Agenda

- Welcome
- Corporate Update
- Poster Session
Welcome Isis’ Board of Directors

Spencer Berthelsen, MD, FACP
Skip Klein
Fred Muto, Esq
Lynne Parshall, Esq
John Reed, MD, PhD
Joe Wender
Isis’ Corporate Strategy

- Innovation
- Technology Platform
- Unique Business Strategy
- Revolutionizing Drug Discovery
- Novel Drugs
We know that sick people depend on us & we are responsible for helping to create a future for them…
Antisense Platform Technology Advantages

Only Direct Route from Genes to Drugs

Efficient Discovery & Early Development

Investment Amortized Across the Entire Pipeline

Generate an Evergreen Pipeline

- Uniquely specific & broadly applicable
- Dramatically reduced cost & increased success in R&D
- Chemistry, manufacturing, formulation, analytical methods
- Robust, diversified pipeline adding 3-5 new drugs per year

Investment Amortized Across the Entire Pipeline

Chemistry, manufacturing, formulation, analytical methods

Generate an Evergreen Pipeline

Robust, diversified pipeline adding 3-5 new drugs per year
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*About half the drugs in our pipeline are partnered and are already generating value*
Isis’ Pipeline – June 2012

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<tr>
<th>Pipeline Key</th>
<th>Indication</th>
<th>Drugs</th>
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We expect similar value creation and success with the other half of the pipeline.
Isis’ Unique Business Strategy

Key Principles

- Create a New Platform for Drug Discovery
  - Antisense Technology Works
  - Continuing advances enhance performance & prolong proprietary control
- Control Technology & Products Through Continued Innovation & Patents
  - Over 1,500 Patents
- Use the Efficiency of the Antisense Platform to Create Broad & Expanding Pipeline
  - 25 drugs in development
- Small Innovation Focused Organization Supporting a Diverse Pipeline
  - Fewer than 350 people → Manageable cost structure
- Employ a Unique Business Strategy
  - Partnership strategy maximizes long-term return & minimizes risk
  - Sustained financial strength
  - Simplified organization
  - Sustained innovation
Types of transactions to take advantage of financial strength

- Preferred Partner/Option Transactions
- Semi-captive marketing and selling company possible for selected franchises
- “Distributorships” at registration
- Geographic transactions
- Late-stage partnerships

Potentially consider a few “strategic partnerships” based on the option model

*The Right Transaction with the Right Partner for Each Drug*
Recent Highlights

- **KYNAMRO™ (Mipomersen):** Significant Commercial Opportunity
  - EU & US filings for initial indications
  - Investing in the future – FOCUS FH study underway

- Positive Clinical Data from 8 Programs
  - ISIS-TTR\textsubscript{Rx} – Transthyretin Amyloidosis
  - ISIS-APOCIII\textsubscript{Rx} – Severe High Triglycerides
  - ISIS-FXI\textsubscript{Rx} – Anti-thrombotic

- Successful Partnerships
  - GSK success milestones
  - Pfizer acquisition of Excaliard
  - Biogen Severe & Rare Disease
KYNAMRO™ (mipomersen sodium)

Treatment of Severely High Cholesterol
KYNAMRO™ Highlights

- KYNAMRO ( mipomersen sodium ) : Significant Commercial Opportunity
  - EU filing for hoFH & severe heFH accepted
  - United States NDA filing for hoFH accepted
  - Preparing for commercial launch

Investing in the future - FOCUS FH study underway
KYNAMRO (Mipomersen): Near-Term Commercial Opportunities
Focusing on the Initial Approvals

1st US Filing
hoFH

1st EU Filing
hoFH & Severe heFH

Genzyme estimate: 40,000 severe and hoFH patients U.S. and EU
KYNAMRO targets & reduces production of all atherogenic, ApoB containing lipoprotein particles.

KYNAMRO has beneficial impact on all measured key atherogenic lipids linked to cardiovascular disease, such as:

- ✔ ApoB
- ✔ Lp(a)
- ✔ Triglycerides
- ✔ VLDL
- ✔ No reduction of HDL
KYNAMRO (Mipomersen)
Novel Treatment for High-Risk Patients with Severely High Cholesterol

- **KYNAMRO**
  - Important first-in-class product opportunity
    - Significant initial commercial opportunity in patients at high risk of CV death
    - Long-term growth potential
  - Four positive placebo-controlled Phase 3 studies
    - All primary, secondary & tertiary endpoints met
    - ~800 drug treated subjects in initial filing; >100 patients treated over 1 year
  - Robust efficacy combined with emerging safety profile supports focus on planned patient populations
KYNAMRO (mipomersen) Value Proposition
Staged Development Strategy Supports Potential Market (Revenue) Expansion

- U.S. launch HoFH
- EU launch HoFH + Severe HeFH
- Potential U.S. launch Severe HeFH
- Potential ROW launch Severe HeFH
- Potential EU launch HeFH
- Potential 3x Week Dose Regimen Available
Isis Value Proposition 2012

- Significant initial commercial opportunity plus continued revenue growth from KYNAMRO ( mipomersen) staged development/commercialization
- Substantial commercial opportunities with multiple potential product launches in the next 5 years:
  - Additional product opportunities from expanding and maturing pipeline in the years following
- Considerable licensing prospects with Phase 2 efficacy data in 2013/2014
- Satellite company strategy may expand opportunities with limited investment and risk
- Advances in antisense technology
Substantial Commercial Opportunities & Potential Launches
Value Proposition Beyond KYNAMRO (mipomersen sodium)

- Potential U.S. launch HoFH
- Potential ROW launch Severe HeFH
- Potential EU launch HeFH + Severe HeFH
- Potential 3x Week Dose Regimen Available
- Potential EU Launch HeFH
- Potential U.S. launch
- Potential ROW launch
- Potential EU launch
- Potential 3x Week Dose Regimen Available
- ISIS-APOCIII
- ISIS-TTR
- ISIS-SMN
- EXC 001
- OGX-011

Timeline:
- 2012
- 2013
- 2014
- 2015
- 2016
- 2017
ISIS-TTR\textsubscript{Rx}

Treatment of TTR Amyloidosis
# Transthyretin (TTR) Amyloidosis

A Fatal Genetic Disease Affecting ~50K Patients Worldwide

## Forms of TTR Hereditary Amyloidosis

<table>
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<tr>
<th>Disease Manifestation</th>
<th>Familial Amyloid Polyneuropathy (FAP)</th>
<th>Familial Amyloid Cardiomyopathy (FAC)</th>
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<td>Target organ</td>
<td>Degeneration of peripheral nerves</td>
<td>Loss of cardiac function</td>
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<td>Peripheral nerves</td>
<td>Heart tissue</td>
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<td>▪ TTR amyloid deposits leads to loss of sensory, autonomic &amp; motor nerve function</td>
<td>▪ TTR amyloid deposits restricts heart function</td>
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<td>Cause of death</td>
<td>Wasting</td>
<td>Heart failure</td>
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<td>Patients worldwide</td>
<td>~10,000</td>
<td>~40,000</td>
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<td>Age on onset</td>
<td>30-50 years</td>
<td>60-70 years</td>
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<tr>
<td>Life expectancy after diagnosis</td>
<td>9-11 years</td>
<td>5-6 years</td>
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</table>
Transthyretin Amyloidosis
Caused by Mutations in the Transthyretin Gene

- Transthyretin (TTR) is produced mainly by the liver
  - Mutations typically resulting in single amino acid substitutions
  - TTR mutations cause the TTR protein to be unstable, causing the tetrameric TTR protein to disassociate into monomeric subunits
  - TTR monomers accumulate in peripheral nerves, heart & other organs as amyloid deposits, causing cell death

Limited Available Current Treatments
Transthyretin Amyloidosis

Drug Mechanisms

- No current drugs available to inhibit aggregation
Limited Available Current Treatments
Transthyretin Amyloidosis

- Tafamidis recently approved in Europe for early stage FAP
  - Protein folding stabilizer
  - Not approved for more severe forms of FAP
  - Not tested in FAC (cardiomyopathy)
**ISIS-TTR$_{RX}$**

Potential to Treat All Forms & Stages of TTR Amyloidosis

- Prevents the production of the TTR protein
- Reduces all known mutations of TTR
- Prevents accumulation of TTR in nerves, heart, & elsewhere
- Potential to reverse pre-existing disease

Drug Mechanisms

- **Expression**
- **Tetramer dissociation**
- **Aggregation**

- Mutated TTR gene
- Mutated TTR protein in plasma
- Amyloidogenic intermediates
- Insoluble fibril deposits (e.g., nerves, heart)

**ISIS-TTR$_{RX}$** Prevents Synthesis

Partnered with: GlaxoSmithKline
ISIS-TTR$_{Rx}$: Phase 1 Normal Volunteers
Dose-Dependent Prolonged Reduction in Serum TTR Levels

Safety Summary

- No SAEs
- No significant AEs
  - Low incidence of FLS & mild ISRs
- No clinically significant changes in lab chemistries
  - No liver enzyme elevations >3X ULN
ISIS-TTR\textsubscript{Rx} Next Steps

- Phase 3 study for ISIS-TTR\textsubscript{Rx} to start in 2012
- 12-month dosing in FAP patients
- NIS (neurological improvement score) as an endpoint

Future expansion of program into additional patient populations
- Cardiomyopathy (FAC)

**Development Candidate**
Phase 1 Study
Phase 3 Study
Open Label Extension
Licensing Decision
File NDA/MAA
NDA/MAA Approval/Launch

License Fee
M/S Payments

Complete
In Progress
Upcoming
Treatment of Patients with Severe High Triglycerides
Hypertriglyceridemia
A Significant & Identifiable Patient Population

- High Triglycerides:
  A Growing Worldwide Epidemic
  - Increased incidence of CVD, NASH & insulin resistance in Eastern Indian males due to elevated levels of ApoC-III
Hypertriglyceridemia
A Significant & Identifiable Patient Population

- High Triglycerides: A Growing Worldwide Epidemic
  - Increased incidence of CVD, NASH & insulin resistance in Eastern Indian males due to elevated levels of ApoC-III
  - ~3 M in US & Europe with triglycerides over 500 mg/dL
  - >200 K in US & Europe with triglycerides of >1,000 mg/dL
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- Treatment Options are Limited & Insufficient
  - Niacin
  - Fibrates
  - Fish oil

Isis estimate based on Atherosclerosis. 2009 Dec;207(2):573-8. Epub 2009 May 27,
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ISIS-APOCIII$_{Rx}$
The Role of ApoC-III in Regulating Lipids

$\Leftarrow = \text{Triglyceride}$
The Role of ApoC-III in Regulating Lipids

Liver

Blood Vessel

VLDL

VLDL → IDL → LDL

Triglyceride
The Role of ApoC-III in Regulating Lipids

Liver
- VLDL

Blood Vessel
- VLDL → IDL → LDL

Energy Use
- Skeletal Muscle
- Adipose
- Myocardium

< = Triglyceride
ISIS-APOCIII<sub>Rx</sub>

The Role of ApoC-III in Regulating Lipids

Liver

Blood Vessel

VLDDL

VLDDL → IDL → LDL

= Triglyceride

Skeletal Muscle

Adipose

Myocardium

Energy Use

LDL Clearance
The Role of ApoC-III in Regulating Lipids

Liver

**VLDL**

Blood Vessel

**VLDL** ➔ **IDL** ➔ **LDL**

Lipase

**= Triglyceride**

Energy Use

- Skeletal Muscle
- Adipose
- Myocardium

LDL Clearance

- Liver
ISIS-APOCIII<sub>Rx</sub>
The Role of ApoC-III in Regulating Lipids
ISIS-APOCIII<sub>Rx</sub>
The Role of ApoC-III in Regulating Lipids
ISIS-APOCIII\textsubscript{Rx}
The Role of ApoC-III in Regulating Lipids & the Effects of ISIS-ApoCIII\textsubscript{Rx}

\( \Leftrightarrow \) = Triglyceride

Liver

Blood Vessel

VLDL

Lipase

IDL

LDL

Skeletal Muscle

Adipose

Myocardium

Energy Use

LDL Clearance
ISIS-APOCIII$_{\text{Rx}}$ Phase I in Healthy Volunteers

Dose-Dependent Reduction in ApoCIII

*2 of 3 subjects below limit of detection*
**ISIS-APOCIII Rx Phase 1 in Healthy Volunteers**

**Dose-Dependent Reduction in Fasting & Diet-Induced Triglycerides**

---

**Fasting TGs increase due to high-fat diet**

---

**Safety Summary**

- No SAEs
- No significant AEs
  - Low incidence & mild injection site reactions
  - No flu-like symptoms
- No significant changes in lab chemistries
  - No liver enzyme elevations
ISIS-APOCIII<sub>Rx</sub>
Staged Development Plan Facilitates A Rapid Path to Market

- Phase 2 initiated March 2012
  - ~100 patients dosing for 13 weeks, measuring ApoCIII and TG, as monotherapy and in combination with fibrates
  - Data expected in 2013
- Potential launch in 2016 (filing in 2015)
  - Triglycerides >1,000 mg/dL
ISIS-SMN$_{\text{Rx}}$

Treatment of Spinal Muscular Atrophy
SMA: A Severe & Fatal Disease
Severe Genetic Neuromuscular Disease

- Leading genetic cause of infant mortality
- Well-defined patient population: 30–35K in US/EU/Japan
- Characterized by muscle atrophy & loss/lack of motor function
- Caused by lack of functional SMN protein due to genetic defects in the SMN1 gene

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<thead>
<tr>
<th>SMA Type</th>
<th>Number of SMN2 Copies</th>
<th>Age of Onset/Functional Milestone Achievement</th>
<th>Estimated Incidence</th>
<th>Estimated Prevalence</th>
<th>Life Expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>1-2</td>
<td>Onset within first 6 months/ Never sit, rapid progression</td>
<td>60%</td>
<td>14%</td>
<td>&lt;2 years</td>
</tr>
<tr>
<td>Type II</td>
<td>2-3</td>
<td>Onset 6-18 months of age/ Sit, but never walk</td>
<td>27%</td>
<td>51%</td>
<td>2&lt;30 years</td>
</tr>
<tr>
<td>Type III</td>
<td>3-5</td>
<td>Onset &gt;18 months of age/ Walk, but with difficulty</td>
<td>12%</td>
<td>35%</td>
<td>Normal</td>
</tr>
<tr>
<td>Type IV</td>
<td>4-6</td>
<td>Onset ≥ 19 years of age Increasing disabilities after onset</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>Normal</td>
</tr>
</tbody>
</table>
ISIS-SMNRx is the 1st drug to treat splicing disorders to enter Isis’ pipeline

- Increases production of functional SMN protein from the dormant SMN2 gene
ISIS-SMNRx
Increases Survival & Muscle Function in a Severe SMA Mouse Model
Rapid Development Path to Market

- Granted Orphan Drug Status in US and EU & Fast Track Status in US
- Currently in Phase 1 with data expected in 2012
- Phase 2 to begin in 2012
- Phase 3
  - ~45 patients in the infant onset study, measuring time to death or >16 hours ventilation
  - ~120 patients in the childhood onset study, measuring SMA Motor Function Testing Score
- Potential filing in 2016-2017, Launch in 2017-2018

Phase 1 Single Dose Study
Phase 2 Multiple Dose Study
Phase 3 Study Infantile-Onset
Phase 3 Study Childhood-Onset
File NDA/MAA
NDA/MAA Approval/Launch

Partnered with:

- License Fee
- Regulatory M/S Payment
Potential value of nearly $300 M plus royalties
- $29 M upfront payment
- $45 M in pre license milestones for clinical trials

Potential to earn additional milestones and royalties post licensing
- $225 M in milestone payments and licensing fee

Isis controls the Phase 3 studies, Biogen has option to license the drug through the completion of the studies
  - Significant regulatory and sales milestone payments
  - Double-Digit Royalties on sales
Treatment of Scarring
Scarring
A Major Commercial Opportunity

- Unsatisfactory skin scarring following a variety of surgical procedures represents a large unmet need
  - >6 M cosmetic & reconstructive procedures performed in the US each year
  - No approved drugs to prevent or treat patients who scar badly
- EXC 001 has the potential to:
  - Reduce risk of disfiguring scar from elective surgery, including cosmetic procedures
  - Enhance scar appearance following scar revision surgery
- Market opportunity estimated to be > $4 B
EXC 001
A Unique Approach to Improve Scar Appearance

- Normal wound healing process goes through well-defined and identified pathways
- Hypertrophic/keloid scarring results when overproduction of collagen in the wound
- EXC 001 reduces the production of Connective Tissue Growth Factor (CTGF)
  - CTGF regulates collagen production in areas of fibrosis, such as scarring
  - Reducing CTGF will decrease fibrosis and lead to improved scarring outcome
Positive Excaliardi Data from 3 Phase 2 Studies of EXC 001
Significant Improvements in Scarring in All Studies

Accelerated Resolution of Fine Line Scarring

Significant Improvements in Scars After Revision Surgery

Placebo  EXC 001 treated

Placebo  EXC 001 TX

Placebo  EXC 001 treated

2 Doses - Week 8

4 Doses - Week 12

4 Doses - Week 24
EXC 001
An All Upside Opportunity With Virtually No Isis Investment

- Development Plan
  - 3 successful Phase 2 studies completed
    - Phase 2b dose ranging study for scar revision in progress
  - Pfizer to conduct additional studies to support registration with potential launch in 2017 timeframe
    - Initial indication for the prevention of the formation or reduction of incidence of hypertrophic scars in patients exhibiting or at high risk for forming these scars

- Isis Commercial Opportunity
  - Nearly $50M in milestone payments
  - Mid-single digit royalties on sales
OGX-011

Treatment for Cancer
OGX-011
Potential Significant Near-Term Commercial Opportunity

- Clusterin expression has been linked to faster rates of cancer progression and shorter survival duration
  - Fast Track designation for the treatment of CRPC in combination with docetaxel for second-line therapy
- OGX-011 is designed to be used in patients who have developed resistance to chemotherapy with few therapeutic options

**Survival benefit = 6.9 months**

Chi et al, ASCO, 2009
OGX-011
Potential Significant Near-Term Commercial Opportunity

- Development Plan
  - Encouraging Phase 2 Data in patients with prostate cancer
  - Phase 3 program for patients with metastatic prostate cancer
    - First-line therapy study under way in patients with metastatic prostate cancer
      - Data expected late 2013
    - Second-line therapy study planned to begin in 2012
    - Finalizing study design for Phase 3 in non-small cell lung cancer to start this year
  - Potential near-term commercial opportunity
    - First filing expected in prostate cancer with additional indications possible

- Isis Commercial Opportunity
  - Teva licensed OGX-011 from OncoGenex in Dec 2009
    - Teva resources ensure robust development plan and commercial success in which Isis participates
  - Isis earned a $10M sublicensing fee, eligible for 30% of milestones (up to $370M) and up to a 7% royalty
Near-Term Licensing Opportunities
### Significant New Partnership Opportunities

**Potentially Robust Phase 2 Data Packages**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Planned Timing for Efficacy Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-FXI_Rx</td>
<td>Thrombosis</td>
<td>2013</td>
</tr>
<tr>
<td>ISIS-CRP_Rx</td>
<td>Multiple (AF, RA &amp; ACS)</td>
<td>2013</td>
</tr>
<tr>
<td>ISIS-APOCIII_Rx</td>
<td>High Triglycerides</td>
<td>2013</td>
</tr>
<tr>
<td>ISIS-EIF4E_Rx</td>
<td>Cancer</td>
<td>2013</td>
</tr>
<tr>
<td>ISIS-GCCR_Rx</td>
<td>T2DM</td>
<td>2014</td>
</tr>
<tr>
<td>ISIS-GCGR_Rx</td>
<td>T2DM</td>
<td>2014</td>
</tr>
<tr>
<td>ISIS-PTP1B_Rx</td>
<td>T2DM</td>
<td>2014</td>
</tr>
</tbody>
</table>
Anticoagulant
Treatment Paradigm in Arterial & Venous Thrombosis
Therapy with Anticoagulant and/or Antiplatelet Agents

Acute Coronary Syndrome, stent thrombosis
(dual antiplatelet therapy-DAPT)

ISIS-FXI_{RX} is expected to be effective broadly in both arterial and venous thrombosis in combination with both anti-platelet and anti-coagulation agents
Selective Reduction of Individual Clotting Factors Produced

*Analysis in murine liver samples

Selectively reducing individual clotting factors supports selection of the best targets
ISIS-FXI<sub>Rx</sub> demonstrated potent antithrombotic activity with no increase in bleeding compared with standard anti-clotting agents, including low-molecular weight heparin, warfarin and Factor Xa inhibitors, which all increased bleeding.
ISIS-FXIRx Phase 1 in Healthy Volunteers
Robust, Sustained & Dose-Dependent Reduction in FXI Activity

Safety Summary
- No SAEs
- No significant AEs
  - Low incidence & mild injection site reactions
  - No flu-like symptoms
- No significant changes in lab chemistries
  - No clinically significant liver enzyme elevations
The value inflection point should be significant upon achieving a robust clinical data package in mid-2013.

If the studies are successful, a compelling data package to present to potential licensing partners will include:

- Phase 2: Up to 400 patients in TKA, to begin in 2012 and if successful will...
  
  - Demonstrate reduced thrombosis equal to or better than enoxaparin and reduced bleeding following knee surgery.

---

**Phase 1 Study**

*PD/DDI*

**Phase 2 Study - TKA**

* Licensing Decision
ISIS-CRP\textsubscript{Rx}

Therapeutic Potential in Multiple Inflammatory Diseases
Targeting C-Reactive Protein (CRP)
Elevated CRP Correlates with Increased Disease Burden

- CRP is elevated in many inflammatory diseases and diseases with inflammatory components, such as
  - Acute Coronary Syndrome
  - Atrial Fibrillation
  - Ulcerative Colitis/Crohn’s Disease
  - Chronic Kidney Disease (CKD)
  - End Stage Renal Disease (ESRD)
  - Organ Transplant

- Elevated CRP levels are associated with increased disease burden

- CRP is a complex glycoprotein, making it difficult to specifically target with small molecule drugs

- Large commercial opportunity
  - Potential broad applications in a number of diseases exacerbated by inflammation
  - Market for inflammatory disease estimated to be > $20B

- Significant partnering opportunity at POC
ISIS-CRP<sub>Rx</sub>
The First Selective CRP Lowering Drug in Man

- Phase 1 clinical study complete
  - ISIS-CRP<sub>Rx</sub> produced statistically significant reductions in CRP
    - Subjects with elevated CRP levels had a median reduction of >70% compared to baseline
  - ISIS-CRP<sub>Rx</sub> was well tolerated at doses up to 600 mg/week

**ISIS-CRP<sub>Rx</sub> Lowers CRP in Healthy Volunteers**

**Median Reduction of >70% Compared to Baseline**

![Graph showing CRP levels over time for ISIS-CRP<sub>Rx</sub> and Placebo](image)
Development Plan
Designed to Produce Compelling Proof of Concept Data

- Phase 2 Study in ~ 50 Patients with Rheumatoid Arthritis
  - Study designed to demonstrate benefit of lowering CRP in patients with chronically elevated CRP levels

- Endotoxin Challenge Study, ~30 Healthy Volunteers
  - Study designed to demonstrate that ISIS-CRP\textsubscript{Rx} can blunt acute CRP and other key inflammatory proteins such as TNF-\(\alpha\), IL-1\(\beta\), IL-6

- Phase 2 Study in ~ 20 Patients with Atrial Fibrillation
  - Study designed to demonstrate CRP reduction has a positive effect on the duration and frequency of atrial fibrillation events
Isis’ Pipeline

A Large Exciting & Maturing Pipeline
### Isis’ Cardiovascular Franchise

#### Multiple Approaches to Cardiovascular Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KYNAMRO™</strong>&lt;br&gt;High Cholesterol apoB</td>
<td>Novel First-in-class Lipid Lowering Drug&lt;br&gt;Lowers LDL-C plus All Atherogenic Lipids&lt;br&gt;Launch Planned for 2012</td>
<td>Data 2012</td>
<td>Ph2 2012</td>
<td>Ph3 2013</td>
</tr>
<tr>
<td><strong>ISIS-CRP&lt;sub&gt;Rx&lt;/sub&gt;</strong>&lt;br&gt;CAD/Inflammation/Renal CRP</td>
<td>Indicated in Wide Variety of Diseases&lt;br&gt;Significant CRP lowering in Phase 1&lt;br&gt;Phase 2 in RA; AF &amp; Endotoxin to start</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ISIS-APOCIII&lt;sub&gt;Rx&lt;/sub&gt;</strong>&lt;br&gt;High Triglycerides apoC-III</td>
<td>Patients at Highest Risk of Pancreatitis&lt;br&gt;Selectively Lowers Triglycerides&lt;br&gt;Significant ApoC-III &amp; TG Reductions in Phase 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ISIS-FXI&lt;sub&gt;Rx&lt;/sub&gt;</strong>&lt;br&gt;Clotting Disorders Factor XI</td>
<td>Potent Anti-thrombotic without Bleeding&lt;br&gt;Genetically Validated Target&lt;br&gt;Significant Reductions in FXI – No Bleeding in Phase 1</td>
<td></td>
<td>Ph1 2012/2013</td>
<td></td>
</tr>
<tr>
<td><strong>ISIS-APOA&lt;sub&gt;Rx&lt;/sub&gt;</strong>&lt;br&gt;CAD Lp(a)</td>
<td>Independent Risk Factor for CVD&lt;br&gt;Lp(a) Promotes Premature Plaque Build-up in Arteries&lt;br&gt;Direct Approach to Lower Lp(a)</td>
<td></td>
<td>Ph1 2012/2013</td>
<td></td>
</tr>
<tr>
<td><strong>ISIS-FVII&lt;sub&gt;Rx&lt;/sub&gt;</strong>&lt;br&gt;Clotting Disorders Factor VII</td>
<td>Validated Target&lt;br&gt;Potential Use in Acute Settings&lt;br&gt;Cancer-associated Thrombosis</td>
<td></td>
<td>Ph1 2012/2013</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Disease</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>
</tr>
<tr>
<td><strong>ATL 1103</strong></td>
<td>Acromegaly GHR</td>
<td>• Potential to Treat All GHR Associated Diseases</td>
<td>Ph2 2012</td>
<td></td>
</tr>
<tr>
<td><strong>ISIS-SMN&lt;sub&gt;Rx&lt;/sub&gt;</strong></td>
<td>Spinal Muscular Atrophy SMN2</td>
<td>• First Splicing Drug in Development</td>
<td>Ph2 2012</td>
<td></td>
</tr>
<tr>
<td><strong>ISIS-TTR&lt;sub&gt;Rx&lt;/sub&gt;</strong></td>
<td>TTR Amyloidosis TTR</td>
<td>• Severe &amp; Rare Disease Opportunity with GSK</td>
<td>Ph3 2012</td>
<td></td>
</tr>
<tr>
<td><strong>ISIS-AAT&lt;sub&gt;Rx&lt;/sub&gt;</strong></td>
<td>AATD-Associated Liver Disease AAT</td>
<td>• Severe &amp; Rare Disease Opportunity with GSK</td>
<td></td>
<td>Ph1 2012</td>
</tr>
</tbody>
</table>
Isis’ Metabolic Franchise
Distinct Novel Complementary Approaches to Diabetes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Novel Mechanism</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-FGFR4Rx</td>
<td>Obesity</td>
<td>Decreases Fat Synthesis &amp; Increases Fat Burning</td>
<td>Data 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FGFR4</td>
<td>Peripherally Active – No CNS Effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lowers Body Weight &amp; Fat in Preclinical Studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-GCGRRx</td>
<td>Diabetes</td>
<td>Effective in both Liver &amp; Pancreas</td>
<td>Data 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GCGR</td>
<td>Lowers Glucose; Increases active GLP-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potentially Disease Modifying</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-GCCRRx</td>
<td>Diabetes</td>
<td>Robust Glucose Control – No Systemic Effects</td>
<td>Data 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GCCR</td>
<td>Lowers Lipids &amp; Lowers Body Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential Value in Diabetes &amp; Obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-PTP1BRx</td>
<td>Diabetes</td>
<td>Safe &amp; Effective Insulin Sensitizer</td>
<td>Data 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PTP-1B</td>
<td>Lowers Glucose &amp; LDL-C with no weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Novel Mechanism Distinct from Glitazones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-DGAT2Rx</td>
<td>NASH</td>
<td>Treatment for NASH</td>
<td>Ph1 2012/2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DGAT2</td>
<td>Lowers TGs &amp; Cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improves Insulin Sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Isis’ Cancer Franchise

**Novel, Undruggable & Broadly Applicable Cancer Drugs**

<table>
<thead>
<tr>
<th></th>
<th><strong>PRECLINICAL</strong></th>
<th><strong>PHASE I</strong></th>
<th><strong>PHASE II</strong></th>
<th><strong>PHASE III</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OGX-011</strong>&lt;br&gt;Cancer clusterin</td>
<td>• Clusterin Linked to Chemoresistance  &lt;br&gt;• Demonstrated Survival Benefit in Phase 2  &lt;br&gt;• Two Phase 3 Studies in Prostate Cancer; NSCLC to begin</td>
<td></td>
<td></td>
<td>Data 2013</td>
</tr>
<tr>
<td><strong>ISIS-EIF4ERx</strong>&lt;br&gt;Cancer eIF-4E</td>
<td>• Target Inhibition Promotes Tumor Suppression  &lt;br&gt;• Multiple Therapeutic Opportunities  &lt;br&gt;• Phase 2 Program in Patients with Prostate &amp; NSCLC</td>
<td></td>
<td></td>
<td>Data 2013</td>
</tr>
<tr>
<td><strong>OGX-427</strong>&lt;br&gt;Cancer Hsp27</td>
<td>• Targeting Hsp27 Supports Cancer Suppression  &lt;br&gt;• Clinical Data in Prostate &amp; Bladder Cancer  &lt;br&gt;• Phase 2 Studies in Prostate &amp; Bladder Cancer</td>
<td></td>
<td></td>
<td>Data 2012</td>
</tr>
<tr>
<td><strong>ISIS-STAT3Rx</strong>&lt;br&gt;Cancer STAT3</td>
<td>• Over-active in a Variety of Cancers  &lt;br&gt;• Elevated STAT3 = Bad Prognosis  &lt;br&gt;• First Gen 2.5 Drug – Currently in Phase 1</td>
<td></td>
<td></td>
<td>Data 2013</td>
</tr>
</tbody>
</table>
Isis 2012

- Commercial revenue from KYNAMRO on the horizon
- Business strategy – continued success
  - Biogen Idec transaction
  - Solid cash position
- Broadening, expanding & maturing pipeline
  - ISIS-APOCIII_Rx – PH2
  - ISIS-STAT3_Rx – PH1
- Multiple exciting clinical programs
  - Numerous 2012 data events
    - ISIS-CRP_Rx
    - ISIS-GCGR_Rx
    - ISIS-GCCR_Rx
    - ISIS-FGFR4_Rx
    - LY2181308
    - ISIS-SOD1_Rx
    - ISIS-SMN_Rx
  - First Gen 2.5 in man
  - 3-5 new drugs into the pipeline
    - XEN 007
Antisense Coming of Age

RNA World Exploding with New Targets
Unlimited Possibilities of Antisense Targets
RNA World Exploding with New Targets
## Enhancing Technology Value with 2\textsuperscript{nd} Generation Drugs

Activity of Multiple Drugs in Multiple Tissues & Diseases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indications</th>
<th>Primary Organs</th>
<th>Endpoints</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mipomersen</td>
<td>apoB100</td>
<td>Hyperlipidemia</td>
<td>Liver</td>
<td>apoB, LDL-C, &amp; Others</td>
<td>Registration - 20 Positive trials</td>
</tr>
<tr>
<td>CRP</td>
<td>CRP</td>
<td>CV Disease Inflammation</td>
<td>Liver</td>
<td>CRP in plasma</td>
<td>Phase 2</td>
</tr>
<tr>
<td>ISIS-FXI\textsubscript{Rx}</td>
<td>Factor XI</td>
<td>Clotting Disorders</td>
<td>Liver</td>
<td>Factor XI levels &amp; bleeding</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ISIS-APOC-III\textsubscript{Rx}</td>
<td>APOC-III</td>
<td>High TGs</td>
<td>Liver</td>
<td>ApoC-III levels &amp; TGs</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ISIS-113715</td>
<td>PTP1B</td>
<td>Diabetes</td>
<td>Liver</td>
<td>Glucose LDL-C</td>
<td>Phase 2</td>
</tr>
<tr>
<td>ISIS-GCGR\textsubscript{Rx}</td>
<td>GCGR</td>
<td>Diabetes</td>
<td>Liver</td>
<td>Normal volunteer</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ISIS-SGLT2\textsubscript{Rx}</td>
<td>SGLT2</td>
<td>Diabetes</td>
<td>Kidney</td>
<td>Increase glucose excretion</td>
<td>Phase 1</td>
</tr>
<tr>
<td>OGX-011</td>
<td>Clusterin</td>
<td>Prostate Cancer</td>
<td>Prostate Lymph nodes</td>
<td>Target reduction, Apoptosis Survival</td>
<td>Phase 3</td>
</tr>
<tr>
<td>ISIS-TTR\textsubscript{Rx}</td>
<td>TTR</td>
<td>TTR Amyloidosis</td>
<td>Liver</td>
<td>TTR levels</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ATL 1103</td>
<td>GHR</td>
<td>Growth Hormone</td>
<td>Liver</td>
<td>Growth Hormone receptor levels</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ATL 1102</td>
<td>VLA4</td>
<td>MS</td>
<td>Bone marrow Lymph nodes</td>
<td>MRS Measurements of CNS lesions</td>
<td>Phase 2</td>
</tr>
<tr>
<td>EXC 001</td>
<td>CTGF</td>
<td>Scarring</td>
<td>Skin</td>
<td>Scaring endpoints CTGF</td>
<td>Phase 2b</td>
</tr>
<tr>
<td>ISIS-104838</td>
<td>TNF\alpha</td>
<td>RA</td>
<td>Joints Lymph nodes</td>
<td>ACS 20 &amp; Target reduction</td>
<td>DC’d</td>
</tr>
</tbody>
</table>
This presentation includes forward-looking statements regarding Isis Pharmaceuticals’ business, Isis’ financial position and outlook, and the therapeutic and commercial potential of Isis’ technologies and products in development, including the business of Regulus, Isis’ jointly owned subsidiary. Any statement describing Isis’ goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of KYNAMRO, 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, 2011 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.

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