This presentation includes forward-looking statements regarding Isis Pharmaceuticals’ financial position and outlook, Isis’ business, and the therapeutic and commercial potential of Isis’ technologies and products in development, including the commercial potential of KYNAMRO®, ISIS-TTR\textsubscript{Rx}, ISIS-SMN\textsubscript{Rx} and volanesorsen. Any statement describing Isis’ 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. Isis’ 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 Isis’ forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis’ programs are described in additional detail in Isis’ annual report on Form 10-K for the year ended December 31, 2014, 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 press release, unless the context requires otherwise, “Isis,” “Company,” “we,” “our,” and “us” refers to Isis Pharmaceuticals and its subsidiaries.

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc. Akcea Therapeutics™ is a trademark of Isis Pharmaceuticals, Inc. Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc. KYNAMRO® is a registered trademark of Genzyme Corporation.
Welcome Isis’ Board of Directors

Spencer Berthelsen, MD, FACP

Skip Klein

Fred Muto, Esq

Lynne Parshall, Esq

Breaux Castleman

Joe Wender

Joseph Loscalzo, MD, PhD
The Year In Review
# Isis’ Pipeline Continues to Grow and Expand

## Commercialized

<table>
<thead>
<tr>
<th>Product</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>KYNAMRO®</td>
<td>Homozygous FH</td>
</tr>
<tr>
<td>Alicaforsen</td>
<td>*Pouchitis</td>
</tr>
<tr>
<td>Vitravene®</td>
<td>CMV Retinitis</td>
</tr>
</tbody>
</table>

* Named Patient Supply

## Phase 2 (cont.)

### Phase 3

<table>
<thead>
<tr>
<th>Product</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-TTR_Rx</td>
<td>TTR Amyloidosis</td>
</tr>
<tr>
<td>ISIS-SMN_Rx</td>
<td>Spinal Muscular Atrophy</td>
</tr>
<tr>
<td>ISIS-SMN_Rx</td>
<td>(Infants)</td>
</tr>
<tr>
<td>Volanesorsen</td>
<td>FCS</td>
</tr>
<tr>
<td>Volanesorsen</td>
<td>Familial Partial Lipodystrophy</td>
</tr>
<tr>
<td>KYNAMRO®</td>
<td>Severe HeFH</td>
</tr>
<tr>
<td>Custirsen (OGX-011)</td>
<td>Prostate / Lung Cancer</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Severe Bacterial Infection</td>
</tr>
</tbody>
</table>

## Phase 2

<table>
<thead>
<tr>
<th>Product</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATL1103</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>ISIS-DMPK-2.5_Rx</td>
<td>Myotonic Dystrophy 1</td>
</tr>
</tbody>
</table>

## Phase 1

<table>
<thead>
<tr>
<th>Product</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-GCCR_Rx</td>
<td>Cushing’s Syndrome</td>
</tr>
<tr>
<td>ISIS-PKK_Rx</td>
<td>Hereditary Angioedema</td>
</tr>
<tr>
<td>RG-012</td>
<td>Alport Syndrome</td>
</tr>
<tr>
<td>ISIS-APO(a)-L_Rx</td>
<td>Very High Lp(a)</td>
</tr>
<tr>
<td>ISIS-FGFR4_Rx</td>
<td>Obesity</td>
</tr>
<tr>
<td>ISIS-HBV_Rx</td>
<td>HBV</td>
</tr>
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</table>

## Preclinical

<table>
<thead>
<tr>
<th>Product</th>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>ISIS-HTT_Rx</td>
<td>Huntington’s Disease</td>
</tr>
<tr>
<td>ISIS-BIBB3_Rx</td>
<td>Neurodegenerative Disease</td>
</tr>
<tr>
<td>ISIS-BIBB4_Rx</td>
<td>Neurodegenerative Disease</td>
</tr>
<tr>
<td>ISIS-RHO-2.5_Rx</td>
<td>Autosomal Dominant Retinitis Pigmentosa</td>
</tr>
<tr>
<td>ISIS-GHR-LRx</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>ISIS-AGT-L_Rx</td>
<td>Treatment-Resistant Hypertension</td>
</tr>
<tr>
<td>ISIS-ANGPTL3-L_Rx</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>ISIS-APOCIII-L_Rx</td>
<td>Severely High TGs</td>
</tr>
<tr>
<td>ISIS-TMPRSS6-L_Rx</td>
<td>β-Thalassemia</td>
</tr>
<tr>
<td>ISIS-DGAT2_Rx</td>
<td>NASH</td>
</tr>
<tr>
<td>RG-125</td>
<td>NASH in Patients with Type 2 Diabetes</td>
</tr>
<tr>
<td>ISIS-GSK4-L_Rx</td>
<td>Ocular Disease</td>
</tr>
<tr>
<td>ISIS-GSK6-L_Rx</td>
<td>Antiviral</td>
</tr>
</tbody>
</table>
2014: A Year of Broad Success and Enhanced Value
Data Published in the New England Journal of Medicine

Targeting APOC3 in the Familial Chylomicronemia Syndrome

Daniel Gaudet, M.D., Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D.,
Veronica J. Alexander, Ph.D., Walter Singleton, M.D., Steven G. Hughes, M.B., B.S.,
Richard S. Geary, Ph.D., Brenda F. Baker, Ph.D.,
Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D.,
and Joseph L. Witztum, M.D.

- First study to demonstrate the key role apoC-III plays as a regulator of LPL-independent pathways of triglyceride TG metabolism
  - apoC-III levels reduced up to 90%
  - TG levels reduced up to 86%
  - All FCS patients in study achieved TG levels <500 mg/dL with treatment

Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

Harry R. Büller, M.D., Claudette Bethune, Ph.D., Sanjay Bhanot, M.D., Ph.D.,
David Gailani, M.D., Brett P. Monia, Ph.D., Gary E. Raskob, Ph.D.,
Annelise Segers, M.D., Peter Verhamme, M.D., and Jeffrey I. Weitz, M.D., for the FXI-ASO TKA Investigators

- Seven-fold lower incidence of VTE in patients treated with 300 mg ISIS-FXI_Rx compared with enoxaparin-treated patients (4% vs. 30%)
- Demonstrates for the first time a clear dissociation between thrombosis and bleeding
## Broad Success and Enhanced Value

### Clinical Study Initiations (2014 & 2015)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-SMN&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Spinal Muscular Atrophy (infants)</td>
<td>3</td>
</tr>
<tr>
<td>ISIS-SMN&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Spinal Muscular Atrophy (children)</td>
<td>3</td>
</tr>
<tr>
<td>Volanesorsen</td>
<td>Familial Chylomicronemia Syndrome</td>
<td>3</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Multi-drug Resistance</td>
<td>3</td>
</tr>
<tr>
<td>ISIS-APO(a)&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>High Lp(a)</td>
<td>2</td>
</tr>
<tr>
<td>ISIS-GCCR&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Type 2 Diabetes</td>
<td>2</td>
</tr>
<tr>
<td>Apatorsen (OGX-427)</td>
<td>Non-small Cell Lung Cancer</td>
<td>2</td>
</tr>
<tr>
<td>ISIS-AR-2.5&lt;sub&gt;Rx&lt;/sub&gt; (AZD5312)</td>
<td>Cancer</td>
<td>2</td>
</tr>
<tr>
<td>ISIS-DMPK-2.5&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Myotonic Dystrophy Type I</td>
<td>1/2</td>
</tr>
<tr>
<td>RG-101</td>
<td>Hepatitis C Virus</td>
<td>1/2</td>
</tr>
<tr>
<td>ISIS-ANGPTL3&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Healthy Volunteers</td>
<td>1</td>
</tr>
<tr>
<td>ISIS-PKK&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Healthy Volunteers</td>
<td>1</td>
</tr>
<tr>
<td>ISIS-APO(a)-L&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Healthy Volunteers</td>
<td>1</td>
</tr>
</tbody>
</table>

✅ completed milestone
### Broad Success and Enhanced Value

**Clinical Data Readouts (2014)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KYNAMRO</strong></td>
<td>One and two-year MACE analysis</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>Custirsen (OGX-011)</strong></td>
<td>Castration-resistant Prostate Cancer</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>ISIS-SMN&lt;sub&gt;Rx&lt;/sub&gt;</strong></td>
<td>Spinal Muscular Atrophy (infants)</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>ISIS-SMN&lt;sub&gt;Rx&lt;/sub&gt;</strong></td>
<td>Spinal Muscular Atrophy (children)</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>Volanesorsen</strong></td>
<td>High to Severely High Triglycerides (monotherapy)</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>Volanesorsen</strong></td>
<td>High to Severely High Triglycerides (add on to fibrates)</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>Volanesorsen</strong></td>
<td>High Triglycerides and Type 2 Diabetes</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>Volanesorsen</strong></td>
<td>Familial Chylomicronemia Syndrome</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>ATL 1103</strong></td>
<td>Acromegaly</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>ISIS-FXI&lt;sub&gt;Rx&lt;/sub&gt;</strong></td>
<td>Thrombosis in Total Knee Replacement</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>ISIS-CRP&lt;sub&gt;Rx&lt;/sub&gt;</strong></td>
<td>Atrial Fibrillation</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>ISIS-GCGR&lt;sub&gt;Rx&lt;/sub&gt;</strong></td>
<td>Type 2 Diabetes</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>ISIS-EIF4E&lt;sub&gt;Rx&lt;/sub&gt;</strong></td>
<td>Prostate Cancer, Lung Cancer</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>ISIS-STAT3-2.5Rx (AZD9150)</strong></td>
<td>Liver Cancer</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>Apatorsen (OGX-427)</strong></td>
<td>Bladder Cancer</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>iCo-007</strong></td>
<td>Diabetic Macular Edema</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>RG-101</strong></td>
<td>Hepatitis B Virus</td>
<td>✓✓</td>
</tr>
<tr>
<td><strong>ISIS-APO(a)&lt;sub&gt;Rx&lt;/sub&gt;</strong></td>
<td>Healthy Volunteers</td>
<td>✓✓</td>
</tr>
</tbody>
</table>

*Positive study

*Negative study


# Broad Success and Enhanced Value
Clinical Data Readouts (2015)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-TTR\textsubscript{Rx}</td>
<td>Familial Amyloid Polyneuropathy</td>
<td>✓ OLE</td>
</tr>
<tr>
<td>ISIS-SMN\textsubscript{Rx}</td>
<td>Spinal Muscular Atrophy (infants) update</td>
<td>✓ 2</td>
</tr>
<tr>
<td>ISIS-SMN\textsubscript{Rx}</td>
<td>Spinal Muscular Atrophy (children) update</td>
<td>✓ 2</td>
</tr>
<tr>
<td>ISIS-PTP1B\textsubscript{Rx}</td>
<td>Type 2 Diabetes</td>
<td>✓ 2</td>
</tr>
<tr>
<td>ISIS-STAT3-2.5\textsubscript{Rx}</td>
<td>Lymphoma</td>
<td>✓ 2</td>
</tr>
<tr>
<td>ISIS-PKK\textsubscript{Rx}</td>
<td>Healthy Volunteers</td>
<td>✓ 1</td>
</tr>
<tr>
<td>ISIS-ANGPTL3\textsubscript{Rx}</td>
<td>Healthy Volunteers</td>
<td>✓ 1</td>
</tr>
</tbody>
</table>

Positive study: ✓
Negative study: ✗
Isis’ Business Model

Strategic Partner
Biogen – CNS

Preferred Partners and Licensee
GSK
AstraZeneca
Roche
Janssen (J&J)
Bayer

Satellite Companies
Regulus
Achaogen
ATL
OncoGenex
Atlantic

Captive development & commercial company
Akcea Therapeutics:
Isis’ wholly owned subsidiary
Isis’ Business Model

Strategic Partner
Biogen – CNS

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Roche
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Captive development & commercial companies

Preferred Partners

Satellite Companies

Strategic Partners
Isis’ Business Model

Strategic Partner
Biogen – CNS

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- GSK
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- Roche
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Isis' wholly owned subsidiary

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Bayer

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Achaogen
ATL
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Atlantic

Captive development & commercial company
Akcea Therapeutics:
Isis’ wholly owned subsidiary
**Broad Success and Enhanced Value**  
Success of Partnered Programs Support Strong Financial Position

**Biogen**
- Strategic Partner — CNS
- \>$330M\) received to date

- **ISIS-SMN$$RX$$Rx**: Spinal Muscular Atrophy (Infants)
- **ISIS-SMN$$RX$$Rx**: Spinal Muscular Atrophy (Children)
- **ISIS-DMPK-2.5$$RX$$Rx**: Myotonic Dystrophy 1
- **ISIS-BIIB3$$RX$$Rx**: Neurodegenerative Disease
- **ISIS-BIIB4$$RX$$Rx**: Neurodegenerative Disease

*Isis’ Pipeline Continues to Grow and Expand*
GlaxoSmithKline
• Preferred Partner — Rare, infectious and ocular diseases
• >$135M received to date

In the image:
- ISIS-TTR\textsubscript{Rx} - TTR Amyloidosis
- ISIS-HBV\textsubscript{Rx} - HBV
- ISIS-RHO-2.5\textsubscript{Rx} - Autosomal Dominant Retinitis Pigmentosa
- ISIS-GSK4-L\textsubscript{Rx} - Ocular Disease
- ISIS-GSK6-L\textsubscript{Rx} - Antiviral

Success of Partnered Programs Support Strong Financial Position
AstraZeneca

- Preferred Partner — Cancer
- >$70M received to date

ISIS-STAT3-2.5<sub>Rx</sub> (AZD9150)

ISIS-AR-2.5<sub>Rx</sub> (AZD5312)

Cancer

Isis’ Pipeline Continues to Grow and Expand
Roche

- Preferred Partner — Huntington's Disease
- >$31M received to date

ISIS-HTT<sub>Rx</sub> Huntington's Disease
Antisense Technology: Current Status and Future
RNase H1 Antisense Mechanism
The Most Advanced Antisense Mechanism

Clinical Experience:
- >6,000 subjects dosed; >3,000 in Isis database
- >60 clinical studies
- Multiple therapeutic indications
- >100 patients dosed for >1 year
- Some patients dosed for >4 years
- Doses as high as 1,200 mg tolerated

Compared to first generation antisense drugs, second generation antisense drugs:
- Increase potency >100 fold
- Increase duration of action 10-20 fold (50-100 fold less drug)
- Decrease unwanted side effects
Isis Antisense Technology is a Proven, Efficient Platform for Creating New Drugs

• Efficient – 1 drug per 11 Isis employees

Traditional Pharma
1 drug / ~1,000 employees

ISIS
1 drug / 11 employees
Isis Antisense Technology is a Proven, Efficient Platform for Creating New Drugs

- **Efficient** – 1 drug / 11 Isis employee

- **Robust** – multiple mechanisms
  - Ability to increase or decrease protein production
  - Single-stranded antisense drugs can effectively target RNAs in cytoplasm AND nucleus of the cell

**Reduces** target RNA & prevents production of protein

Reduces target RNA & prevents production of protein

- Antisense
  - RNase H
  - mRNA for disease-causing protein

- Example: Volanesorsen

**Increases** production of therapeutic protein

Increases production of therapeutic protein

- Example: ISIS-SMN<sub>Rx</sub>

**Removes** toxic RNA

Removes toxic RNA

- Example: ISIS-DMPK-2.5<sub>Rx</sub>
- RNase H
Isis Antisense Technology is a Proven, Efficient Platform for Creating New Drugs

- **Efficient** – 1 drug / 11 Isis employee
- **Robust** – multiple mechanisms
- **Robust** – multiple routes of delivery
Isis Antisense Technology is a Proven, Efficient Platform for Creating New Drugs

- **Efficient** – 1 drug / 11 Isis employee
- **Robust** – multiple mechanisms
- **Robust** – multiple routes of delivery

- **Robust** – broad clinical activity in multiple tissues
# Gen 2.0 Antisense Drugs

Activity of Multiple Drugs in Multiple Tissues and Multiple Diseases by Multiple Routes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indications</th>
<th>Primary Organs</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kynamro®</td>
<td>ApoB-100</td>
<td>Hyperlipidemia</td>
<td>Liver</td>
<td>ApoB, LDL-C, &amp; Others</td>
</tr>
<tr>
<td>Volanesorsen</td>
<td>ApoC-III</td>
<td>High TGs</td>
<td>Liver</td>
<td>ApoC-III levels &amp; TGs</td>
</tr>
<tr>
<td>ISIS-SMN$_{Rx}$</td>
<td>SMN2</td>
<td>SMA</td>
<td>Brain &amp; spinal cord</td>
<td>SMN RNA, SMN Protein</td>
</tr>
<tr>
<td>Custirsen</td>
<td>Clusterin</td>
<td>Prostate Cancer</td>
<td>Prostate, Lymph nodes</td>
<td>Target reduction, Apoptosis, Survival</td>
</tr>
<tr>
<td>ISIS-TTR$_{Rx}$</td>
<td>TTR</td>
<td>TTR Amyloidosis</td>
<td>Liver</td>
<td>TTR levels</td>
</tr>
<tr>
<td>ISIS-FXI$_{Rx}$</td>
<td>Factor XI</td>
<td>Clotting Disorders</td>
<td>Liver</td>
<td>Factor XI levels &amp; decreased clotting</td>
</tr>
<tr>
<td>EXC 001</td>
<td>CTGF</td>
<td>Scarring</td>
<td>Skin</td>
<td>Scarring endpoints, CTGF in skin</td>
</tr>
<tr>
<td>ISIS-113715$_{Rx}$</td>
<td>PTP1B</td>
<td>Diabetes</td>
<td>Liver, Fat cells</td>
<td>Glucose, LDL-C</td>
</tr>
<tr>
<td>ISIS-PTP1BR$_{Rx}$</td>
<td>PTP1B</td>
<td>Diabetes</td>
<td>Liver, Fat cells</td>
<td>Glucose, LDL-C</td>
</tr>
<tr>
<td>ISIS-APO(a)$_{Rx}$</td>
<td>Apo(a)</td>
<td>Lipid Disorders</td>
<td>Liver</td>
<td>Lp(a) levels</td>
</tr>
<tr>
<td>ISIS-CRP$_{Rx}$</td>
<td>CRP</td>
<td>CV Disease Inflammation</td>
<td>Liver</td>
<td>CRP in plasma</td>
</tr>
<tr>
<td>ATL1102</td>
<td>VLA4</td>
<td>MS</td>
<td>Bone marrow, Lymph nodes</td>
<td>MRS Measurements of CNS lesions</td>
</tr>
<tr>
<td>ISIS-GCGR$_{Rx}$</td>
<td>GCGR</td>
<td>Diabetes</td>
<td>Liver</td>
<td>Glucose &amp; glycogen in plasma</td>
</tr>
<tr>
<td>ATL1103</td>
<td>GHR</td>
<td>Acromegaly</td>
<td>Liver</td>
<td>IGF1 levels</td>
</tr>
<tr>
<td>ISIS-104838</td>
<td>TNFα</td>
<td>RA</td>
<td>Joints, Lymph nodes</td>
<td>ACR 20 &amp; Target reduction</td>
</tr>
<tr>
<td>ISIS-STAT3-2.5$_{Rx}$</td>
<td>STAT3</td>
<td>Cancer</td>
<td>Tumors / tumor stromal cells</td>
<td>STAT3 RNA and protein</td>
</tr>
<tr>
<td>ISIS-ANPTL3$_{Rx}$</td>
<td>ANPTL3</td>
<td>Lipid Disorders</td>
<td>Liver</td>
<td>ANPTL3, TGs in plasma</td>
</tr>
<tr>
<td>ISIS-SGLT2$_{Rx}$</td>
<td>SGLT2</td>
<td>Diabetes</td>
<td>Kidney</td>
<td>Increase glucose in urine</td>
</tr>
<tr>
<td>ISIS-PKK$_{Rx}$</td>
<td>PKK</td>
<td>HAE</td>
<td>Liver</td>
<td>PKK in plasma</td>
</tr>
</tbody>
</table>
Improvement in Side Effects Observed in Newer Gen 2.0 Antisense Drugs Compared to KYNAMRO in Phase 1 Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Volanesorsen</th>
<th>ISIS-FXIRx</th>
<th>ISIS-TTRRx</th>
<th>ISIS-PKKRx</th>
<th>ISIS-ANGPTL3Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site Reactions (% SC Injections)</td>
<td>89% fewer ISRs</td>
<td>64% fewer ISRs</td>
<td>65% fewer ISRs</td>
<td>50% fewer ISRs</td>
<td>65% fewer ISRs</td>
</tr>
<tr>
<td>Flu-like Symptoms</td>
<td>None</td>
<td>None</td>
<td>Very low incidence</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Advances in Antisense Technology Broaden Utility and Value

- **Generation 2.5 drugs:**
  - Enhance affinity for target sequence
  - Up to 10-fold increase in potency
  - Enhance target engagement in new tissues
    - Activity in cancer and stromal cells
    - ISIS-DMPK-2.5\textsubscript{Rx} program to evaluate activity in muscle cells
  - Good safety profile observed with Generation 2.5 chemistry to date
  - Four Generation 2.5 drugs in pipeline:
    - ISIS-STAT3-2.5\textsubscript{Rx} (AZD9150)
    - ISIS-AR-2.5\textsubscript{Rx} (AZD5312)
    - ISIS-DMPK-2.5\textsubscript{Rx}
    - ISIS-RHO-2.5\textsubscript{Rx}

<table>
<thead>
<tr>
<th>Antisense Compound</th>
<th>ID\textsubscript{50} in Humans (mg/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gen 2.0</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>Gen 2.5</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>

Advances in Antisense Technology Broaden Utility and Value
Advances in Antisense Technology Broaden Utility and Value
LICA Conjugation

- LICA conjugation technology
  - Enhance effective distribution for liver targets
  - Up to 10-fold increase in potency
  - First LICA drug in clinical development
  - Additional drugs with LICA conjugation nearing clinical stage for liver targets
    - Optimal for use in broader indications, lower dosing and less frequent dosing
  - Eight LICA drugs in pipeline

<table>
<thead>
<tr>
<th>Antisense</th>
<th>ID_{50} in Humans (mg/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td></td>
</tr>
<tr>
<td>Gen 2.0</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Gen 2.0-LICA</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

Advances in Antisense Technology Broaden Utility and Value
LICA Conjugation

- LICA conjugation technology
  - Enhance effective distribution for liver targets
  - Up to 10-fold increase in potency
  - First LICA drug in clinical development
  - Additional drugs with LICA conjugation nearing clinical stage for liver targets
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<table>
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<th>ID_{50} in Humans (mg/wk)</th>
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</thead>
<tbody>
<tr>
<td>Compound</td>
<td></td>
</tr>
<tr>
<td>Gen 2.0</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Gen 2.0-LICA</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>
LICA Improves Potency of Gen 2.0 and Gen 2.5 Antisense Compounds
Continue to Advance Antisense Technology

Enhanced affinity and enhanced distribution

<table>
<thead>
<tr>
<th>Antisense Compound</th>
<th>Projected Dose in Humans (mg/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gen 2.0</td>
<td>100 – 300</td>
</tr>
<tr>
<td>Gen 2.0-LICA</td>
<td>10 – 30</td>
</tr>
<tr>
<td>Gen 2.5</td>
<td>10 – 30</td>
</tr>
<tr>
<td>Gen 2.5-LICA</td>
<td>1.0 – 3.0</td>
</tr>
</tbody>
</table>
Isis’ Flexible Development and Partnership Strategy
Maximizes Value, Minimizes Risk and Decreases Time to Market

<table>
<thead>
<tr>
<th>Partner Early</th>
<th>License After POC</th>
<th>Keep Longer</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Significant technical or target risk</td>
<td>- Complex, expensive Phase 3 development</td>
<td>- Clear Phase 2, Phase 3 development path</td>
</tr>
<tr>
<td>- Complex, difficult, expensive Phase 2 program</td>
<td>- Straightforward, effective Phase 2 program with definitive endpoints</td>
<td>- Low to moderate total development costs</td>
</tr>
<tr>
<td>- Challenging endpoints</td>
<td>- Multiple indications</td>
<td>- Potential for initial rare disease opportunity</td>
</tr>
<tr>
<td>- Expertise from partner could provide increased likelihood of success</td>
<td>- Large patient population</td>
<td>- Consistent with Isis intellectual franchises</td>
</tr>
<tr>
<td></td>
<td>- Large marketing and sales effort</td>
<td></td>
</tr>
</tbody>
</table>

Examples:
- ISIS-SMN<sub>Rx</sub>
- ISIS-DMPK-2.5<sub>Rx</sub>
- ISIS-STAT3-2.5<sub>Rx</sub> (AZD9150)
- ISIS-AR-2.5<sub>Rx</sub> (AZD5312)
- ISIS-FXI<sub>Rx</sub> (Bayer)
- Volanesorsen
- ISIS-APO(a)<sub>Rx</sub>
- ISIS-ANGPTL3-L<sub>Rx</sub>
  + follow-on drugs

Janssen (J&J)
Isis - Janssen Collaboration
RNA-targeted Therapies for Autoimmune Diseases in GI Tract

- Collaboration provides several advantages
  - Combines Isis’ RNA-targeted technology with Janssen’s expertise in autoimmune disorders and therapeutic formulation
  - Provides Isis with a low-risk, low-cost opportunity to expand our technology into oral local delivery for GI and autoimmune diseases

- $35 million in upfront payments

- ~$800 million in development, regulatory, sales milestones and license fees

- Average royalties on sales in the double-digits
Isis — Bayer License Agreement

$155M in Near-term Payments; Bayer to Develop ISIS-FXIr for the Prevention of Thrombosis

- Bayer is a leader in the treatment of thrombotic diseases with the global reach to support robust development program
- Bayer plans to invest substantially in a broad development plan designed to take advantage of the profile of ISIS-FXIr and maximize its value
  - Initially, plans to evaluate the therapeutic profile of ISIS-FXIr in patients for whom currently available anticoagulants may not be used
  - Additional plans to develop ISIS-FXIr for patients who are underserved by current antithrombotics
- Tiered royalties in the low to high 20 percent range on gross margins of ISIS-FXIr
- $155 million in near-term payments
  - $100 million up-front payment
  - $55 million payment upon advancement of the program following the Phase 2 study in patients with compromised kidney function
- In total, Isis has the opportunity to earn up to $375 million in payments, plus royalties
In 2015, we have generated more than $195 million in payments from partners, including the following:

- $100 million from Bayer
- $42 million from Biogen
- $35 million from Janssen (J&J)
- $19 million from GSK

Total: $196M
KYNAMRO

Position Strengthening
KYNAMRO: Position Strengthening

- KYNAMRO is marketed and approved in the U.S. and additional countries

- Genzyme continues to invest significantly in KYNAMRO

- Increased sales growth in 2014

- Projected increase in sales for 2015
KYNAMRO: Position Strengthening

- Results from a retrospective analysis reported at the 2014 American Heart Association annual meeting showed that, in HoFH and HeFH patients, the rate of major adverse cardiovascular events decreased seven-fold after two years of KYNAMRO treatment vs. the two years prior to treatment (3.6 vs. 25.7; per 1000 patient-months).

- Study of 7 patients who had liver biopsies published in Journal of Clinical Lipidology*. Findings suggest that in these patients during treatment with KYNAMRO measured liver fat is benign, simple steatosis without significant inflammation or fibrosis and therefore different and distinct from nonalcoholic steatohepatitis.

- Continuing advancement with FOCUS FH, a Phase 3 study in patients with Severe HeFH
  - Enrollment completed
  - FOCUS FH data planned mid 2015

ISIS-SMN$_{Rx}$

For Patients with Spinal Muscular Atrophy
SMA is a rare disease that affects approximately 30-35K children in United States, Europe and Japan

- Number one genetic cause of death in infants
- Caused by genetic defects in the SMN1 gene that result in a lack of functional SMN protein
- Characterized by progressive muscle atrophy and loss of motor function

Over half of all SMA patients are born with the most severe form of SMA (Type I)

- Very short life expectancy
- Unable to sit or stand

No currently approved therapies for SMA
Type I Spinal Muscular Atrophy

**Type I**
- Median time to death or permanent ventilation: 6.1* to 10.5** months
- Steady decline in muscle function over time
  - Mean rate of decline in CHOP INTEND is 1.27/yr**

Median Event-free Age Continues to Increase in Type I SMA Infants Treated with ISIS-SMN$_{RX}$

Phase 2 Open-label Study as of Sept 2, 2014 and as of April 17, 2015

*SMN2 copy number of 3; **SMN2 copy number not known; all other infants have SMN2 copy number of 2
In the 12 mg cohort, 12 of 15 infants achieved increases in CHOP INTEND scores.

A substantial number of SMA Infants (53%) achieved a CHOP INTEND Score of 40 or greater.

- Median baseline score* = 26.0

“A score of 40 on the CHOP INTEND is at the lower end of the range of normal for healthy infants 3 to 12 months of age, whereas it is very uncommon for an infant with Type I SMA to ever score above 40 points.” –Dr. Richard Finkel

*CHOP INTEND scores can range on a scale from 0 to 64
Summary of ISIS-SMN$_{Rx}$ Phase 2 Study in Infants with SMA

As of April 17, 2015

- Safety profile of ISIS-SMN$_{Rx}$ in infants with SMA supports continued development
- Totality and consistency of clinical data gives us encouragement about the performance of ISIS-SMN$_{Rx}$
- The median event-free age in infants treated with ISIS-SMN$_{Rx}$ continues to increase
  - In the 12 mg cohort, 73% of the infants (11 of 15) remain event-free and all of these infants are older than 15 months
  - In the 6 mg cohort, 50% of the infants (2 of 4) are event free and both infants are older than 27 months
- ISIS-SMN$_{Rx}$-treated SMA infants continue to demonstrate increases in motor function scores
  - CHOP INTEND: mean increase in the 12 mg cohort of 17 points at 15 months; 53% achieved score of 40 or greater
  - Motor milestones: nearly all ISIS-SMN$_{Rx}$-treated SMA infants achieved new motor milestones; five now sitting
- Clinical data are consistent with the mechanism by which ISIS-SMN$_{Rx}$ was designed to work
Type II / Type III Natural History

- Prospective studies show continued decline in motor function scores (HFMSE) in children with Type II / Type III SMA, mean change in HFMSE score at:
  - Year 1 = 0.15*
  - Year 2 = - 0.54**
  - Year 3 = - 1.71**

**Kaufmann et al. Neurology. 2012 October; 79(18) 1889-1897
Study Design for ISIS-SMN_Rx Phase 2 and OLE Studies in Children with SMA

**Phase 2 Study**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Total Dose</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg</td>
<td>9 mg</td>
<td>8</td>
</tr>
<tr>
<td>6 mg</td>
<td>18 mg</td>
<td>8</td>
</tr>
<tr>
<td>9 mg</td>
<td>18 mg</td>
<td>9</td>
</tr>
<tr>
<td>12 mg</td>
<td>36 mg</td>
<td>9</td>
</tr>
</tbody>
</table>

**Interval between studies:**
- 3 mg: ~13 months
- 6 mg: ~10 months
- 9 mg: ~10 months
- 12 mg: ~7 months

**OLE Study**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Total Dose</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mg</td>
<td>36 mg</td>
<td>9</td>
</tr>
</tbody>
</table>

**Post-Treatment f/u Period**
- 24 weeks

**Day 1 Dose**

**Day 169 Dose**

**Day 351 Dose**

**Day 533 Dose**

**Screening (≤28 days)**

**Day 29 f/u & Dose**

**Day 85 f/u & Dose**

**24 weeks**
Summary of ISIS-SMN$_{Rx}$ Phase 2/OLE Study in Children with SMA
As of May 15, 2015

- Safety profile of ISIS-SMN$_{Rx}$ in children with SMA supports continued development

- Continued and durable increases in measures of muscle function with 57% of children achieving a 3 point or greater change in HFMSE scores

- Increases in multiple measures of muscle function at Day 260
  - Mean increase of 3.8 points in HFMSE score (n=22)
    - In a subgroup analysis of children who had incoming HFMSE scores that met the inclusion criteria for the ongoing Phase 3 CHERISH study (≥10 and ≤54; n=17) mean increase in HFMSE score was 4.4 points
  - Mean 6MWT scores increased by 55 meters (n=11)
  - Mean ULM scores increased by 2.0 points (n=12)
Durable and Consistent Increases in Motor Function Scores (HFMSE) in Children with SMA
Open-label Extension Study After Nine Months Dosing with ISIS-SMN$_{Rx}$
As of May 15, 2015

Subgroup analysis of children with SMA with Phase 2 baseline score ≥10 and ≤54 (CHERISH Phase 3 study criteria)
Substantial Increases in Motor Function Score (6-Minute Walk Test) in Children with SMA
As of May 15, 2015

Mean 6MWT scores increased by 55 meters at Day 260 in all ambulant subjects
ISIS-SMN_\text{Rx} \text{ Phase 3 Program}

- **ENDEAR (Isis study): Infant Onset SMA Registration Trial**
  - First patient dosed in August 2014
  - Eligible patients may continue in open label extension
  - Data planned 2016/2017

- **CHERISH (Isis study): Childhood Onset SMA Registration Trial**
  - First patient dosed in November 2014
  - Eligible patients may continue in open label extension study
  - Data planned 2016/2017

- **NURTURE (Biogen study): Phase 2 study in pre-symptomatic newborns that are genetically predisposed to the disease**
  - Study is designed to enhance our understanding of early diagnosis and treatment

- **EMBRACE (Biogen study): Phase 2 study in patients with infantile or childhood-onset SMA**
  - Study is designed to bridge the gap in a small subset of patients that do not meet the age and inclusion criteria of ENDEAR and CHERISH studies
ISIS-TTR\textsubscript{Rx}

For Patients with
Transthyretin (TTR) Amyloidosis
ISIS-TTR\textsubscript{Rx}  
A Potential Treatment for TTR Amyloidosis

Unmet Medical Need  
Mutant TTR forms amyloid deposits in nerves, heart and other organs, resulting in poor quality of life and eventually death

Patient Population (World Wide)  
- Familial Amyloid Polyneuropathy \( \sim 10,000 \) (FAP)
- Familial Amyloid Cardiomyopathy \( \sim 40,000 \) (FAC)

Current Treatment Options  
- Treatments limited
- No treatments halt or reverse disease
- Liver transplant for early stage FAP (not FAC)
**ISIS-TTR_{Rx}**: Phase 3 Program Well Underway
Potentially First-In-Class & Best-In-Class

- Most advanced TTR RNA targeted therapeutic drug in development
  - First patient dosed early 2013
  - Open-label extension study initiated
- Once-weekly SC injections
  - Self administered at home
  - Low volume single injection
- Safety and tolerability profile continues to support Phase 3 development
Robust TTR Reductions in ISIS-TTR<sub>Rx</sub> Open-Label Extension Study
Analysis From First 13 Patients to Reach Three Months of Treatment*

- >90% participation in the Open Label Extension Study
- Blinded safety analysis of the ongoing Phase 3 study showed that ISRs occurred in ~1% of all injections

### Median Absolute TTR Levels (mg/dL)

<table>
<thead>
<tr>
<th>TTR (mg/dL)</th>
<th>Phase 3 Baseline</th>
<th>OLE Week 13</th>
</tr>
</thead>
</table>

### TTR % Reduction
ISIS-TTR<sub>Rx</sub> 300 mg (N=13)

- Median = 78%
- Up to = 92%

### 8 Different TTR Mutations
- Val30Met
- Asp38Ala
- Thr49Ala
- Thr60Ala
- Gly67Arg
- Lys70Asn
- Ser77Phe
- Ile84Ser

* Data presented at the American Academy of Neurology Annual Meeting, April 23, 2015
ISIS-TTR_{Rx} Program

- **In Progress**
  - Phase 3 FAP study – Data planned 1H 2017
  - Open-label extension for FAP
  - Investigator-initiated open-label study in patients with familial cardiomyopathy and senile systemic amyloidosis
    - Conducted by Dr. Merrill Benson, University of Indiana

- **Additional Studies**
  - GSK initiating a Phase 3 study in patients with TTR-related cardiomyopathy
  - GSK initiating a Phase 3 study in Japan in patients with FAP
Volanesorsen and ISIS-APOCIII-L<sub>Rx</sub>

For Patients with Familial Chylomicronemia Syndrome (FCS), Familial Partial Lipodystrophy (FPL) and Severely High Triglycerides
Familial Chylomicronemia Syndrome (FCS): Ultra-Orphan Disease Caused by Lipoprotein Lipase (LPL) Deficiency

- FCS is a rare lipid disorder (~3-5K patients worldwide) associated with extremely high levels of triglycerides, often >2,000 mg/dL

- FCS is caused by genetic defects in genes known to modulate LPL activity, including LPL, apoCII, GPIHBP1, ApoA5 and LMF1

- Patients with FCS are at extreme risk for acute pancreatitis events and other serious conditions

- Limited treatment options for patients with FCS

  - Glybera® – approved in EU for patients with LPL deficiency

-Lindsey
Familial Partial Lipodystrophy (FPL)
A Second Ultra-orphan Indication for Volanesorsen

- FPL is a rare lipid disorder (~3-5K patients) characterized by elevated levels of ApoC-III and triglycerides
  - FPL is distinct from generalized lipodystrophy, which is a disease primarily driven by inadequate leptin activity
- Patients with FPL exhibit:
  - Loss of fat from extremities, trunk and gluteal region with excess fat deposits around neck and face
  - Extremely high levels of serum triglycerides and ApoC-III
  - Increased risk for pancreatitis and early atherosclerosis
  - Severe insulin resistance/diabetes
  - Accumulation of fat in liver can cause scarring and cirrhosis, and eventually, liver dysfunction
  - Early cardiovascular events & other co-morbidities
- No approved treatments for patients with FPL
  - Conventional drugs to reduce triglycerides and control glucose do not work well in FPL patients
Targeting APOC3 in the Familial Chylomicronemia Syndrome

Daniel Gaudet, M.D., Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D., Veronica J. Alexander, Ph.D., Walter Singleton, M.D., Steven G. Hughes, M.B., B.S., Richard S. Geary, Ph.D., Brenda F. Baker, Ph.D., Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D., and Joseph L. Witztum, M.D.

The graphs illustrate the changes in APOC3 and triglyceride levels over time for three patients (Patient 1, Patient 2, and Patient 3) during the treatment period. The x-axis represents study days, and the y-axis shows the levels of APOC3 (mg/dL) and triglycerides (mg/dL). The treatment period is highlighted in the graphs.
Volanesorsen Phase 2 Program
Robust TG Lowering in Multiple Patient Populations,
As Monotherapy and in Combination with Fibrates

**Triglyceride Reductions**
Mean % Decrease from Baseline

- **MONOTHERAPY**
  - TG
  - -71%

- **ADD-ON TO FIBRATE**
  - TG
  - -64%

- **HIGH TG WITH T2D**
  - TG
  - -69%

- **FCS**
  - TG
  - -69%
Volanesorsen: Potential for Additional Profile Benefits
Improved Glucose Control By Multiple Measures

HbA1c Analysis in Diabetic Patients

- Decreased HbA1c
  - 1.22 percentage-point decrease (Pbo-adjusted)
- Improved Insulin Sensitivity
- Decreased:
  - Glycated Albumin
  - Fasting Fructosamine

Euglycemic Clamp
A Measure of Tissue Insulin Sensitivity
ISIS-APOCIII-L_{Rx}: Follow-on to Volanesorsen

- ISIS-APOCIII-L_{Rx} incorporates our LICA technology
  - Up to 10-fold increase in potency
  - Possibility for monthly dosing – enhance patient convenience
- Enhanced profile for broader utility in patients with severely high triglycerides and patients with high triglycerides and type 2 diabetes
- Extends ApoC-III product life cycle
- Phase 1 study initiation planned 1H 2016
Staged Development Plan for Volanesorsen & LICA Follow-on
Maximizes Short, Mid, Long Term Value Creation

Volanesorsen
ISIS-APOCIII-LRX

PRICING per year
$100K's
$10K's

Highest unmet need
Increasing market size

No CV Event Outcome Study Expected to be Required

CV Risk and Patients w/High TG w/Type 2 Diabetes
Severely High TG >880 mg/dL
Severely High TG >500 mg/dL
Volanesorsen: Phase 3 Program

FCS

- Phase 3 Study in Patients with FCS
- Initiated August 2014
- 52-week study designed to evaluate the efficacy and safety of 300 mg volanesorsen in patients diagnosed with FCS
- Data planned late 2016/early 2017

FPL

- Phase 3 study initiation planned mid-2015
- Data planned late 2016/early 2017
Toward a More Effective, Safer Antithrombotic for Patients at High Risk for Thrombosis
Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

Harry R. Büller, M.D., Claudette Bethune, Ph.D., Sanjay Bhanot, M.D., Ph.D., David Gailani, M.D., Brett P. Monia, Ph.D., Gary E. Raskob, Ph.D., Annelise Segers, M.D., Peter Verhamme, M.D., and Jeffrey I. Weitz, M.D., for the FXI-ASO TKA Investigators

- Seven-fold lower incidence of VTE in patients treated with 300 mg ISIS-FXI$_{Rx}$ compared with enoxaparin-treated patients (4% vs. 30%)
- Demonstrates for the first time a clear dissociation between thrombosis and bleeding
Results From ISIS-FXIRx Phase 2 Study – Lowest Reported VTE Incidence and 7-fold Reduction vs. Enoxaparin

<table>
<thead>
<tr>
<th>Drug</th>
<th>ISIS-FXIRx (Phase 2)</th>
<th>enoxaparin*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>300mg sub-q weekly</td>
<td>40mg sub-q daily</td>
</tr>
<tr>
<td><strong>Rates of VTE and all cause death</strong></td>
<td>4.2%</td>
<td>30.4%</td>
</tr>
<tr>
<td><strong>Fold reduction in rates of all VTE and all cause death vs. enoxaparin</strong></td>
<td>7.0</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Rates of Major/CRNM bleeding</strong></td>
<td>2.6%‡</td>
<td>8.3%‡</td>
</tr>
<tr>
<td><strong>Fold reduction in Major/CRNM bleeding vs. enoxaparin</strong></td>
<td>2.7‡</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Enoxaparin results in ISIS-FXIRx Phase 2 study were consistent with previously published data for enoxaparin in this population

‡Safety set for time period from first study drug administration to end of study
Strengthening Isis Leadership

Strengthening management
Sarah Boyce, CBO Isis

Strengthening management
Paula Sotropoulos, CEO
Akcea Therapeutics
Sarah Boyce – Isis Chief Business Officer
Adds Strategic Business and Commercial Expertise to Isis

- Senior business leader who led global commercialization activities
  - Novartis
  - Alexion
  - Forest Laboratories

- As a member of Isis’ senior management team, provides strategic leadership to all business activities
  - Lead Isis’ corporate development and patient advocacy groups
  - Oversee Isis’ broad alliance activities
  - Provide valuable commercial expertise to Isis’ research and development activities
Akcea Therapeutics
Transformative Medicines for Cardiometabolic Lipid Disorders

A development and commercialization company

Focused on delivering transformative medicines for patients with serious cardiometabolic lipid disorders

Near term global commercial opportunity with volanesorsen
## Akcea’s Pipeline
Advancing Medicines for Cardiometabolic Lipid Disorders

<table>
<thead>
<tr>
<th>Target Franchise (Genetically Validated Targets)</th>
<th>Lipid Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rare Diseases</td>
</tr>
<tr>
<td><strong>APOCIII</strong></td>
<td>Familial Chylomicronemia Syndrome – Phase 3</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td>Familial Partial Lipodystrophy – Phase 3</td>
</tr>
<tr>
<td><strong>APO(a)</strong></td>
<td>Recurrent CVD with High Lp(a) – Phase 2</td>
</tr>
<tr>
<td><strong>Lp(a)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ANGPTL3</strong></td>
<td>Mixed Dyslipidemias</td>
</tr>
</tbody>
</table>
Building an Experienced Leadership Team
Rare Disease, Lipid and Cardiovascular Focus

Paula Soteropoulos, President & CEO
- 25+ years in Biotech/Pharma/Life Sciences
- Moderna SVP, Rare Diseases, Cardiometabolic and Strategic Alliances; Genzyme GM, Cardiovascular
- Led global development, commercialization, manufacturing ops, strategic alliances, business dvpt
- Rare disease, cardiovascular, oncology, infectious disease, renal

Jeff Goldberg, COO
- 20+ years in Biotech/Pharma/Life Sciences
- Proteostasis, Sanofi, Genzyme
- Led program management, brand leadership, business development & business operations, product launch & commercialization
- Rare disease, neurology, oncology, renal

Molly Harper, VP, Commercial Development
- 15+ years in Biotech/Pharma/Life Sciences
- Genzyme, Merck, UBS Warburg
- Led global marketing, sales; US Commercial Endocrine business
- Rare disease, lipids, atherosclerosis, CV, endocrine

Andres DiGenio, MD, PhD
VP, Clinical Development
- Board certified physician/extensive clinical practice
- 15 years in Biotech/Pharma Industry
- Isis, Sanofi, Pfizer, Vanderbilt Cardiovascular Dept
- Clinical development, medical affairs, IND to filing
- Cardiovascular, metabolic/endocrine, rare disease

Jonathan Guerriero, Clinical Operations
- 15+ years in Biotech/Pharma/Life Sciences
- Synageva, Radius Health, EMD Serono,
- Program & Operations Leader from Early Stage (Pre-IND) to Late stage (Phase 3, BLA filing)
- Rare disease, neurology, women’s health, osteoporosis

Alan Gilstrap, Patient Advocacy & Policy
- 24 years in Biotech/Pharma/Life Sciences
- Genzyme, Abbott, Glaxo, Syntex
- Led Patient Advocacy, Sales & marketing, Field sales leadership, Sales training
- Rare disease, lipids and cardiovascular, endocrine
Antisense Technology: The Future

Continue to Advance the Technology
New Mechanisms to Increase Protein Synthesis

Recent Progress Suggests:

- Many, if not most, mRNAs regulate their own translation
- Sequence and structural motifs throughout mRNAs appear to play key roles in regulating translation
- Several new mechanisms identified to enhance protein production
- More than 80% of cellular proteins may be increased specifically using these mechanisms
- Preliminary SAR (structure activity relationship) defined
Isis Antisense Drug Technology
A Proven Drug Discovery Platform

Validated
3 commercialized RNA-targeted drugs

Efficient
1 drug per 11 Isis employees

Broadly Applicable
Clinical activity in multiple tissues

Versatile
Multiple mechanisms, multiple routes of delivery

Mature
Large pipeline of drugs represents major advances in potential treatment of multiple diseases

Advancing
More potent, better tolerated drugs
- Additional mechanisms
- Additional routes of administration
- Broader utility
2015 Objectives – On Track

- Continue to successfully execute business strategy to generate revenue and cash
- Advance the pipeline
- Broaden pipeline by adding new drugs in both partnered and unpartnered programs
- Advance the technology
Isis’ Broad and Deep Pipeline Creates a Continuous Stream of News

Planned Data Releases

- ISIS-APO(a)Rx – P2 in High Lp(a)
- ISIS-DMPK-2.5Rx – P2 in DM1
  - Custirsen – P3 in prostate cancer
  - RG-101 – P2 in HCV

Planned Study Initiations

2015

- ISIS-APO(a)-LRx – P1
- RG-012 – P1
- ISIS-FGFR4Rx – P2 in obesity
  - RG-101 Phase 2 combo and as a single agent in HCV
  - ISIS-HBVRx – P2 in hepatitis B
  - ISIS-PKKRx – P2 in HAE
  - ISIS-FXIRx – P2 in AF pts with ESRD
  - Volanesorsen – P3 in familial partial lipodystrophy
  - ISIS-GCGRRx – P2 dose optimization
  - ISIS-HTTRx – P1/2 in HD
  - ISIS-DGAT2Rx – P1
  - ISIS-BIIB3Rx – P1
  - ISIS-GSK4-LRx – P1

2016

- ISIS-PTP1BRx – P2 in T2D
- ISIS-PKKRx – P1
- RG-101 – P2 in HCV
  - ISIS-ANGPTL3Rx – P1
  - ISIS-TTRRx – OLE in FAP
  - ISIS-STAT3-2.5Rx (AZD9150) – P2 in lymphoma
  - ISIS-SMNRx – P2 in SMA
  - ISIS-GCCRRx – P2 in T2D
  - KYNAMRO – FOCUS FH
  - ISIS-AR-2.5Rx (AZD5312) – P1/2 in prostate cancer
Isis 2015 Guidance
On Track to Improve Upon 2015 Guidance

- Pro Forma NOL: Mid $50M range
- Cash: Year-end cash of >$630M
- We are on track to significantly improve upon 2015 guidance

UPDATE 2015 FINANCIAL GUIDANCE MID-YEAR
Isis Pharmaceuticals: The Leader in RNA-targeted Drug Discovery and Development

COMMERCIAL OPPORTUNITIES
Potential for multiple near-term commercial opportunities in lipid and severe and rare diseases

EXPANDING PIPELINE
Broad, mature pipeline of 38 potential first-in-class or best-in-class drugs that will continue to grow

UNIQUE BUSINESS STRATEGY MAXIMIZES VALUE
Broad successes in partnered programs, newly formed development and commercial subsidiary (Akcea), and satellite companies

ADVANCING TECHNOLOGY
Advances in antisense technology improve performance and breadth of utility of our drugs: more potent, better tolerated, enhanced distribution, multiple mechanisms of action

FINANCIAL GROWTH
Unique business strategy coupled to efficiencies of antisense technology enables potential for long-term financial success