Studying ISIS-TTR$_{\text{Rx}}$ for the Treatment of Transthyretin Amyloidosis

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What is ISIS-TTR<sub>Rx</sub> & How does it Work?

- Isis’ drug, ISIS-TTR<sub>Rx</sub> is an antisense drug that works by reducing the amount of mutant and normal TTR protein made by your body.
- The build-up of TTR can cause nerve damage and/or heart disease.
- Most patients with TTR amyloidosis produce both normal and mutated forms of the TTR protein.
- It has been shown that both forms of TTR protein build-up in tissues as amyloid deposits.
- It is predicted that lowering the amount of TTR protein will result in a lower amount of amyloid deposits that build-up in tissues, thus slowing or halting disease progression.
- As with liver transplantation, ISIS-TTR<sub>Rx</sub> decreases the amount of mutant TTR produced, however ISIS-TTR<sub>Rx</sub> also lowers normal TTR, offering a unique approach to treating this disease. Because normal TTR can continue to deposit as amyloid fibers after liver transplant, this distinction may even represent a therapeutic alternative or advantage.
Proteins Are Made from RNA

Many drugs work by binding to the protein that is causing the disease:
- Tafamidis (Transthyretin)

Antisense drugs work by binding to the RNA that makes the protein:
- ISIS TTR_{Rx}
Antisense Drugs Bind to RNA & Destroy the RNA

Less RNA = Less PROTEIN
Development of ISIS-TTR\textsubscript{Rx}

Target Identification

Oligo Synthesis  Lead Oligo ID  Cell Culture Assay  Animal Studies  In Man

Preclinical

Phase 1 Study
Healthy volunteers

Studied 5 different single and multiple doses of ISIS-TTR$_{Rx}$

Designed to test effects of ISIS-TTR$_{Rx}$ on:

- Side Effects = Safety
- Amount of Drug in Blood = Pharmacokinetics
- TTR Levels in Plasma = Pharmacodynamics

Study Completed
Potent & Durable Reductions in Transthyretin Levels in Healthy Volunteers Treated with ISIS-TTR$_{Rx}$

Results

✓ TTR Reductions in plasma observed
✓ Identification of Phase 3 dose → 300mg
Phase 3 Study

ISIS-TTR\textsubscript{Rx} Phase 3 Enrolling Now

### Purpose
- Does ISIS-TTR\textsubscript{Rx} slow or stop the nerve damage caused by TTR deposits
  - mNIS+7 test will be used to help make this determination

### Inclusion Criteria
- Must have signs of polyneuropathy
- Late Stage 1 or Early Stage 2
- Patients with liver transplantation are not eligible

### Patients
- 195 TTR Amyloidosis Patients

### Evaluate Safety
- Determine the safety of ISIS-TTR\textsubscript{Rx} given for 15 months
  - Blood tests, eye exams and other tests will be used to make this determination
ISIS-TTR\textsubscript{Rx} Phase 3 Study Design

- **Double-blind and Placebo Controlled**
  - Neither the Study doctors, nor the patients will know who is getting placebo and who is getting ISIS-TTR\textsubscript{Rx}

- **2:1 Randomization**
  - 2/3 of the patients will receive drug
  - 1/3 of the patients will receive placebo

- **OLE (open-label extension)** – After finishing the Phase 3 study, patients can participate in the OLE study. In the OLE study all patients will receive ISIS-TTR\textsubscript{Rx}
ISIS-TTR\textsubscript{Rx} Phase 3 Study

**Treatment**

- 15-month treatment
  - 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 to take home
- Self-administered by patient or by family members/caregivers
mNIS+7: An Important Phase 3 Study Test

mNIS+7 will help evaluate if ISIS-TTR\textsubscript{Rx} is helping slow the progression of disease in patients with TTR FAP

Tests Include:
- Neuropathy Impairment Score (NIS)
- Nerve conduction tests
- Tests to measure your ability to feel heat or touch
Seven Participating Trial Sites in the United States

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Interested in Knowing More?

- Ask your doctor
- Talk to physicians here at the meeting
- Talk to Isis representatives here at the meeting
- Go to [www.clintrials.gov](http://www.clintrials.gov) for more information

Volunteers Needed