Studying ISIS-TTR_{Rx} for the Treatment of Transthyretin Amyloidosis

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Isis Pharmaceuticals, Inc.

Amyloidosis Support Group Meeting
Chicago, IL
October 31, 2015
Isis Pharmaceuticals

- Founded: 1989
- Company Focus: RNA-Targeted Therapeutics
  - Antisense Drugs
- Location: Carlsbad, California
- ~ 400 Employees
### Isis’ Pipeline is Broad, Diverse and Mature

#### Phase 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</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>
<tr>
<td>ISIS-TTRRx</td>
<td>TTR Amyloidosis</td>
</tr>
<tr>
<td>ISIS-SMNRx</td>
<td>Spinal Muscular Atrophy (Infants)</td>
</tr>
<tr>
<td>ISIS-SMNRx</td>
<td>Spinal Muscular Atrophy (Children)</td>
</tr>
<tr>
<td>ISIS-APOCIIIRx</td>
<td>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>Partial Lipodystrophy</td>
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#### Phase 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATL1103</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>ISIS-DMPK-2.5Rx</td>
<td>Myotonic Dystrophy 1</td>
</tr>
<tr>
<td>ISIS-APO(a)Rx</td>
<td>Very High Lp(a)</td>
</tr>
<tr>
<td>ISIS-FXIRx</td>
<td>Clotting Disorders</td>
</tr>
<tr>
<td>ISIS-GCCRRx</td>
<td>Diabetes</td>
</tr>
<tr>
<td>ISIS-GCCRRx</td>
<td>Diabetes</td>
</tr>
<tr>
<td>ISIS-PTP1BRx</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Apatorsen (OGX-427)</td>
<td>Cancer</td>
</tr>
<tr>
<td>ISIS-STAT3-2.5Rx</td>
<td>Cancer</td>
</tr>
<tr>
<td>ISIS-AR-2.5Rx</td>
<td>Cancer</td>
</tr>
<tr>
<td>EXC 001 (PF-06473271)</td>
<td>Scarring</td>
</tr>
<tr>
<td>ATL1102</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>RG-101</td>
<td>HCV</td>
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#### Phase 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
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<tbody>
<tr>
<td>ISIS-GCCRRx</td>
<td>Cushing’s Syndrome</td>
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<tr>
<td>ISIS-PKRx</td>
<td>Hereditary Angioedema</td>
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<tr>
<td>ISIS-ANGPTL3Rx</td>
<td>Hyperlipidemia</td>
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<tr>
<td>ISIS-FGFR4Rx</td>
<td>Obesity</td>
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<tr>
<td>ISIS-HBVRx</td>
<td>HBV</td>
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#### Preclinical

<table>
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<th>Drug</th>
<th>Indication</th>
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<tr>
<td>ISIS-HTTRx</td>
<td>Huntington’s Disease</td>
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<tr>
<td>ISIS-BIIB3Rx</td>
<td>Neurodegenerative Disease</td>
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<tr>
<td>ISIS-BIIB4Rx</td>
<td>Neurodegenerative Disease</td>
</tr>
<tr>
<td>RG-012</td>
<td>Alport Syndrome</td>
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<tr>
<td>ISIS-RHORx</td>
<td>Autosomal Dominant Retinitis Pigmentosa</td>
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<tr>
<td>ISIS-GHR-LRx</td>
<td>Acromegaly</td>
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<tr>
<td>ISIS-AGT-LRx</td>
<td>Treatment-Resistant Hypertension</td>
</tr>
<tr>
<td>ISIS-ANGPTL3-LRx</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>ISIS-APO(a)-LRx</td>
<td>Very High Lp(a)</td>
</tr>
<tr>
<td>ISIS-APOCIII-LRx</td>
<td>Severely High TGs</td>
</tr>
<tr>
<td>ISIS-TMPRSS6-LRx</td>
<td>β-Thalassemia</td>
</tr>
<tr>
<td>ISIS-DGAT2Rx</td>
<td>NASH</td>
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<tr>
<td>ISIS-GSK4-LRx</td>
<td>Ocular Disease</td>
</tr>
<tr>
<td>ISIS-GSK6-LRx</td>
<td>Antiviral</td>
</tr>
</tbody>
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Isis’ Severe and Rare Programs

Commercialized

KYNAMRO®
Alicaforsen
Homozygous FH
*Pouchitis

* Named Patient Supply

Phase 3

ISIS-TTR\text{Rx}
TTR Amyloidosis

ISIS-SMN\text{Rx}\textit{ biogen idec}
Spinal Muscular Atrophy (Infants)

ISIS-SMN\text{Rx}\textit{ biogen idec}
Spinal Muscular Atrophy (Children)

ISIS-APOCIII\text{Rx}\textit{ AKCEA}
Partial Lipodystrophy

Phase 2

ATL1103
Acromegaly

ISIS-DMPK-2.5\text{Rx}\textit{ biogen idec}
Myotonic Dystrophy 1

Phase 1

ISIS-GCCR\text{Rx}
Cushing’s Syndrome

ISIS-PKK\text{Rx}
Hereditary Angioedema

Preclinical

ISIS-HTT\text{Rx}\textit{ Roche}
Huntington’s Disease

ISIS-BIIB3\text{Rx}\textit{ biogen idec}
Neurodegenerative Disease

ISIS-BIIB4\text{Rx}\textit{ biogen idec}
Alport Syndrome

RG-012
Autosomal Dominant Retinitis Pigmentosa

ISIS-RHO-2.5\text{Rx}
Acromegaly

ISIS-GHR-L\text{Rx}
**ISIS-TTR\textsubscript{Rx}: Designed to Bind to TTR mRNA**

- **TTR Gene**
- **TTR mRNA**

mRNA is transcribed to produce a protein

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ISIS-TTR\textsubscript{Rx}: Designed to Bind to TTR mRNA

TTR Gene → TTR mRNA → ISIS-TTR\textsubscript{Rx} (ANTISENSE DRUG) Binds to mRNA

Transthyretin Protein
ISIS-TTR$_{Rx}$: Designed to Bind to TTR mRNA

**Antisense Drug ISIS-TTR$_{Rx}$**

- Binds to mRNA
- Causes the mRNA to be destroyed
**ISIS-TTR\textsubscript{Rx}: Designed to Bind to TTR mRNA**

- **TTR Gene** → **TTR mRNA** → **ISIS-TTR\textsubscript{Rx}**
- **ISIS-TTR\textsubscript{Rx}** binding to mRNA causes the mRNA to be destroyed.

**Without mRNA, protein is not made**

- Formation of Mutant & Normal TTR Protein is reduced

**Less TTR RNA = Less TTR PROTEIN**

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Three Major Forms of ATTR

ATTR is a Single Disease Caused by the Formation of TTR Amyloid Deposits in Various Tissues

1. FAP
2. FAC
3. WT-TTR

Phase 3 On-going

ISIS-TTR$_{Rx}$
ISIS-\textsuperscript{TTR}_{\text{Rx}} in Familial Amyloid Polyneuropathy
Developing \( \text{ISIS-TTR}_{\text{Rx}} \)

- Preclinical Studies Tests in the Lab (COMPLETED)
- Phase 1 Study Normal Subjects (COMPLETED)
- Phase 3 Study FAP Patients (ONGOING)
- Open-Label Study FAP Patients (ONGOING)

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• Healthy volunteers
• Studied 5 different single and multiple doses of ISIS-TTR\textsubscript{Rx}
• ISIS-TTR\textsubscript{Rx} was given as a subcutaneous injection
• Designed to test effects of ISIS-TTR\textsubscript{Rx} on:
  − Side Effects = Safety
  − Amount of Drug in Blood = Pharmacokinetics
  − TTR Levels in Plasma = Pharmacodynamics
• Study Completed
**Results**

- Significant reductions in plasma TTR observed
- Phase 3 dose identified → 300mg
• **Double-blind and Placebo Controlled**
  - Neither the Study doctors, nor the patients will know who is getting placebo and who is getting ISIS-TTR_{Rx}

• **2:1 Randomization**
  - A majority of patients receive active drug
  - 2/3 (66%) of the patients receive ISIS-TTR_{Rx}
  - 1/3 (33%) of the patients receive placebo
• Does ISIS-TTR\text{Rx} slow or stop the nerve damage caused by TTR deposits
  - mNIS+7 test will be used to help make this determination

Evaluate Efficacy

Evaluate Safety

• Determine the safety of ISIS-TTR\text{Rx} given for 15 months
  - Blood tests, eye exams, and other tests will be used to make this determination

Inclusion Criteria *

• Must have signs of polyneuropathy
• Stage 1 or Stage 2 Disease
• Patients with liver transplantation are not eligible
  *This is not a complete list of inclusion criteria

Patient Enrollment

• ~195 TTR Amyloidosis Patients
**ISIS-TTR\textsubscript{Rx} Phase 3 Study**

**“The Isis Study”**

**Treatment**

- 15-month treatment period
  - Weekly injections
- Subcutaneous injections
  - Both Placebo and ISIS-TTR\textsubscript{Rx} are given as a shot under the skin

**Home Administration**

- Patients take the drug home
- Patients & caregivers are trained and given detailed instructions
- Self-administered by patient or by family members/caregivers
Patient and caregiver expenses for accommodations and travel to the clinical site will be reimbursed.

Patients can choose to have a professional home healthcare nurse come to their home to administer study drug.
ISIS-TTR\textsubscript{Rx} FAP Open-Label Extension (OLE) Study

All patients receive ISIS-TTR\textsubscript{Rx}
Open-Label Extension (OLE) Study – In Progress

Purpose

- To evaluate the safety and efficacy of ISIS-TTR$_{Rx}$ when given for long periods

Eligibility

- Patients must complete the Phase 3 study to be able to participate

Design

- Patients receive treatment (300mg weekly) for 18 months
- All patients receive study drug: no placebo
- Patients take the drug home
  - can be administered by patient, family member, caregiver, or home healthcare nurse
- Periodic visits to the clinical site for evaluations are required
- Travel and expenses are reimbursed
ISIS-TTR$_{\text{Rx}}$ Phase 3 Global Study

Nine Participating Trial Sites in the United States

- Steve Heitner, Portland, OR
- Annabel Wang, Irvine, CA
- Morie Gertz, Rochester, MN
- Merrill Benson, Indianapolis, IN
- Thomas Brannagan, New York, NY
- Brian Drachman, Philadelphia, PA
- Peter Gorevic, New York, NY
- John Berk, Boston, MA
- Michael Polydefkis, Baltimore, MD
Do you have TTR Amyloidosis?

Isis Pharmaceuticals is currently enrolling a Phase 3 study that is designed to evaluate the safety and efficacy of ISIS-TTRRx in patients with Familial Amyloid Polyneuropathy (FAP), the form of TTR amyloidosis that causes nerve damage.

Find Information on the ISIS TTR Amyloidosis Website
www.ttrstudy.com
Interested in Knowing More?

- Ask your doctor
- Talk to physicians here at the meeting
- Go to www.ttrstudy.com and www.clintrials.gov for more information
Thank You

Patients and Families

Investigators and Site Staff