

# Studying ISIS-TTR<sub>Rx</sub> for the Treatment of Transthyretin Amyloidosis

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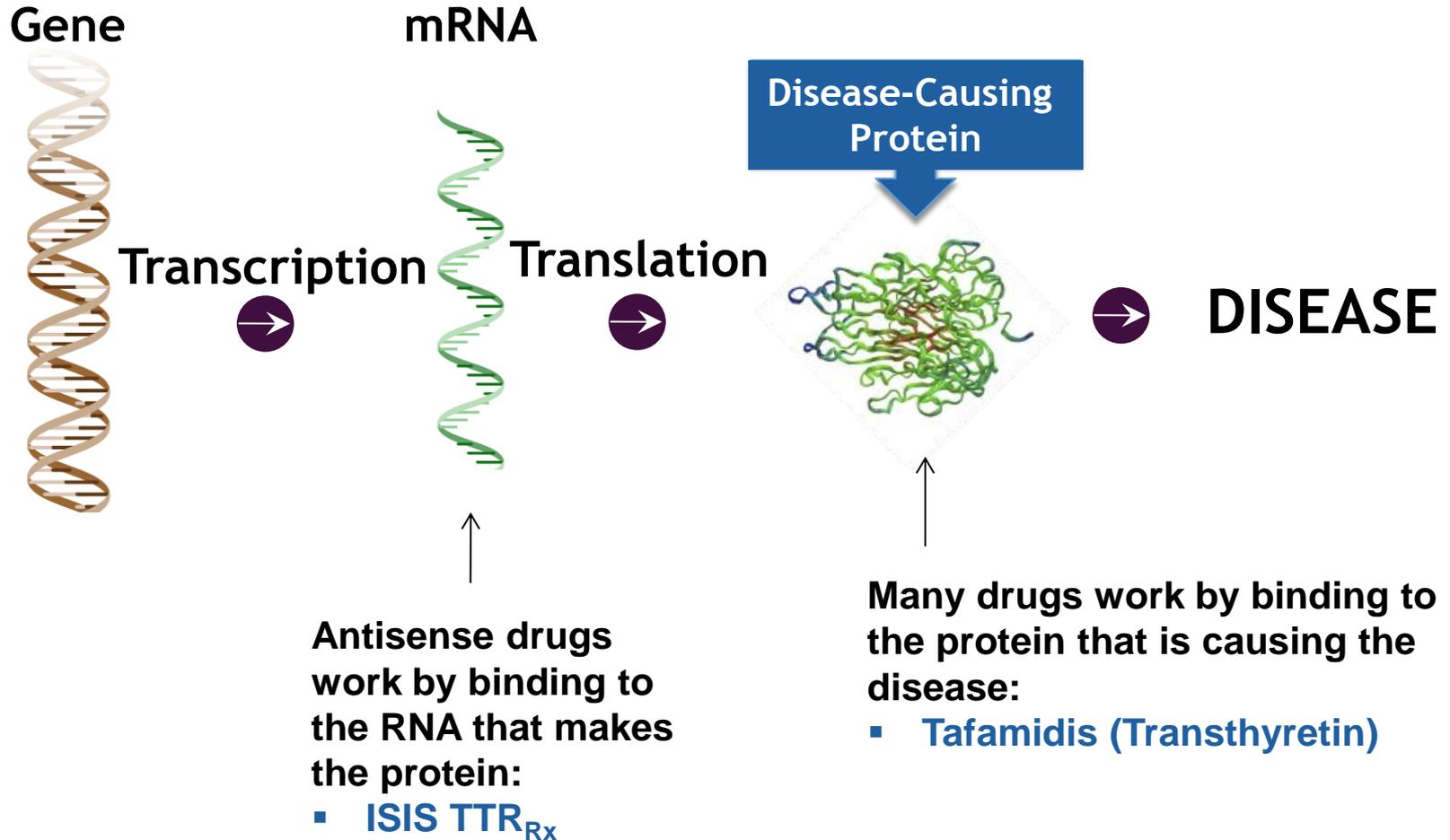
# What is ISIS-TTR<sub>Rx</sub> & How does it Work?

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- 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.

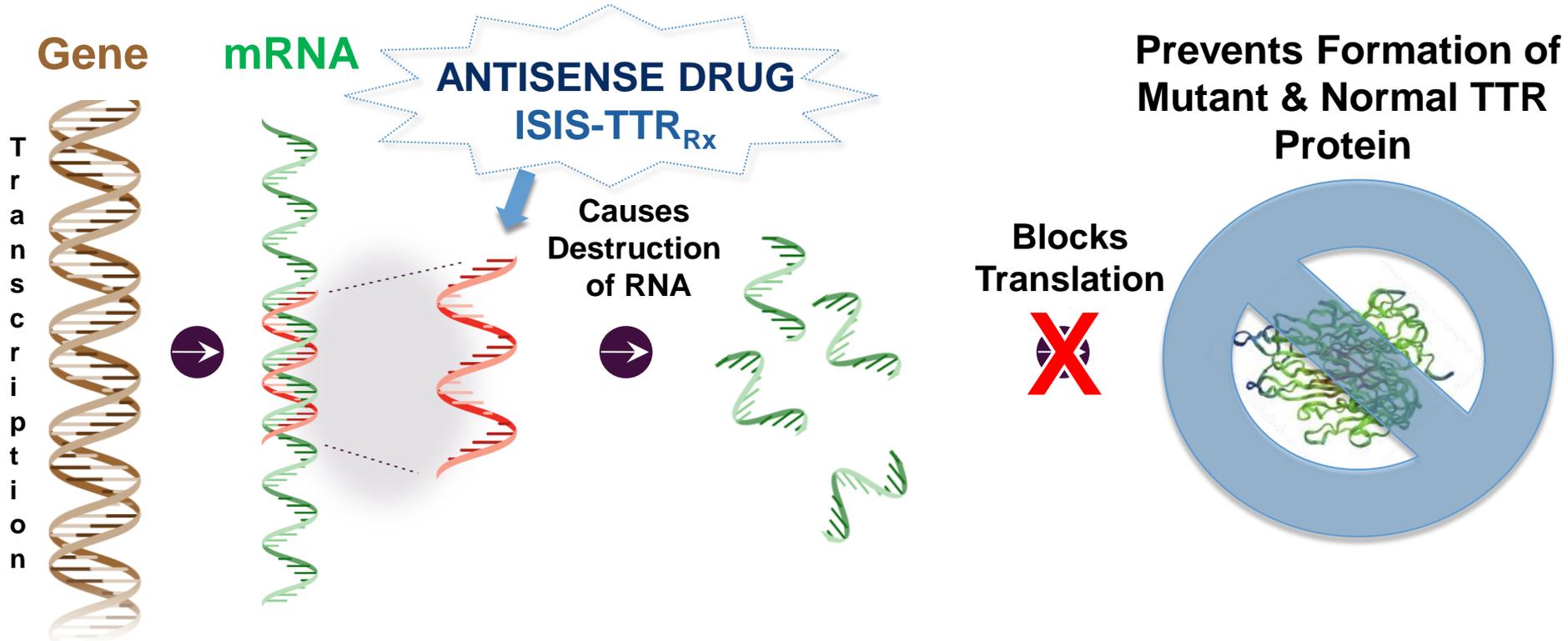
# Proteins Are Made from RNA

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# Antisense Drugs Bind to RNA & Destroy the RNA

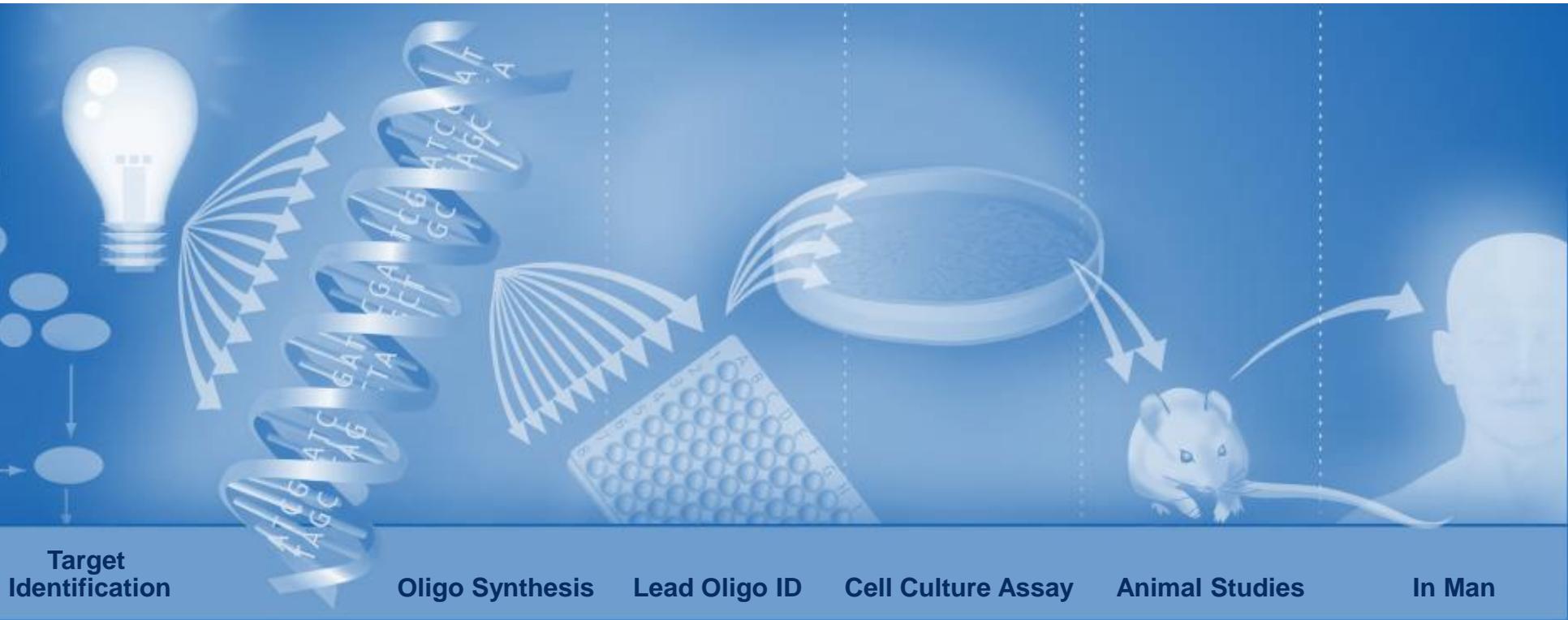
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**Less RNA = Less PROTEIN**

# Development of ISIS-TTR<sub>Rx</sub>

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Preclinical

Phase 1 Study

# ISIS-TTR<sub>Rx</sub> Phase 1 Study

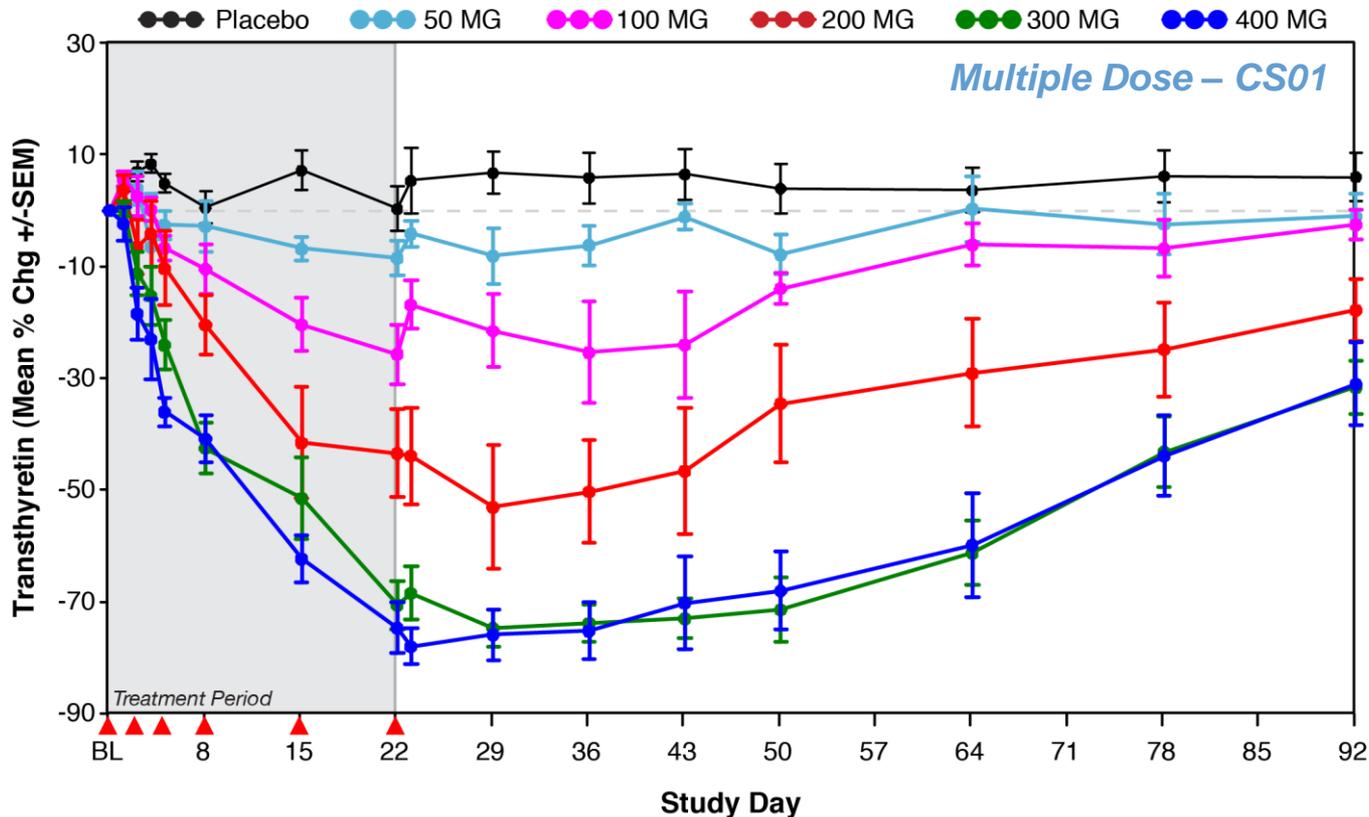
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- Healthy volunteers
- Studied 5 different single and multiple doses of ISIS-TTR<sub>Rx</sub>
- Designed to test effects of ISIS-TTR<sub>Rx</sub> on:
  - ▣ Side Effects = Safety
  - ▣ Amount of Drug in Blood = Pharmacokinetics
  - ▣ TTR Levels in Plasma = Pharmacodynamics
- Study Completed



# Potent & Durable Reductions in Transthyretin Levels in Healthy Volunteers Treated with ISIS-TTR<sub>Rx</sub>

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## Results

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

### Purpose

- Does ISIS-TTR<sub>Rx</sub> slow or stop the nerve damage caused by TTR deposits
  - ▣ mNIS+7 test will be used to help make this determination

### Patients

- 195 TTR Amyloidosis Patients

### Inclusion Criteria

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

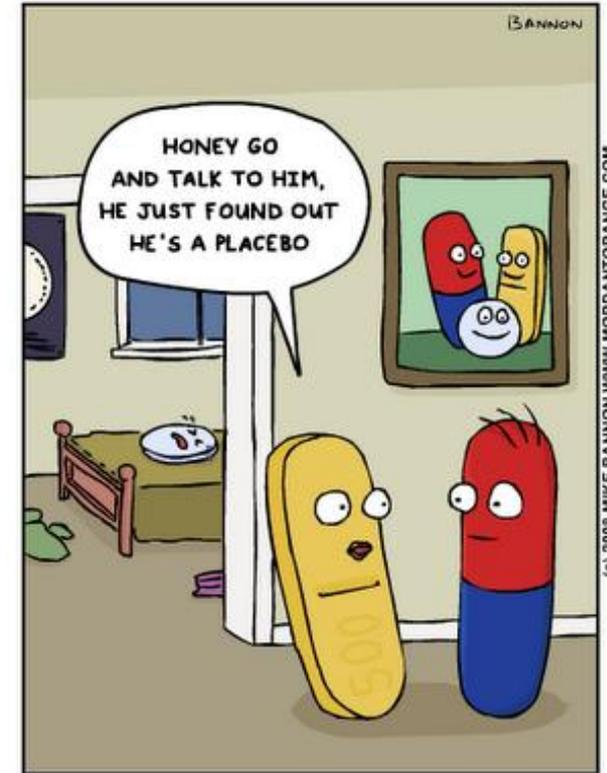
### Evaluate Safety

- Determine the safety of ISIS-TTR<sub>Rx</sub> given for 15 months
  - ▣ Blood tests, eye exams and other tests will be used to make this determination

# ISIS-TTR<sub>Rx</sub> Phase 3 Study Design

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- Double-blind and Placebo Controlled
  - ▣ Neither the Study doctors, nor the patients will know who is getting placebo and who is getting ISIS-TTR<sub>Rx</sub>
- 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<sub>Rx</sub>



# ISIS-TTR<sub>Rx</sub> Phase 3 Study

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## Treatment

- 15-month treatment
  - ▣ Weekly injections
- Subcutaneous injections
  - ▣ Both Placebo and ISIS-TTR<sub>Rx</sub> 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



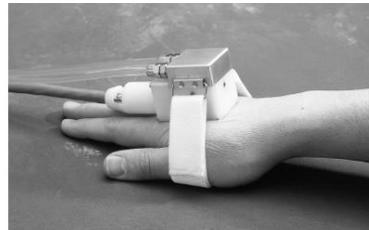
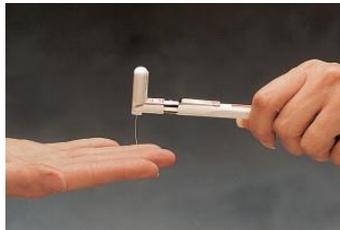
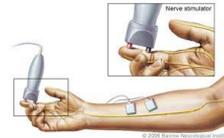
# mNIS+7: An Important Phase 3 Study Test

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mNIS+7 will help evaluate if ISIS-TTR<sub>Rx</sub> is helping slow the progression of disease in patients with TTR FAP

## Tests Include:

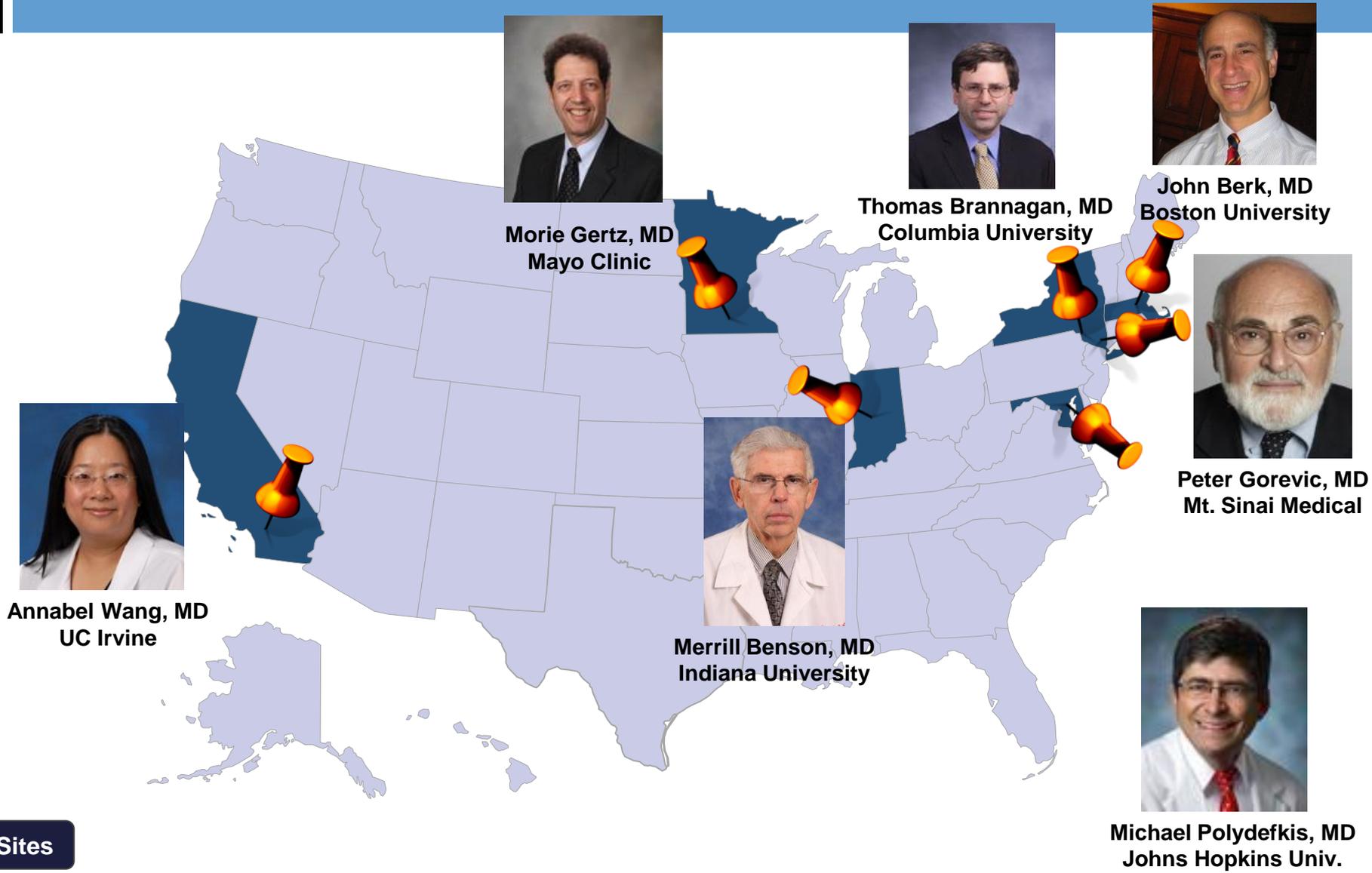
- Neuropathy Impairment Score (NIS)
- Nerve conduction tests
- Tests to measure your ability to feel heat or touch



# Seven Participating Trial Sites in the United States



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# Interested in Knowing More?

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- 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

