Applying Antisense Technology for the Treatment of Transthyretin Amyloidosis

Elizabeth “Lisa” Ackermann, Ph.D.
Associate Director Clinical Development

October 29, 2011
Isis Pharmaceuticals

- Founded: 1989
- Location: Carlsbad, California
- Company Focus: RNA Targeted Therapeutics
  - Antisense Drugs
- ~300 employees
- Capabilities:
  - Drug discovery
  - Early development
  - Manufacturing
Proteins are Made from Genes via mRNA

Gene

mRNA

Transcription

Translation

Disease-Causing Protein

DISEASE

Amyloidosis Support Meeting_EJA_29Oct2011
Small Molecules & Biologics Target Proteins

Gene → mRNA → Translation → Disease-Causing Protein → DISEASE → Treat Disease

Small Molecule Drugs (traditional approach) → Treat Disease

BIOLOGICS → Treat Disease
Antisense Drugs Target RNA, not Proteins

Gene

mRNA

ANTISENSE DRUGS (Oligonucleotides)

No Translation of Disease-Causing Protein

TREAT DISEASE
Natural Nucleic Acids Have Poor Drug-like Properties

- Rapid degradation by nucleases present in plasma and tissues
- Rapid clearance by kidney
- Poor cellular uptake
2\textsuperscript{nd} Generation Antisense Oligos have been Developed that have Better Drug-Like Properties

Chemistry Attributes

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases potency</td>
<td></td>
</tr>
<tr>
<td>Increases stability to nucleases</td>
<td></td>
</tr>
<tr>
<td>Reduces toxicities observed with PS modified DNA oligos.</td>
<td>No new toxicities</td>
</tr>
</tbody>
</table>

Drug Properties

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potency</strong></td>
<td>~50 to 400 mg/week</td>
</tr>
<tr>
<td><strong>Dose Frequency</strong></td>
<td>Weekly to monthly</td>
</tr>
<tr>
<td><strong>Cost of Therapy</strong></td>
<td>Competitive with upper end of branded small molecules</td>
</tr>
<tr>
<td><strong>Routes of Administration</strong></td>
<td>Sub Q, I.V., inhalation, topical, intrathecal</td>
</tr>
</tbody>
</table>
# Isis Pipeline (2011)

<table>
<thead>
<tr>
<th>PROJECT</th>
<th>INDICATION</th>
<th>TARGET</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
<th>PHASE II</th>
<th>PHASE III</th>
<th>APPROVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mipomersen</td>
<td>High Cholesterol</td>
<td>apoB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-CRP&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>CAD/Inflammation/Renal</td>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-APOCIII&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>High Triglycerides</td>
<td>apoC-III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-FXI&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Clotting Disorders</td>
<td>Factor XI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS-PCSK9&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>CAD</td>
<td>PCSK9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS 113715</td>
<td>Diabetes</td>
<td>PTP-1B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-SGLT2&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Diabetes</td>
<td>SGLT2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-GCCR&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Diabetes</td>
<td>GCCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-GCGR&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Diabetes</td>
<td>GCGR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-FGFR4&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Obesity</td>
<td>FGFR4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OGX-011</td>
<td>Cancer</td>
<td>clusterin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LY2181308</td>
<td>Cancer</td>
<td>survivin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-EIF4E&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Cancer</td>
<td>eIF-4E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OGX-427</td>
<td>Cancer</td>
<td>Hsp27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-STAT3&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Cancer</td>
<td>STAT3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-SOD1&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>ALS</td>
<td>SOD1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-TTR&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Severe &amp; Rare</td>
<td>TTR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-SMN&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Spinal Muscular Atrophy</td>
<td>SMN2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISIS-AAT&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>AAT-Liver Disease</td>
<td>α1-Antitrypsin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitravene®</td>
<td>CMV Retinitis</td>
<td>CMV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alicaforsen</td>
<td>Ulcerative Colitis</td>
<td>ICAM-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACHN-490</td>
<td>Severe Bacterial Infection</td>
<td>Aminoglycoside</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATL1102</td>
<td>MS</td>
<td>VLA-4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXC 001</td>
<td>Local Fibrosis</td>
<td>CTGF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iCo-007</td>
<td>Ocular Disease</td>
<td>C-raf kinase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATL1103</td>
<td>Acromegaly</td>
<td>GHr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Isis Clinical Experience

- > 5,000 patients treated, approximately 2,900 with 2\textsuperscript{nd} generation (2’-MOE) drugs

- > 500 patients treated ≥ 12 weeks, > 280 treated ≥ 6 months, > 120 treated ≥ 1 year

- 2\textsuperscript{nd} generation antisense oligos have been well tolerated

- 2\textsuperscript{nd} generation antisense oligos are generally given as once weekly sc injections

- Liver and kidney are sensitive tissues to antisense oligo treatment
Developing ISIS-TTR_{Rx} for Treating Transthyretin Amyloidosis
What is ISIS-\textsubscript{TTR\text{Rx}}?

- ISIS-\textsubscript{TTR\text{Rx}} is a second generation antisense drug that destroys the TTR mRNA.
- This prevents the production of both mutant and normal TTR protein.
Rationale for ISIS-TTRRx

- Mutant and normal TTR protein can form amyloid deposits in tissue and cause transthyretin amyloidosis.
- The only currently approved therapy for transthyretin amyloidosis is liver transplant which lowers the levels of mutant TTR.
- TTR is produced by the liver which is particularly sensitive tissue to the action of antisense oligos.
- Thus, ISIS-TTRRx treatment strategy which lowers both mutant and wild-type TTR may be an effective approach to treating this disease.

**Antisense Drug**

- Inhibit synthesis
- Stabilize tetramers
- Inhibit aggregation

Modified from Saraiva MJ. Expert reviews in molecular medicine, 2002.
First many antisense oligos are made that will bind to the TTR mRNA

Oligos are then screened in tissue culture cells

A subset of those oligos are tested in mouse and monkey animal models
  ➤ Demonstrate lowering of TTR protein in plasma
  ➤ Demonstrate lowering of TTR mRNA in liver
  ➤ Study safety

The best oligo is selected to test in clinical trials
Status of ISIS-TTR$_{Rx}$

- Drug identified and characterized
- Efficacy in mouse and monkey models shown
- Required toxicology studies are completed
- Phase 1 clinical trial in healthy volunteers is ongoing
Importance of Phase 1 Clinical Trials

• The first study to deliver a drug to humans is very important

• Provides key information about:
  - Safety in humans (what are the side effects?)
  - Pharmacokinetics (what are the drug levels in the human body?)
  - In some cases it can also provide information that the drug is working as predicted

• Results from Phase 1 studies are used to design future studies of the drug
A Phase 1 study in healthy volunteers was initiated in May 2011

Single and multiple doses of ISIS-TTR$_{Rx}$ are being evaluated at 4 different dose levels

The study is designed to evaluate effects of ISIS-TTR$_{Rx}$ on:

- safety (are there any side effects?)
- pharmacokinetics (what are the levels of drug in the blood?)
- pharmacodynamics (do plasma TTR levels go down?)

To date, ISIS-TTR$_{Rx}$ appears to be well tolerated

Reductions in plasma TTR levels have been observed

The study is on track to complete on schedule. All patients will have completed the treatment period by Dec 2011
Antisense Approaches Against Transthyretin

Summary

- Antisense oligonucleotides have been shown in multiple animal and human studies to reduce levels of disease-causing proteins and have been generally well tolerated.

- ISIS-TTR$_{Rx}$ is an antisense drug that targets normal and mutant TTR and effectively lowers TTR levels in animals including non-human primates.

- ISIS-TTR$_{Rx}$ is currently being tested in healthy human volunteers in a Phase 1 safety study.

- Evaluation of ISIS-TTR$_{Rx}$ in patients with familial amyloid polyneuropathy is projected to start in the second half of 2012.