Ionis: Creating Value

Near-term: Three groundbreaking Phase 3 drugs close to commercialization

Mid-term: Advanced, diverse pipeline of first-in-class medicines of high value for patients with significant unmet medical need

Long-term: Ionis innovations in technology broaden utility and enhance value of platform
Three Groundbreaking Medicines Close to Commercialization

Volanesorsen

Nusinersen

IONIS-TTR$_{Rx}$
Volanesorsen
For Familial Chylomicronemia Syndrome (FCS)
and Familial Partial Lipodystrophy (FPL)
Volanesorsen: For Severe, Triglyceride-driven Orphan Diseases with No Treatment Today

First and only drug to specifically and robustly reduce Apolipoprotein C-III (ApoCIII) to dramatically decrease triglycerides

Potential to improve the life-altering, and in many cases life-threatening, manifestations of FCS and FPL

Significant near-term commercial opportunity
Two Life-threatening, Genetic, Orphan Diseases Marked by Extreme Triglyceride Levels

**Risk of potentially fatal pancreatitis**

<table>
<thead>
<tr>
<th>FCS</th>
<th>FPL</th>
</tr>
</thead>
<tbody>
<tr>
<td>~3-5k patients worldwide</td>
<td>~3-5k patients worldwide</td>
</tr>
<tr>
<td>LPL deficiency, resulting in triglycerides in the 1,000s</td>
<td>Inability to store fat, resulting in triglycerides in the 1,000s</td>
</tr>
<tr>
<td>Inability to metabolize and clear triglyceride packets resulting in chronic pancreatitis</td>
<td>Disturbance of adipose tissue storage resulting in physical abnormalities</td>
</tr>
<tr>
<td>Metabolic abnormalities, increased risk of diabetes</td>
<td>Extreme insulin resistance, T2DM</td>
</tr>
<tr>
<td>Severe lipemia in blood</td>
<td>Premature death from pancreatitis, liver cirrhosis and cardiovascular disease</td>
</tr>
</tbody>
</table>

No adequate treatments available
Volanesorsen: Ideal Profile as a Potential Treatment for Patients with FCS and FPL

- In FCS patients reduced triglyceride levels up to 86%
- Only drug to specifically lower ApoCIII
- Improved glucose control, insulin sensitivity
- Improved lipid profile including increased HDL-cholesterol

Mean Changes:
- ApoCIII: -71% to -88%
- TG: -64% to -71%
- Non-HDL-C: -11% to -58%
- HDL-C: +42% to +78%
Nusinersen
For Patients with Spinal Muscular Atrophy (SMA)
Nusinersen is Positioned to be the First and Best-in-class Therapy for Infants and Children with SMA

SMA is a rare, severe genetic neuromuscular disease defined by progressive muscle atrophy and loss of motor function.

Ongoing Phase 2 studies show improvements in survival and continued achievement of motor milestones compared to natural history.

Phase 3 studies in infants and children with SMA fully enrolled and data expected by H1:17.

Ionis and Biogen are committed to bringing nusinersen to the market as quickly as possible.
SMA: Progressive Muscle Atrophy Caused by Genetic Defects in the SMN1 Gene

- Number one genetic cause of infant death
- Absent of supportive care, most infants will never see their 2nd birthday

**Infantile Onset**

- Miller, Survived 87 days

**Childhood Onset**

- Peter
- Shortened life expectancy
- Difficulty sitting, raising arms, lifting, standing and walking

~30-35k patients worldwide for all forms of SMA

No currently approved therapies
Robust Development Plan to Support Commercialization of Nusinersen

- **Pre-symptomatic Newborns**: Biogen Study
  - *nurture*

- **Infant Onset**
  - Phase 2 Open Label *(Infants)*
  - *endear*
  - Phase 3

- **Infant and Childhood Onset**
  - Biogen Study
    - *embrace*
  - OLE Study for Phase 3 Studies
    - *shine*

- **Childhood Onset**
  - Phase 3
  - *cherish*
  - Phase 2 Open Label *(Children)*
IONIS-TTR Rx
Toward a Treatment for Patients with Transthyretin (TTR) Amyloidosis
TTR Amyloidosis
One Disease Caused by the Formation of TTR Amyloid Deposits Leading to Organ Failure

Severe, Progressive and Fatal Disease

- Fabio
- Dawn
- Eric

**FAP**
- ~10k patients worldwide
- Age of onset: 30 – 50
- TTR amyloid primarily infiltrates peripheral nerves
- Loss of nerve function
- Multi-organ failure
- Fatal in 5 – 15 years

**TTR Cardiomyopathy**
- TTR amyloid primarily infiltrates the heart
- Congestive heart failure
- Fatal in 3 – 5 years

**FAC**
- ~40k patients worldwide
- Age of onset: 60 – 70 years

**Wild-type**
- ~200k patients worldwide
- Age of onset: >70 years
IONIS-TTR_{Rx}: Potentially First-in-class and Best-in-class Drug to Treat All Forms of TTR Amyloidosis

TTR amyloidosis is a progressive, debilitating, fatal disease caused by TTR amyloid deposits leading to multi-organ failure.

IONIS-TTR_{Rx} is close to potential filing and launch for patients with familial amyloid polyneuropathy (FAP).

Evidence of disease stabilization in patients with TTR cardiomyopathy from an investigator-initiated Phase 2 study.

GSK is the right development and commercial partner for IONIS-TTR_{Rx}.
Robust Phase 3 NEURO-TTR study design

- Includes stage 1 and 2 FAP patients with a broad range of genotypes
- Majority of patients have both polyneuropathy and cardiomyopathy
- Cardiomyopathy analyses will provide data on cardiovascular endpoints

Robust and sustained TTR knockdown in patients

- Maximum TTR reductions of up to 95%

Safety and tolerability profile supports continued development

- Study on-track to complete in H1:17
- Strong patient retention in NEURO-TTR and robust participation in the OLE
- Injection site reactions occurring in approximately 1% of all injections, which were predominantly mild
- Very low incidence of serious platelet declines observed in NEURO-TTR
- Patients treated over 3 years (and continuing)
Ionis Pipeline
Value Beyond the Phase 3 Programs

Richard Geary, Ph.D., Senior Vice President, Development
**Phase 2 Pipeline Poised to Deliver a Broad Range of Transformative Medicines**

<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>IONIS-DMPK-2.5Rx</td>
<td>Myotonic Dystrophy 1</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-HTT_Rx</td>
<td>Huntington’s Disease</td>
<td>Roche</td>
<td></td>
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</tr>
<tr>
<td>IONIS-SOD1_Rx</td>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Biogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-APO(a)-LRx</td>
<td>Hypolipoproteinemia(a) with Premature CVD with Recurrent MACE</td>
<td>Ionis/Akcea</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IONIS-ANGPTL3-L_Rx</td>
<td>Rare Mixed Dyslipidemias</td>
<td>Ionis/Akcea</td>
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</tr>
<tr>
<td>IONIS-FXI_Rx</td>
<td>Rare Dyslipidemias</td>
<td>ionis/Akcea</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IONIS-APO(a)-L_Rx</td>
<td>Hypolipoproteinemia(a) with CAVS</td>
<td>ionis/Akcea</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IONIS-APO(a)-L_Rx</td>
<td>Hypolipoproteinemia(a) with CV Risk</td>
<td>ionis/Akcea</td>
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<tr>
<td>IONIS-ANGPTL3-L_Rx</td>
<td>Mixed Dyslipidemias</td>
<td>ionis/Akcea</td>
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<td></td>
</tr>
<tr>
<td>IONIS-AR-2.5Rx</td>
<td>Cancer</td>
<td>ionis</td>
<td></td>
<td></td>
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<tr>
<td>IONIS-STAT3-2.5Rx</td>
<td>Cancer</td>
<td>AstraZeneca</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IONIS-GCGR_Rx</td>
<td>Diabetes</td>
<td>ionis</td>
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<tr>
<td>IONIS-GCCR_Rx</td>
<td>Diabetes</td>
<td>ionis</td>
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<tr>
<td>IONIS-PTP1B_Rx</td>
<td>Diabetes</td>
<td>ionis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IONIS-FGFR4_Rx</td>
<td>Obesity</td>
<td>ionis</td>
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</tbody>
</table>

All Programs in Position to Advance to Phase 3 within the Next 1-3 Years
First and only antithrombotic to disassociate prevention of thrombotic events and bleeding risk

IONIS-FXIRx demonstrated a 7-fold lower incidence in VTE in patients undergoing total knee replacement*

Well tolerated with no flu-like symptoms and infrequent, mild injection site reactions

Commercial potential in wide array of therapeutic settings for which other anticoagulants are not currently effective

*Incidence of venous thromboemboli compared to patients treated with enoxaparin undergoing total knee replacement
IONIS-GCGR<sub>Rx</sub>: A Promising New Therapeutic Approach for Type 2 Diabetes

Potential first-in-class and best-in-class glucagon receptor (GCGR) inhibitor for patients with severe diabetes

>2% reduction in HbA1c at 75mg dose and >1% at 50mg dose observed in ongoing Phase 2 study

Significant glucose control achieved at lower weekly doses with minimal GCGR-related liver enzyme elevations

Well tolerated with no flu-like symptoms and infrequent, mild injection site reactions
First and only program to selectively and robustly reduce Lp(a), a key driver of cardiovascular disease

LICA technology in IONIS-APO(a)-L_{Rx} increases potency and allows for lower doses and flexibility in dosing frequency

Well tolerated with no flu-like symptoms and no injection site reactions observed to date

Multi-billion dollar commercial potential targeting both rare and broad patient populations

IONIS-APO(a)-L_{Rx}: The Next Frontier in Cardiovascular Disease Management

LICA Drug
**Significant Ongoing Progress in Our Oncology Franchise**

<table>
<thead>
<tr>
<th><strong>IONIS-STAT3-2.5\textsubscript{Rx}</strong></th>
<th>Multiple durable clinical responses in heavily pre-treated patients, including 2 complete responses</th>
</tr>
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<tr>
<td><strong>IONIS-AR-2.5\textsubscript{Rx}</strong></td>
<td>Multiple durable PSA responses with prolonged stable disease in heavily pre-treated patients with metastatic castration resistant prostate cancer (CRPC)</td>
</tr>
<tr>
<td><strong>MD Anderson Cancer Center</strong></td>
<td>Strategic partnership provides access to MDACC’s novel, traditionally undruggable cancer targets</td>
</tr>
</tbody>
</table>
Key Clinical Data Planned in 2016 and Early 2017

<table>
<thead>
<tr>
<th>Q3:16</th>
<th>Q4:16</th>
<th>Ph. 3 Events H1:17</th>
</tr>
</thead>
<tbody>
<tr>
<td>IONIS-TTR\textsubscript{Rx}: Ph. 3 Data</td>
<td>IONIS-FXI\textsubscript{Rx}: Ph. 2 Data</td>
<td>Nusinersen: Ph. 3 Data for CHERISH</td>
</tr>
<tr>
<td>Update in FAP OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-TTR\textsubscript{Rx}: Ph. 2 Data</td>
<td>IONIS-DMPK-2.5\textsubscript{Rx}: Ph. 1/2 (MAD) Data</td>
<td>Nusinersen: Ph. 3 Data for ENDEAR</td>
</tr>
<tr>
<td>in ATTR-CM (Benson)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-ANGPTL3-L\textsubscript{Rx}: Ph. 2 Data</td>
<td>IONIS-STAT3-2.5\textsubscript{Rx}: Ph. 2 Data</td>
<td>IONIS-TTR\textsubscript{Rx}: Ph. 3 Data for NEURO-TTR</td>
</tr>
<tr>
<td>IONIS-GSK4-L\textsubscript{Rx} Ph. 1 (SAD) Data</td>
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<td></td>
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<tr>
<td>IONIS-GCGR\textsubscript{Rx} Ph. 2 Data (Interim)</td>
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<td>IONIS-AR-2.5\textsubscript{Rx} Ph. 2 Data</td>
<td></td>
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</tr>
<tr>
<td>IONIS-DGAT2\textsubscript{Rx}: Ph. 1 Data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IONIS-FGFR4\textsubscript{Rx}: Ph. 2 Data</td>
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<tr>
<td>Volanesorsen: Ph. 3 Data for FCS</td>
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</table>
Ionis Technology: Creating Better Medicines and Expanding Opportunities

Stanley Crooke, M.D., Ph.D., CEO and Chairman
Advances in our Technology in the Pipeline Today

Continued Investment in Core Antisense Research

Gen 2+
Gen 2.5
LICA
Large Safety Database Provides Evidence of Good Safety Profile of 2nd Generation Antisense Drugs

- Large clinical safety database (Ionis safety experience)
  - >6,000 patients treated with Ionis 2nd Generation antisense drugs (iv/sc)
    - Doses: 0.6-15 mg/kg
  - >3,000 patients in the integrated safety database
- Integrated safety database:
  - No platform generic liver or renal toxicities identified
  - No platform generic platelet toxicities identified
  - No platform safety issues identified in clinical studies for the following systems:
    - Cardiac, CNS, muscle, hematology, liver, kidney
  - **No clinically significant drug-drug interactions observed**
    - Lack of P450 metabolism interactions
    - Lack of major transporter interactions
Generation 2.5 Broadens Utility and Value of Antisense Technology

1. Enhanced affinity for target sequence

2. Up to 10-fold increase in potency

3. Enhanced target engagement in new tissues, i.e. stromal cells, muscle cells

4. Good tolerability observed in clinical studies
Advances in Ionis Technology are Translating into Real Value in the Pipeline Today

### 4 Generation 2.5 Drugs in Clinical Development

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>IONIS-DMPK-2.5_{Rx}</td>
<td>Myotonic Dystrophy 1</td>
<td>Ph. 2</td>
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</tr>
<tr>
<td>IONIS-AR-2.5_{Rx}</td>
<td>Cancer</td>
<td>Ph. 2</td>
</tr>
<tr>
<td>IONIS-RHO-2.5_{Rx}</td>
<td>Autosomal Dominant Retinitis Pigmentosa</td>
<td>PC</td>
</tr>
</tbody>
</table>

- **Severe & Rare**
- **Oncology**
LICA is a Game Changing Advance in the Potency of Ionis’ Antisense Drugs

1. Ultra-low dose

2. >30-fold more potent in humans as demonstrated by Ionis’ first LICA drug

3. Easy to administer, flexible dosing: weekly, monthly, quarterly or less frequently

4. Good tolerability observed in clinical studies
Advances in Ionis’ Technology are Translating into Real Value in the Pipeline Today

8 LICA Drugs in Clinical Development

<table>
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<td>Rare Mixed Dyslipidemias</td>
<td>Ph. 2</td>
</tr>
<tr>
<td>IONIS-GSK4-L(_{Rx})</td>
<td>Ocular Disease</td>
<td>Ph. 1</td>
</tr>
<tr>
<td>IONIS-HBV-L(_{Rx})</td>
<td>HBV</td>
<td>Ph. 1</td>
</tr>
<tr>
<td>IONIS-GHR-L(_{Rx})</td>
<td>Acromegaly</td>
<td>PC</td>
</tr>
<tr>
<td>IONIS-TMPRSS6-L(_{Rx})</td>
<td>β-Thalassemia</td>
<td>PC</td>
</tr>
<tr>
<td>IONIS-AGT-L(_{Rx})</td>
<td>Treatment-Resistant Hypertension</td>
<td>PC</td>
</tr>
<tr>
<td>IONIS-APOCIII-L(_{Rx})</td>
<td>Severely High TGs</td>
<td>PC</td>
</tr>
</tbody>
</table>

- **Severe & Rare**
- **Cardiovascular**
- **Other**
Continued Investment in Core Antisense Research Broadens the Utility of Ionis Medicines

Gen 2+

Gen 2.5

LICA

GEN 2.5 + LICA

Generation 2.5 + LICA Dev Candidate Planned in Late 2016/Early 2017
Potential for 1-5 mg dose per week

Ultra-low doses for patients has potential to broaden addressable patient populations

1st development candidate planned for late 2016/early 2017
Advances in Ionis’ Technology Greatly Expand our Ability to Treat Disease

- **Generation 2+**: Enhances potency and tolerability
- **Generation 2.5**: Enhances target engagement in new tissues
- **LICA**: Dramatically and additively improves potency in liver and now other tissues
- **Generation 2.5 + LICA**: Enables very low dose volumes
- **New Antisense Mechanisms**: Broadens applicability and enhances value of platform
Partners' Extensive R&D Activities Support Robust Pipeline

- Researching novel delivery methods
- Researching antisense medicines to treat metabolic cardiovascular and renal diseases
- Performing clinical and pre-clinical studies
- Initiated 2 Phase 2 studies for nusinersen
- Contributing significantly to core antisense research
- Researching and developing antisense medicines to treat neuro diseases
- Initiating Phase 2 for IONIS-HBV-L_Rx and Phase 2 for IONIS-HBV_Rx
- Researching oral formulation of antisense medicines to treat autoimmune disorders of the GI tract
- PoC work in animal models
- Conducting biomarker work to support IONIS-HTTRx development plan
- Developing IONIS-FXI_Rx broadly for the prevention of thrombosis
Ionis Has Built a Strong Financial Foundation

Pro Forma Operating Loss 2012 – 2015

2012 2013 2014 2015

Revenue 2012 – 2015

2012 2013 2014 2015

$102M $147M $214M $284M

Cash 2012 – 2015

2012 2013 2014 2015

$374M $657M $729M $779M

Profitable in 6 Quarters Since the Beginning of 2012

Sustainable Revenue and Cash Base from Partnerships
**Ionis’ Future Focused on Value**

### 2017 / 2018 Launch Potential

<table>
<thead>
<tr>
<th>Product</th>
<th>Pre-launch Milestones &amp; Licensing Revenue</th>
<th>Tiered Royalty Rate Up to the Mid-teens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nusinersen</strong></td>
<td>Biogen, Responsible for 100% of Launch Cost</td>
<td>Pre-launch Milestones &amp; Licensing Revenue</td>
</tr>
<tr>
<td></td>
<td>~30,000 – 35,000 Patients Worldwide</td>
<td>~10,000 Patients for Initial Indication</td>
</tr>
<tr>
<td></td>
<td><em>(Initial indication is subset of total patients worldwide)</em></td>
<td>~250,000 Patients Worldwide</td>
</tr>
</tbody>
</table>

| **IONIS-TTR\text{Rx}** | gsk, Responsible for 100% of Launch Cost | Pre-launch Milestones & Licensing Revenue | Tiered Royalty Rate Up to the Mid-teens |
| **Volanesorsen** | Ionis & Akcea, Responsible for 100% of Launch Cost | Retain 100% of Revenue |
|                  | ~3,000 – 5,000 Patients Worldwide       | ~6,000 – 10,000 Patients Worldwide | ~6,000 – 10,000 Patients Worldwide |

*If option to license is exercised*