Kick horizontal, legs do not lift</td>
<td>Upward (vertical)</td>
<td>Touches leg</td>
</tr>
<tr>
<td>Head Control</td>
<td>Unable to maintain upright</td>
<td>Wobbles</td>
<td>All the time upright</td>
<td></td>
</tr>
<tr>
<td>Rolling</td>
<td>No rolling</td>
<td>Rolling to side</td>
<td>Prone to supine</td>
<td>Supine to prone</td>
</tr>
<tr>
<td>Sitting</td>
<td>Cannot sit</td>
<td>Sit with support at hips</td>
<td>Props</td>
<td>Stable sit</td>
</tr>
<tr>
<td>Crawling</td>
<td>Does not lift head</td>
<td>On elbow</td>
<td>On outstretched hand</td>
<td>Crawling flat on abdomen</td>
</tr>
<tr>
<td>Standing</td>
<td>Does not support weight</td>
<td>Supports weight</td>
<td>Stands with support</td>
<td>Stands unaided</td>
</tr>
<tr>
<td>Walking</td>
<td>No walking</td>
<td>Bouncing</td>
<td>Cruising (holding on)</td>
<td>Walking independently</td>
</tr>
</tbody>
</table>
Achievement of New Motor Milestones Observed in Nusinersen-treated Infants: Sitting

Blue—6 mg, Red—12 mg

<table>
<thead>
<tr>
<th>Baseline Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

As of January 26th, 2016

<table>
<thead>
<tr>
<th>As of January 26th, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Achieving new sitting motor milestones
Achievement of New Motor Milestones Observed in Nusinersen-treated Infants: Standing

Blue—6 mg, Red—12 mg

### Baseline Milestones

<table>
<thead>
<tr>
<th>Standing</th>
<th>Does not support weight</th>
<th>Supports weight</th>
<th>Stands with support</th>
<th>Stands unaided</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**As of January 26th, 2016**

<table>
<thead>
<tr>
<th>Standing</th>
<th>Does not support weight</th>
<th>Supports weight</th>
<th>Stands with support</th>
<th>Stands unaided</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Achievement of New Motor Milestones Observed in Nusinersen-treated Infants: Walking

Blue—6 mg, Red—12 mg

Baseline Milestones

<table>
<thead>
<tr>
<th>Walking</th>
<th>No walking</th>
<th>Bouncing</th>
<th>Cruising (holding on)</th>
<th>Walking independently</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blue</strong> - 6 mg</td>
<td>![No walking]</td>
<td>![Bouncing]</td>
<td>![Cruising]</td>
<td>![Walking independently]</td>
</tr>
<tr>
<td><strong>Red</strong> - 12 mg</td>
<td>![No walking]</td>
<td>![Bouncing]</td>
<td>![Cruising]</td>
<td>![Walking independently]</td>
</tr>
</tbody>
</table>

As of January 26th, 2016

Achieving new walking motor milestones
Substantial Increases in Full Length SMN2 mRNA in Nusinersen-treated SMA Infants Compared to Untreated SMA Infants

Confirmation of Mechanism of Action

Semi-Quantitative RT-PCR Analysis of Thoracic Spinal Cord Tissue

% Full Length by Group (Mean ± SD)
- Non SMA = 21.7 ± 3.8
- Untreated SMA = 20.8 ± 5.6
- Nusinersen Tx = 57 ± 10.4
No Nusinersen-related Safety or Tolerability Concerns Identified

• In the latest analysis, some infants have been dosed for nearly two years, some for nearly three years
  - No drug-related SAEs
  - No discontinuations due to drug-related AEs
  - No drug-related adverse changes on neurological exams
  - No clinically significant changes in CSF or other safety labs

• Intrathecal delivery in infants (now children) with SMA has been well tolerated to date
Phase 2 Data Suggests that Nusinersen Treatment Could Provide Benefit to Infants with Type 1 SMA

- No new events since December 2014
- Median event-free age in treated infants continues to increase
  - 73% of the infants (11 of 15) in the 12 mg cohort remain event-free and all are older than 2 years
  - 50% of the infants (2 of 4) in the 6 mg cohort have now passed their 3rd birthday
- Most treated infants continue to see increases in motor function scores and objective measures of neuromuscular integrity
  - CHOP INTEND
  - Motor milestones
  - CMAP
- No nusinersen-related safety concerns identified to date
Agenda

• Welcome and Introductions
  − Dr. Stanley Crooke, Chairman of the Board & Chief Executive Officer at Ionis Pharmaceuticals

• Nusinersen Phase 2 Open Label Study in Infants with Type 1 SMA Update
  − Dr. Richard Finkel, Chief, Division of Neurology, Department of Pediatrics, Nemours Children’s Hospital in Orlando, Florida

• Nusinersen Program Update
  − Dr. Eugene Schneider, VP Clinical Development at Ionis Pharmaceuticals

• Ionis’ Large and Growing Neurological Disease Pipeline
  − Dr. Eugene Schneider, VP Clinical Development at Ionis Pharmaceuticals

• Addressing a Broad Spectrum of Neurological Diseases with Antisense
  − Dr. Frank Bennett, SVP Research at Ionis Pharmaceuticals

• Closing Remarks and Q&A
  − Dr. Stanley Crooke, Chairman of the Board & Chief Executive Officer at Ionis Pharmaceuticals
Robust Development Plan to Support Commercialization of Nusinersen

<table>
<thead>
<tr>
<th>Infant Onset</th>
<th>Childhood Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-symptomatic Newborns</td>
<td>Biogen Study</td>
</tr>
<tr>
<td>Phase 2 Open Label (Infants)</td>
<td>Biogen Study</td>
</tr>
<tr>
<td>Phase 3</td>
<td>OLE Study for Phase 3 Studies</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Phase 2 Open Label (Children)</td>
</tr>
</tbody>
</table>

Global Commercial Opportunity
Increased Muscle Function Scores Observed in Nusinersen-treated Children with SMA
Phase 2 Data as of May 2015

Increase in multiple measures of muscle function

**Increase in Mean HFMSE Score**

**Increase in Mean 6MWT Distance**
Robust Development Plan to Support Commercialization of Nusinersen

Infant Onset

Pre-symptomatic Newborns
- Biogen Study
- Phase 2 Open Label (Infants)
- Phase 3

Childhood Onset
- Biogen Study
- OLE Study for Phase 3 Studies
- Phase 3
- Phase 2 Open Label (Children)

Global Commercial Opportunity
<table>
<thead>
<tr>
<th>Enrollment Update</th>
<th>Enrollment complete</th>
<th>Enrollment nearing completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Next Steps</td>
<td>• Ionis and Biogen are committed to achieving the most rapid approval possible</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ongoing, productive conversations with regulatory agencies focused on the fastest path to approval</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Actively preparing for potential filing and commercial launch</td>
<td></td>
</tr>
</tbody>
</table>
Ionis’ Neurological Disease Pipeline
## Substantial Progress in Ionis’ Neurological Disease Pipeline

Addressing a Broad Spectrum of Severe Neurological Diseases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Partner</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nusinersen</td>
<td>Infantile Onset SMA</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nusinersen</td>
<td>Childhood Onset SMA</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-TTR\text{Rx}</td>
<td>TTR Amyloidosis</td>
<td>GSK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-DMPK-2.5\text{Rx}</td>
<td>Myotonic Dystrophy Type 1</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-HTT\text{Rx}</td>
<td>Huntington’s Disease</td>
<td>Roche</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-SOD\text{1Rx}</td>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-BIIB4\text{Rx}</td>
<td>Neurological Disease</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-BIIB5\text{Rx}</td>
<td>Neurological Disease</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-BIIB6\text{Rx}</td>
<td>Neurological Disease</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Through the efficiency of antisense we have moved 8 drugs into development in 6 years
IONS-TTR$_{Rx}$: Potentially First-in-class and Best-in-class Drug to Treat All Forms of TTR Amyloidosis

TTR Amyloidosis (ATTR)
- One disease caused by the formation of TTR amyloid deposits in various tissues
- FAP: TTR amyloid primarily infiltrates peripheral nerves
- Fatal, genetic disease that results in multi-organ failure

IONS-TTR$_{Rx}$
- One drug for all forms of ATTR
- Demonstrated robust, sustained knockdown of TTR protein in multiple patient populations
- GSK is the right partner to optimize the launch and commercialization of IONS-TTR$_{Rx}$

Phase 3 Studies:
- NEURO-TTR – Enrollment Complete
- CARDIO-TTR – GSK Plans to Initiate
Ionis-Dmpk-2.5Rx: Potentially First-in-class and Best-in-class Drug to Treat Myotonic Dystrophy Type 1

Myotonic Dystrophy Type 1 (DM1)
- Severe, autosomal dominant genetic disease caused by a toxic RNA
- Broad spectrum of symptoms including muscle dysfunction and GI tract issues
- No treatments stop or slow the progression of DM1

Ionis-Dmpk-2.5Rx
- Antisense is uniquely suited to address the root cause of the disease
- Generation 2.5 chemistry enables knockdown of toxic DMPK RNAs in multiple tissues, including muscle

Phase 2 Study Ongoing
IONS-DMPK-2.5_Rx significantly reduced DMPK mRNA in multiple tissues.
IONIS-DMPK-2.5\textsubscript{Rx} Phase 2 Study in Patients with DM1 Progressing on Track

- First potentially disease-modifying therapy to be evaluated in patients with DM1
- First Gen 2.5 drug designed to address a muscle target
- Additional cohorts added to study to explore larger patient numbers and longer treatment duration
  - Evaluate key biochemical markers and exploratory measures of muscle function
- Interim data planned by the end of 2016
IONIS-HTT<sub>Rx</sub>: Potentially First-in-class and Best-in-class Drug to Treat Huntington's Disease

Huntington's Disease (HD)
- Fatal, autosomal dominant disorder that results in the progressive loss of mental faculties and physical control
- Death occurs 15-20 years after onset
- No treatments stop or slow the progression of HD

IONIS-HTT<sub>Rx</sub>
- Designed to specifically reduce HTT protein, the primary disease mechanism
- First potentially disease-modifying therapy to enter the clinic for the treatment of HD

Phase 2 Study Ongoing
Antisense Targeting of HTT Produced a Robust & Durable Reduction in Huntingtin mRNA and Protein

From: Kordasiewicz et al. (2012) Neuron. 74: 1031-1044
IONIS-HTT$_{Rx}$ Phase 2 Study in Patients with HD Progressing on Track

- First potentially disease-modifying therapy to be evaluated in patients with HD

- **Study objectives:**
  - Evaluate safety, tolerability and pharmacokinetics in the CSF
  - Evaluate several potential markers of target engagement and exploratory measures relevant to Huntington’s disease
IONIS-SOD1\textsubscript{Rx}: Potential First-in-class and Best-in-class Drug to Treat SOD1 Familial Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS)
- Severe, rare disease characterized by progressive muscle weakness and respiratory failure
- Fatal within 2-5 years
- SOD1-ALS is a familial form of the ALS
- No drugs that significantly slow disease progression

IONIS-SOD1\textsubscript{Rx}
- Designed to specifically reduce SOD1 protein, a well-characterized cause of ALS
- Marked increase in survival of multiple disease models of ALS

Phase 2 Study Ongoing
SOD1 Targeted Antisense Significantly Increases Survival in a Mouse Model of ALS

Median Survival Increase of 72.5 days with Antisense Treatment Compared to Control
Substantial Progress in Ionis’ Neurological Disease Pipeline
Three Preclinical Drugs to Enter the Clinic in the Next 12–18 Months

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Partner</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nusinersen</td>
<td>Infantile Onset SMA</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nusinersen</td>
<td>Childhood Onset SMA</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-TTR_{Rx}</td>
<td>Familial Amyloid Polyneuropathy</td>
<td>GSK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-DMPK-2.5_{Rx}</td>
<td>Myotonic Dystrophy Type 1</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-HTT_{Rx}</td>
<td>Huntington’s Disease</td>
<td>Roche</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-SOD1_{Rx}</td>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-BIIB4_{Rx}</td>
<td>Neurological Disease</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-BIIB5_{Rx}</td>
<td>Neurological Disease</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-BIIB6_{Rx}</td>
<td>Neurological Disease</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Agenda

• Welcome and Introductions
  – Dr. Stanley Crooke, Chairman of the Board & Chief Executive Officer at Ionis Pharmaceuticals

• Nusinersen Phase 2 Open Label Study in Infants with Type 1 SMA Update
  – Dr. Richard Finkel, Chief, Division of Neurology, Department of Pediatrics, Nemours Children’s Hospital in Orlando, Florida

• Nusinersen Program Update
  – Dr. Eugene Schneider, VP Clinical Development at Ionis Pharmaceuticals

• Ionis’ Large and Growing Neurological Disease Pipeline
  – Dr. Eugene Schneider, VP Clinical Development at Ionis Pharmaceuticals

• Addressing a Broad Spectrum of Neurological Diseases with Antisense
  – Dr. Frank Bennett, SVP Research at Ionis Pharmaceuticals

• Closing Remarks and Q&A
  – Dr. Stanley Crooke, Chairman of the Board & Chief Executive Officer at Ionis Pharmaceuticals
Ionis’ Neurological Disease Pipeline: Large Near-Term Value, Even Greater Potential Long-Term Value

Two Phase 3 drugs close to commercialization for patients with neurological diseases

Antisense is uniquely suited to address previously untreatable neurological diseases

Expanding opportunities to new targets and regions in the CNS

Rapid growth in Ionis’ neurological disease pipeline enabled by the efficiency of antisense
Ionis’ Strategy has Created a World-class Neurological Disease Pipeline

- Initial focus on genetically validated targets
- Expand to larger more complex diseases
- Target easily accessible regions of the brain
- Expand into deeper regions of the brain
- Leverage disease expertise from academic collaborators
- Access experience and resources from commercial partners to advance drugs to patients
Broad Distribution Supports Treatment of Systemic Neurological Diseases

- **IONIS-TTR$_{Rx}$**
  - Liver target to treat patients with TTR Amyloidosis

- **IONIS-DMPK-2.5$_{Rx}$**
  - Muscle target to treat patients with Myotonic Dystrophy Type 1
Ionis has Demonstrated Robust Activity in the Spinal Cord

- **Nusinersen**
  - Spinal Muscular Atrophy (SMA)

- **IONIS-SOD1Rx**
  - Amyotrophic lateral sclerosis (ALS)

- **IONIS-BIIB5Rx**
  - Undisclosed Neurological Disease
Ionis has Demonstrated Robust Activity in the Cortex

IONIS-HTT$_{Rx}$
- Huntington’s Disease (HD)

IONIS-BIIB4$_{Rx}$
- Undisclosed Neurological Disease

IONIS-BIIB6$_{Rx}$
- Undisclosed Neurological Disease

Research
- Parkinson's Disease
- Alzheimer’s Disease
Ionis has Demonstrated Robust Activity in the Cerebellum and the Hippocampus

IONIS-BIIB4_{Rx}
- Undisclosed Neurological Disease

Research
- Spinocerebellar Ataxias
Expanding Opportunities for Deeper Brain Structures

Research
• Multiple Diseases
Ionis Programs Highlighted at AAN Covering All Targeted Brain Regions

AAN Presentations Covering Diseases

- SMA
- HD
- SCA’s
- PD
- AD
- DM1
Ionis’ Strategy has Created a World-class Neurological Disease Pipeline

Initial focus on genetically validated targets

Expand to larger more complex diseases

Target easily accessible regions of the brain

Expand into deeper regions of the brain

Leverage disease expertise from academic collaborators

Access experience and resources from commercial partners to advance drugs to patients
Ionis Technology Furthers Academic Research and Brings New Drug Opportunities to Patients
Multiple Partnerships Demonstrate Value and Enhance Growth of Neurological Disease Pipeline
Ionis’ Neurological Disease Franchise has Been Highly Productive

<table>
<thead>
<tr>
<th>Clinical Development</th>
<th>Preclinical Development</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3</td>
<td>Preclinical</td>
<td>Multiple programs in various stages of research</td>
</tr>
<tr>
<td>• Nusinersen and IONIS-TTR(_{Rx})</td>
<td>• IONIS-BIIB4(<em>{Rx}), IONIS-BIIB5(</em>{Rx}), IONIS-BIIB6(_{Rx})</td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• IONIS-DMPK-2.5(<em>{Rx}), IONIS-HTT(</em>{Rx}) and IONIS-SOD1(_{Rx})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nearly $500M generated to date related to Ionis’ neurological disease franchise
Antisense Technology Uniquely Addresses Challenging Neurological Diseases

Broad Distribution
- e.g. spinal cord, cortical regions and deep brain structures

Exquisite Specificity
- for targeting protein isoforms and genetic variants

Currently Undruggable Targets
- such as toxic and nuclear retained RNAs

Multiple Mechanisms
- e.g. decrease and increase production and splicing modulation
Agenda

• Welcome and Introductions
  - Stanley Crooke M.D., Ph.D., Chairman of the Board & Chief Executive Officer at Ionis Pharmaceuticals

• Nusinersen Phase 2 Open Label Study in Infants with Type 1 SMA Update
  - Dr. Richard Finkel, Chief, Division of Neurology Department of Pediatrics, Nemours Children’s Hospital in Orlando, Florida

• Nusinersen Program Update
  - Dr. Eugene Schneider, VP Clinical Development at Ionis Pharmaceuticals

• Ionis’ Large and Growing Neurological Disease Pipeline
  - Dr. Eugene Schneider, VP Clinical Development at Ionis Pharmaceuticals

• Addressing a Broad Spectrum of Neurological Diseases with Antisense
  - Dr. Frank Bennett, SVP Research at Ionis Pharmaceuticals

• Closing Remarks and Q&A
  - Stanley Crooke M.D., Ph.D., Chairman of the Board & Chief Executive Officer at Ionis Pharmaceuticals
Ionis’ Neurological Disease Pipeline: Large Near-Term Value, Even Greater Potential Long-Term Value

Two Phase 3 drugs close to commercialization for patients with neurological diseases

Antisense is uniquely suited to address previously untreatable neurological diseases

Expanding opportunities to new targets, new diseases and new regions in the CNS

Rapid growth in Ionis’ neurological disease pipeline enabled by the efficiency of antisense
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Indication</th>
<th>Partner</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nusinersen</td>
<td>Infantile Onset SMA</td>
<td>Biogen</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>Nusinersen</td>
<td>Childhood Onset SMA</td>
<td>Biogen</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-TTR Rx</td>
<td>Familial Amyloid Polyneuropathy</td>
<td>GSK</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-DMPK-2.5 Rx</td>
<td>Myotonic Dystrophy Type 1</td>
<td>Biogen</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-HTT Rx</td>
<td>Huntington’s Disease</td>
<td>Roche</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-SOD1Rx</td>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Biogen</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>Kynamro® HoFH</td>
<td></td>
<td>Ionis</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-TTR Rx</td>
<td>Familial Amyloid Cardiomyopathy</td>
<td>GSK</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>Volanesorsen</td>
<td>Familial Chylomicronemia Syndrome</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>Volanesorsen</td>
<td>Familial Partial Lipodystrophy</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-APO(a)-L Rx</td>
<td>Recurring CVD with High Lp(a)</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-ANGPTL3-L Rx</td>
<td>Rare Mixed Dyslipidemias</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-PKK Rx</td>
<td>Hereditary Angioedema</td>
<td>Ionis</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-TTR Rx</td>
<td>wt-TTR Amyloidosis</td>
<td>GSK</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-FXI Rx</td>
<td>Clotting Disorders</td>
<td>Bayer</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-APO(a)-L Rx</td>
<td>CAVS with High Lp(a)</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-APO(a)-L Rx</td>
<td>CVD with High Lp(a)</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-ANGPTL3-L Rx</td>
<td>Mixed Dyslipidemias</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-AR-2.5Rx</td>
<td>Cancer</td>
<td>Ionis</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-STAT3-2.5Rx</td>
<td>Cancer</td>
<td>AstraZeneca</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-GSK4-L Rx</td>
<td>Ocular Disease</td>
<td>GSK</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-HBV Rx</td>
<td>HBV</td>
<td>GSK</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-HBV-L Rx</td>
<td>HBV</td>
<td>GSK</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-GGCR Rx</td>
<td>Diabetes</td>
<td>Ionis</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-GCCR Rx</td>
<td>Diabetes</td>
<td>Ionis</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-PTP1B Rx</td>
<td>Diabetes</td>
<td>Ionis</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-FGFR4 Rx</td>
<td>Obesity</td>
<td>Ionis</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>IONIS-DGAT2 Rx</td>
<td>NASH</td>
<td>Ionis</td>
<td></td>
<td></td>
<td>On the Market</td>
</tr>
<tr>
<td>Drugs</td>
<td>Indication</td>
<td>Partner</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------------</td>
<td>------------------</td>
<td>---------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Nusinersen</td>
<td>Infantile Onset SMA</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nusinersen</td>
<td>Childhood Onset SMA</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-TTRRx</td>
<td>Familial Amyloid Polyneuropathy</td>
<td>GSK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-DMPK-2.5Rx</td>
<td>Myotonic Dystrophy Type 1</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-HTTRx</td>
<td>Huntington’s Disease</td>
<td>Roche</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-SOD1Rx</td>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kynamro®</td>
<td>HoFH</td>
<td>Ionis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-TTRRx</td>
<td>Familial Amyloid Cardiomyopathy</td>
<td>GSK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volanesorsen</td>
<td>Familial Chylomicronemia Syndrome</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volanesorsen</td>
<td>Familial Partial Lipodystrophy</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-APO(a)-L_Rx</td>
<td>Recurring CVD with High Lp(a)</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-ANGPTL3-L_Rx</td>
<td>Rare Mixed Dyslipidemias</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-PKK_Rx</td>
<td>Hereditary Angioedema</td>
<td>Ionis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-GCGRRx</td>
<td>Diabetes</td>
<td>Ionis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-GCCRRx</td>
<td>Diabetes</td>
<td>Ionis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-PTP1BRx</td>
<td>Diabetes</td>
<td>Ionis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-FGFR4Rx</td>
<td>Obesity</td>
<td>Ionis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-DGAT2Rx</td>
<td>NASH</td>
<td>Ionis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Substantial Increases Observed in Peroneal CMAP Amplitude

As of January 26th, 2016

Peroneal CMAP Amplitude: 2 SMN2 Copy Set (N=17)