

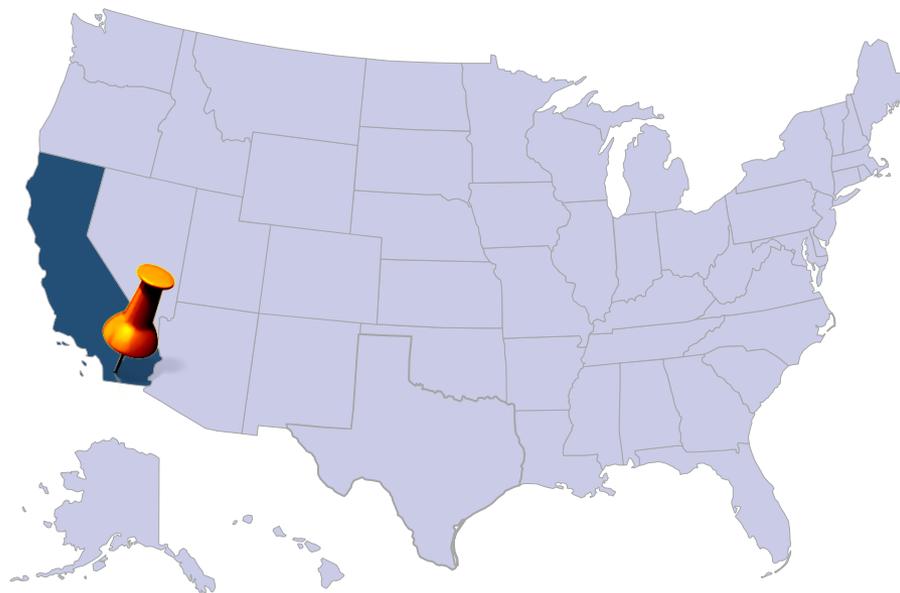
Studying ISIS-TTR_{Rx} for the Treatment of Transthyretin Amyloidosis

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Executive Director Clinical Development/Project Team Leader
Isis Pharmaceuticals, Inc.

Amyloidosis Support Group Meeting
Chicago, IL
October 31, 2015

Isis Pharmaceuticals

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- **Founded: 1989**
- **Company Focus: RNA-Targeted Therapeutics**
 - Antisense Drugs
- **Location: Carlsbad, California**
- **~ 400 Employees**



Isis' Pipeline is Broad, Diverse and Mature

Commercialized

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KYNAMRO®	genzyme A SANOFI COMPANY	Homozygous FH
Alicaforsen	Atlantic	*Pouchitis
Vitravene®	NOVARTIS	CMV Retinitis

* Named Patient Supply

Phase 3

ISIS-TTR _{Rx}	gsk	TTR Amyloidosis
ISIS-SMN _{Rx}	biogen idec.	Spinal Muscular Atrophy (Infants)
ISIS-SMN _{Rx}	biogen idec.	Spinal Muscular Atrophy (Children)
ISIS-APOCIII _{Rx}	AKCEA	FCS
ISIS-APOCIII _{Rx}	AKCEA	Partial Lipodystrophy
KYNAMRO®	genzyme A SANOFI COMPANY	Severe HeFH
Custirsen (OGX-011)	TEVA, OncoGenex	Prostate / Lung Cancer
Plazomicin	ACHAOPEN	Severe Bacterial Infection

Phase 2

ATL1103	antisense THERAPEUTICS	Acromegaly
ISIS-DMPK-2.5 _{Rx}	biogen idec.	Myotonic Dystrophy 1
ISIS-APO(a) _{Rx}	AKCEA	Very High Lp(a)
ISIS-FXI _{Rx}	Bayer HealthCare	Clotting Disorders
ISIS-GCGR _{Rx}		Diabetes
ISIS-GCCR _{Rx}		Diabetes
ISIS-PTP1B _{Rx}		Diabetes
Apatorsen (OGX-427)	OncoGenex	Cancer
ISIS-STAT3-2.5	AstraZeneca	Cancer
ISIS-AR-2.5 _{Rx}	AstraZeneca	Cancer
EXC 001 (PF-06473074)	EXCALIARD, Pfizer	Scarring
ATL1102	antisense THERAPEUTICS	Multiple Sclerosis
RG-101	REGULUS THERAPEUTICS	HCV

Phase 1

ISIS-GCCR _{Rx}		Cushing's Syndrome
ISIS-PKK _{Rx}		Hereditary Angioedema
ISIS-ANGPTL3 _{Rx}	AKCEA	Hyperlipidemia
ISIS-FGFR4 _{Rx}		Obesity
ISIS-HBV _{Rx}	gsk	HBV

Preclinical

ISIS-HTT _{Rx}	Roche	Huntington's Disease
ISIS-BIIB3 _{Rx}	biogen idec.	Neurodegenerative Disease
ISIS-BIIB4 _{Rx}	biogen idec.	Neurodegenerative Disease
RG-012	REGULUS THERAPEUTICS	Alport Syndrome
ISIS-RHO-2.5 _{Rx}		Autosomal Dominant Retinitis Pigmentosa
ISIS-GHR-L _{Rx}		Acromegaly
ISIS-AGT-L _{Rx}		Treatment-Resistant Hypertension
ISIS-ANGPTL3-L _{Rx}	AKCEA	Hyperlipidemia
ISIS-APO(a)-L _{Rx}	AKCEA	Very High Lp(a)
ISIS-APOCIII-L _{Rx}	AKCEA	Severely High TGs
ISIS-TMPRSS6-L _{Rx}		β-Thalassemia
ISIS-DGAT2 _{Rx}		NASH
ISIS-GSK4-L _{Rx}	gsk	Ocular Disease
ISIS-GSK6-L _{Rx}	gsk	Antiviral

Severe & Rare
 Cardiovascular
 Metabolic
 Cancer
 Other

Isis' Severe and Rare Programs

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Commercialized

KYNAMRO®  Homozygous FH
 Alicaforsen  *Pouchitis

* Named Patient Supply



Phase 3

ISIS-TTR_{Rx}  TTR Amyloidosis
 ISIS-SMN_{Rx}  Spinal Muscular Atrophy (Infants)
 ISIS-SMN_{Rx}  Spinal Muscular Atrophy (Children)
 ISIS-APOCIII_{Rx}  FCS
 ISIS-APOCIII_{Rx}  Partial Lipodystrophy

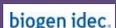
Phase 2

ATL1103  Acromegaly
 ISIS-DMPK-2.5_{Rx}  Myotonic Dystrophy 1

Phase 1

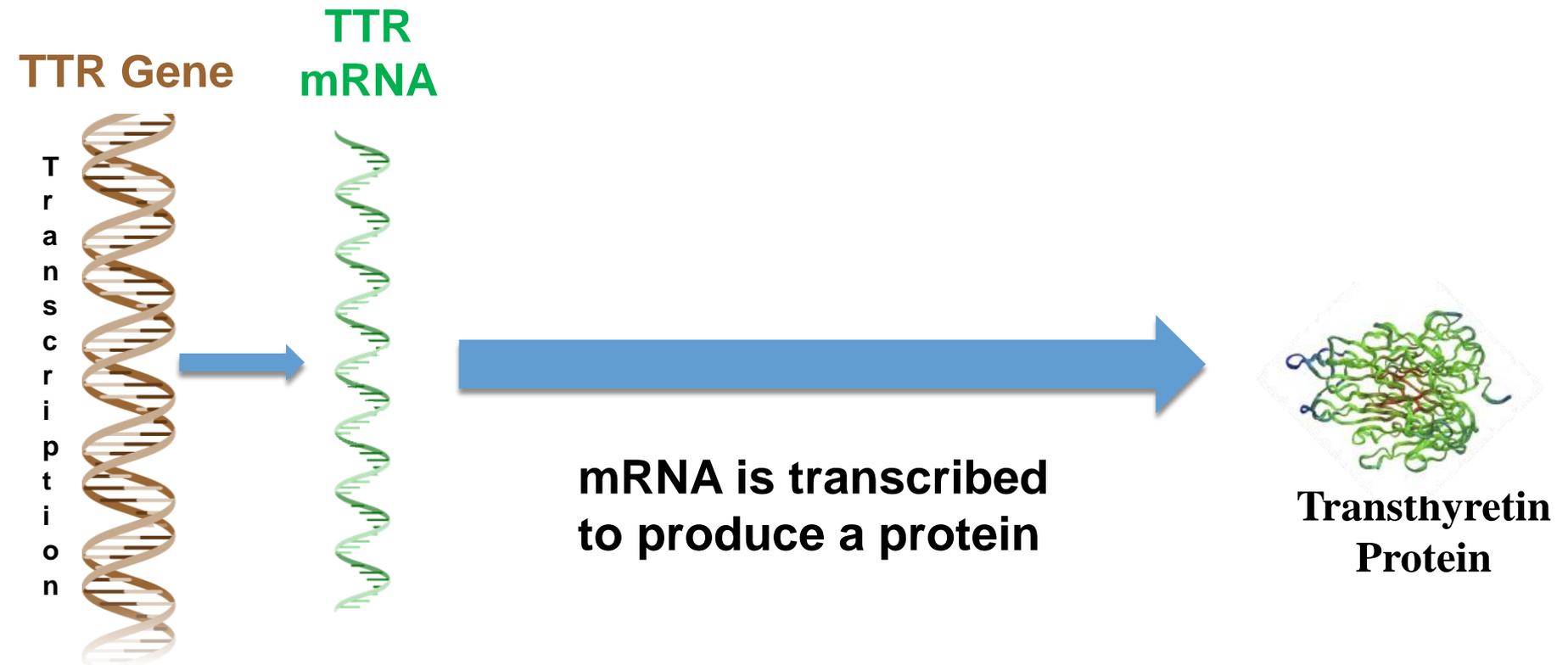
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Preclinical

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 ISIS-BIIB4_{Rx}  Neurodegenerative Disease
 RG-012  Alport Syndrome
 ISIS-RHO-2.5_{Rx} Autosomal Dominant Retinitis Pigmentosa
 ISIS-GHR-L_{Rx} Acromegaly

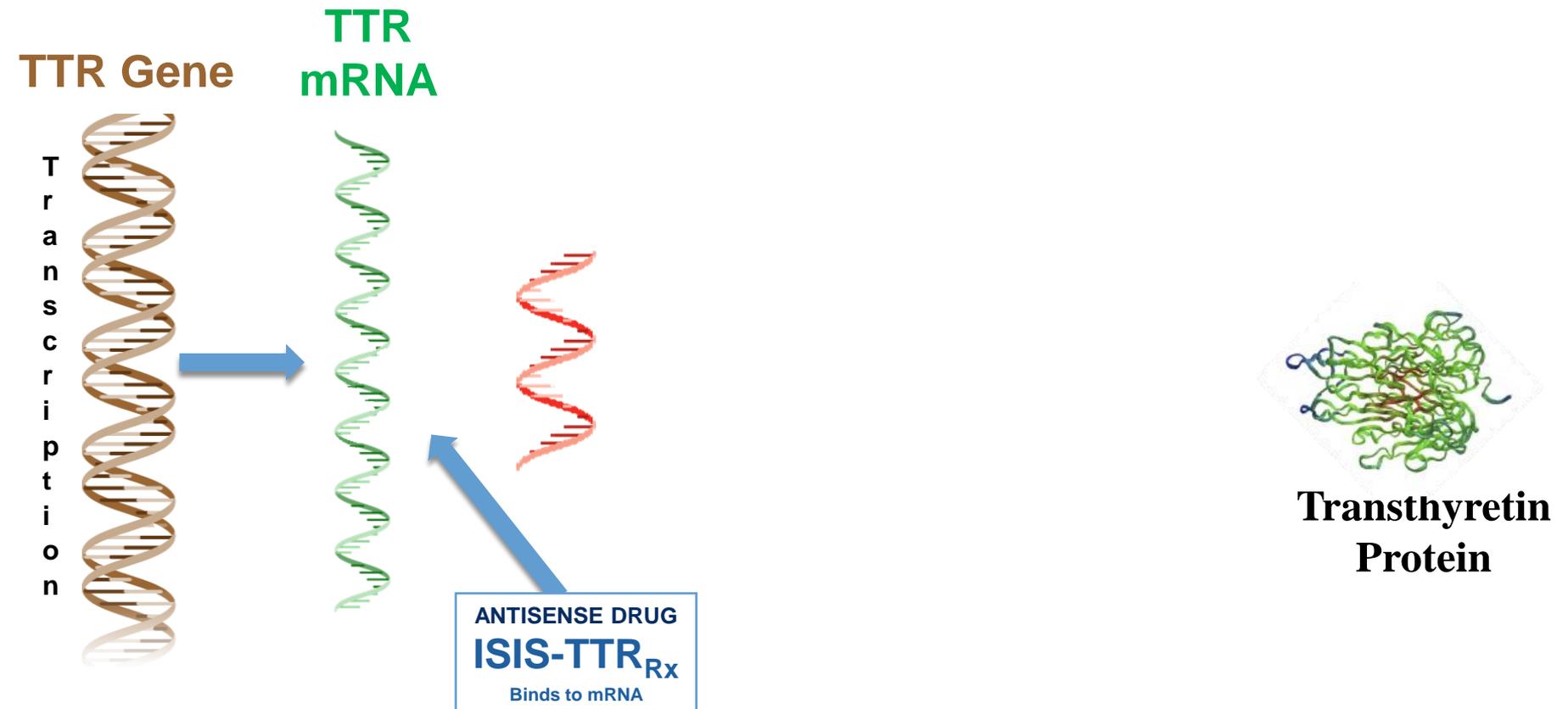
ISIS-TTR_{Rx}: Designed to Bind to TTR mRNA

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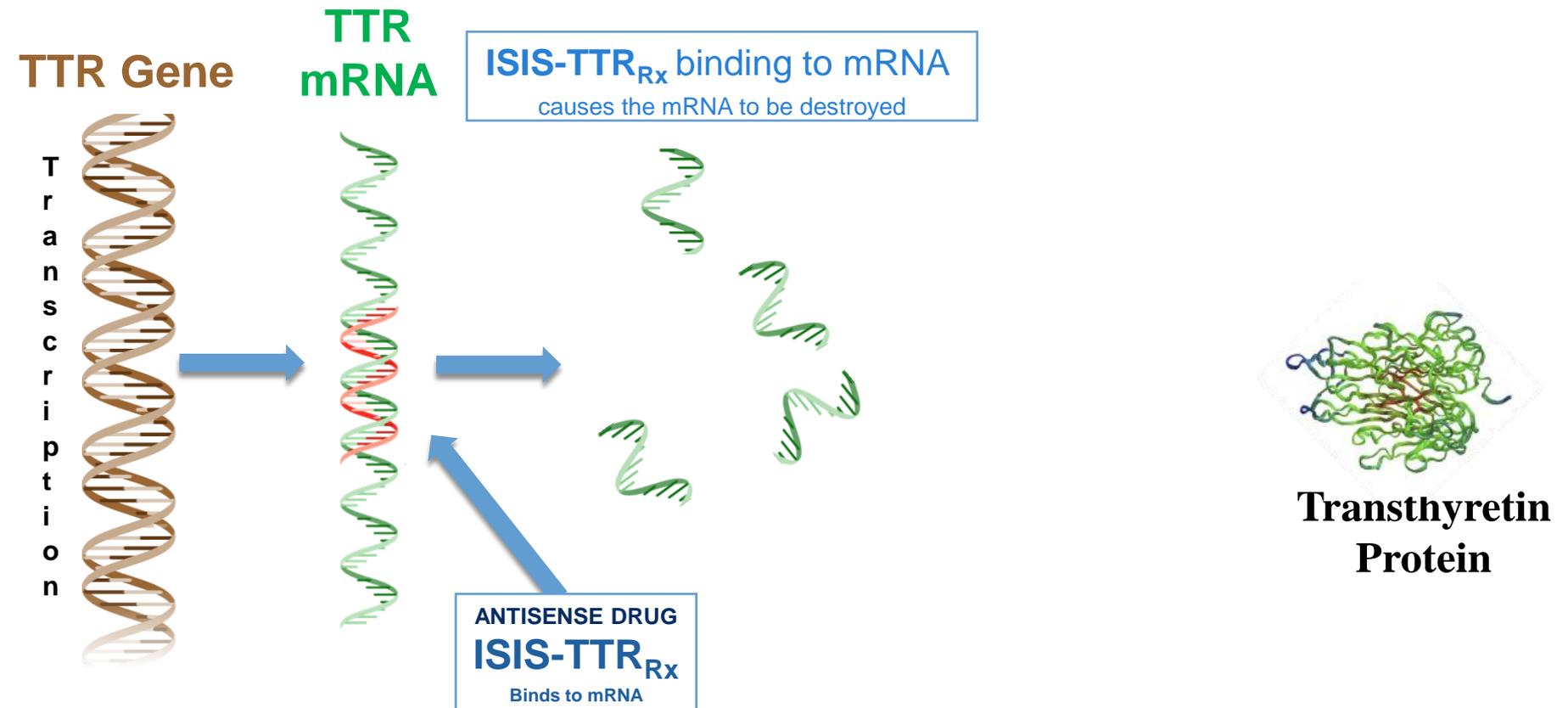
ISIS-TTR_{Rx}: Designed to Bind to TTR mRNA

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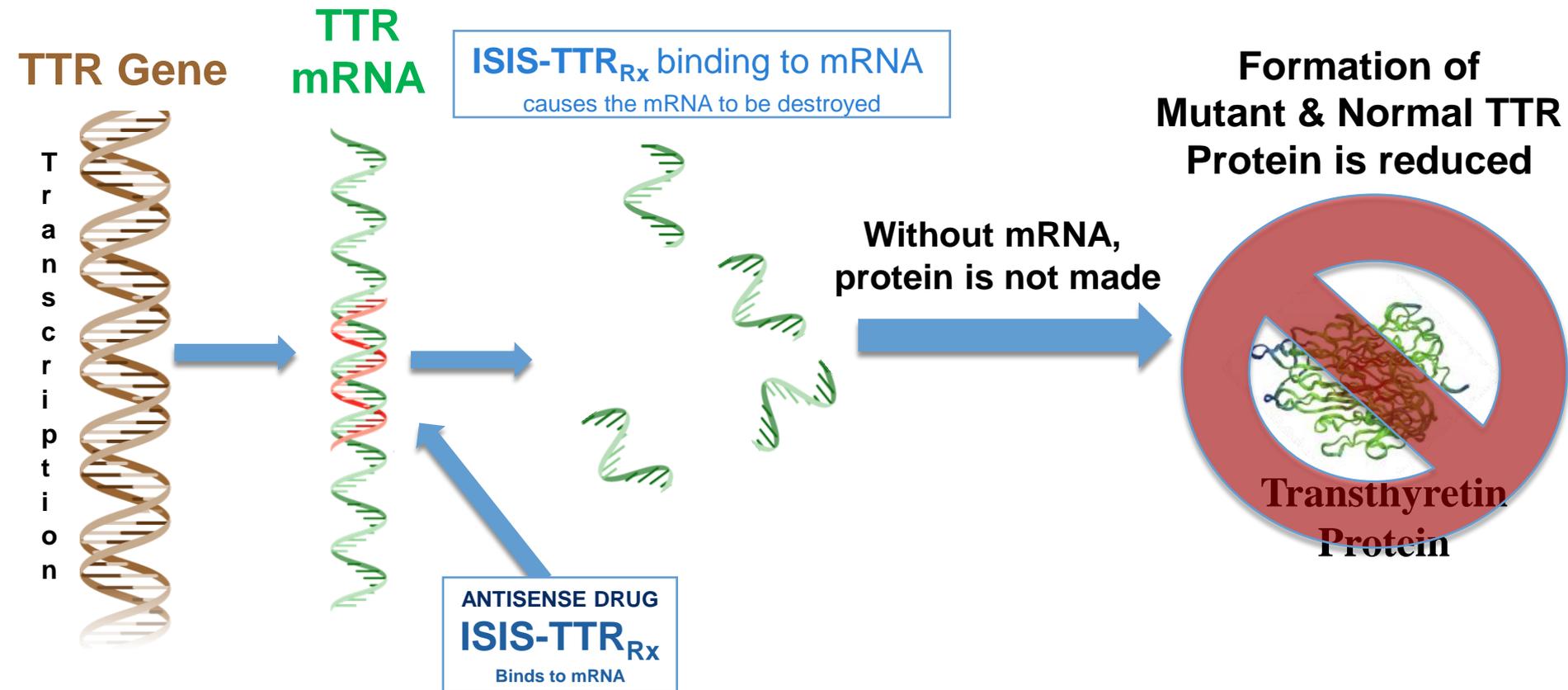
ISIS-TTR_{Rx}: Designed to Bind to TTR mRNA

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ISIS-TTR_{Rx}: Designed to Bind to TTR mRNA

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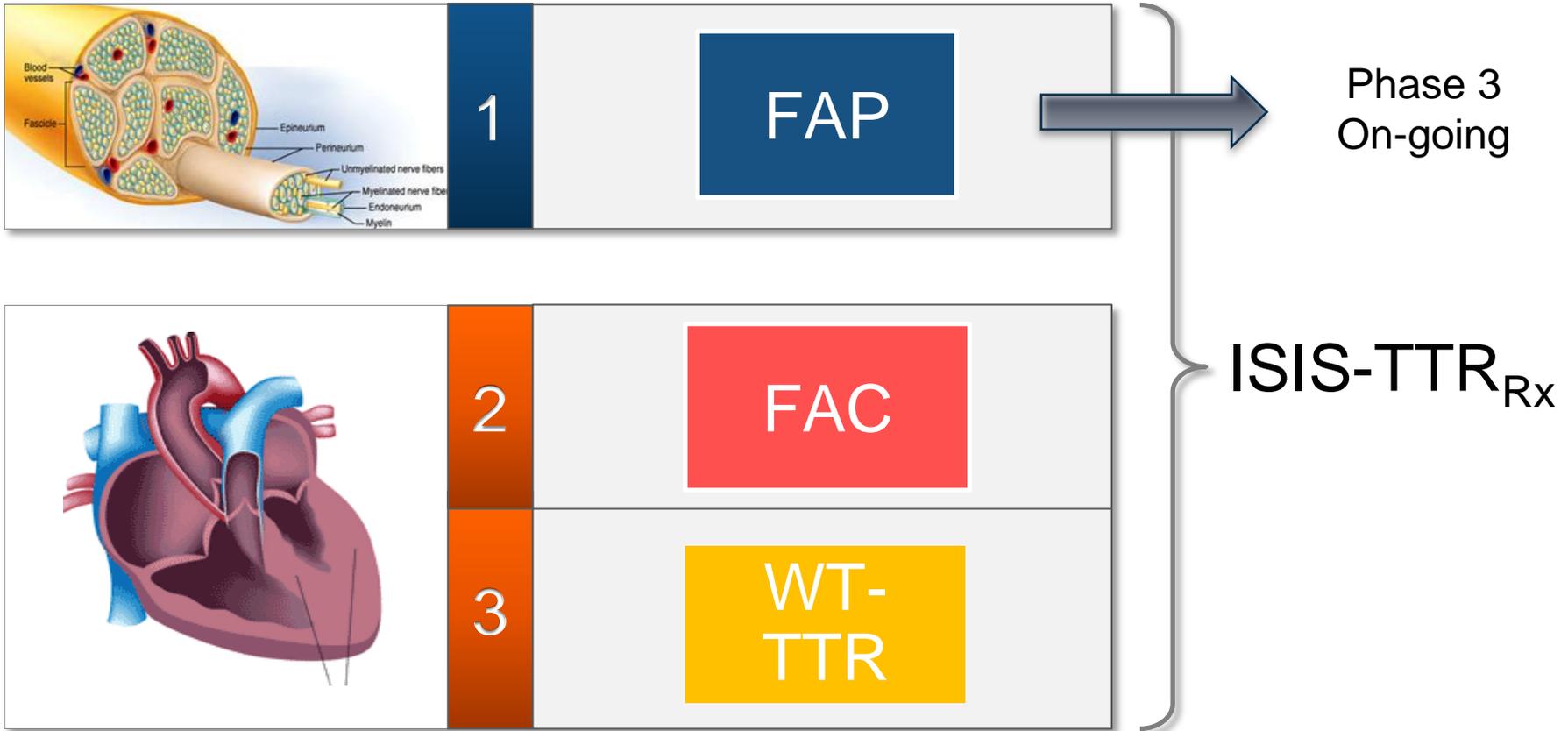


Less TTR RNA = Less TTR PROTEIN

Three Major Forms of ATTR

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

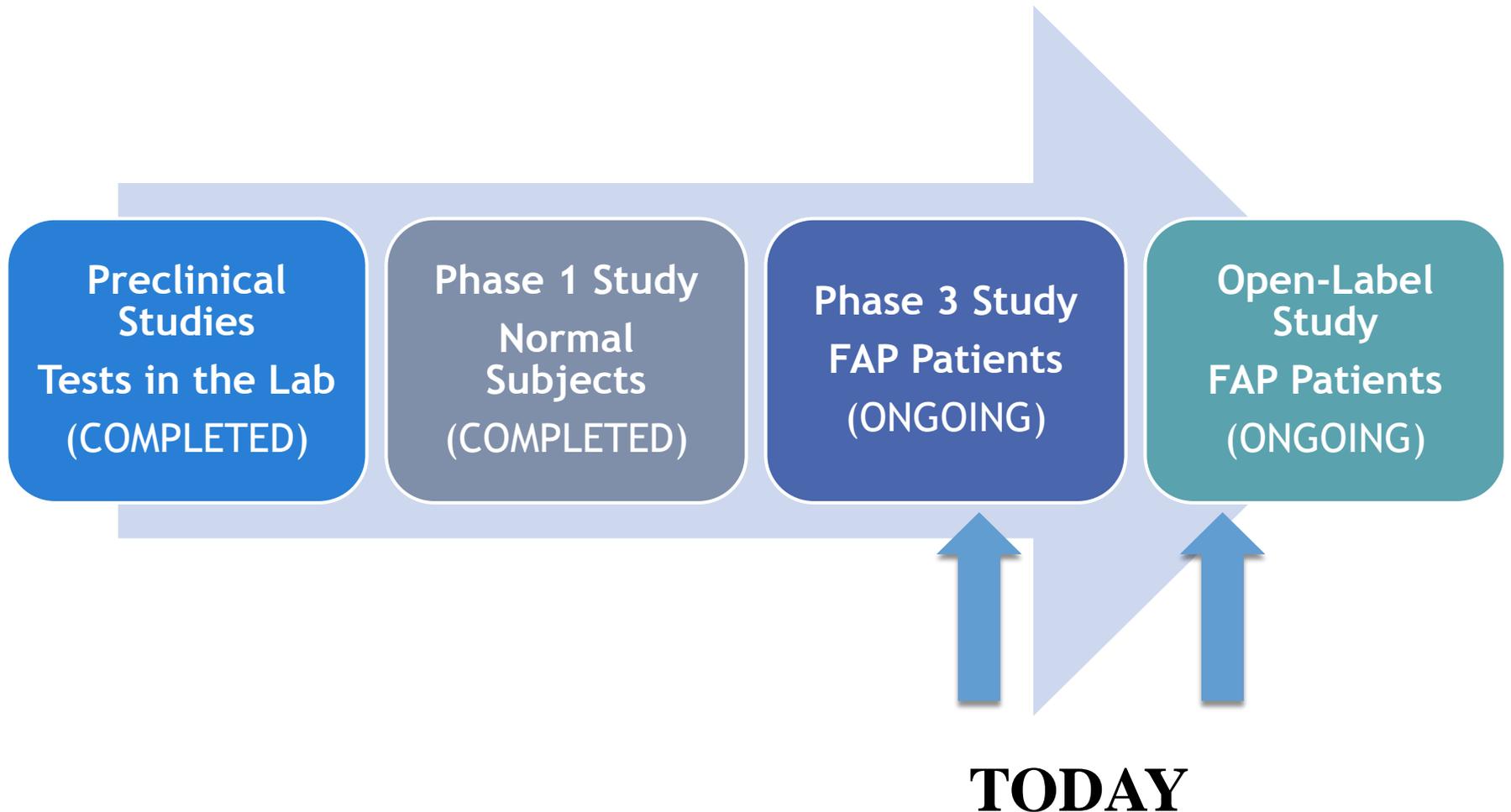
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ISIS-TTR_{Rx} in Familial Amyloid Polyneuropathy

Developing ISIS-TTR_{Rx}

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ISIS-TTR_{Rx} Phase 1 Study

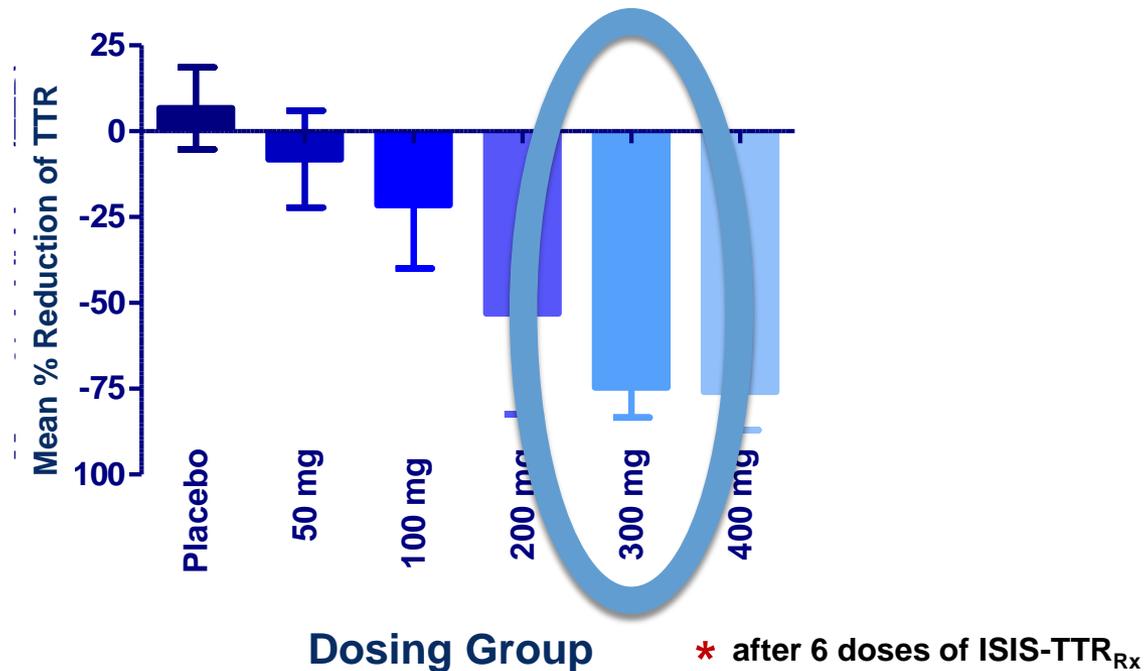
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- **Healthy volunteers**
- **Studied 5 different single and multiple doses of ISIS-TTR_{Rx}**
- **ISIS-TTR_{Rx} was given as a subcutaneous injection**
- **Designed to test effects of ISIS-TTR_{Rx} on:**
 - **Side Effects = Safety**
 - **Amount of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



Transthyretin Levels in Healthy Volunteers Treated with ISIS TTR_{RX}

Change in Plasma TTR, Phase 1 Study*



Results

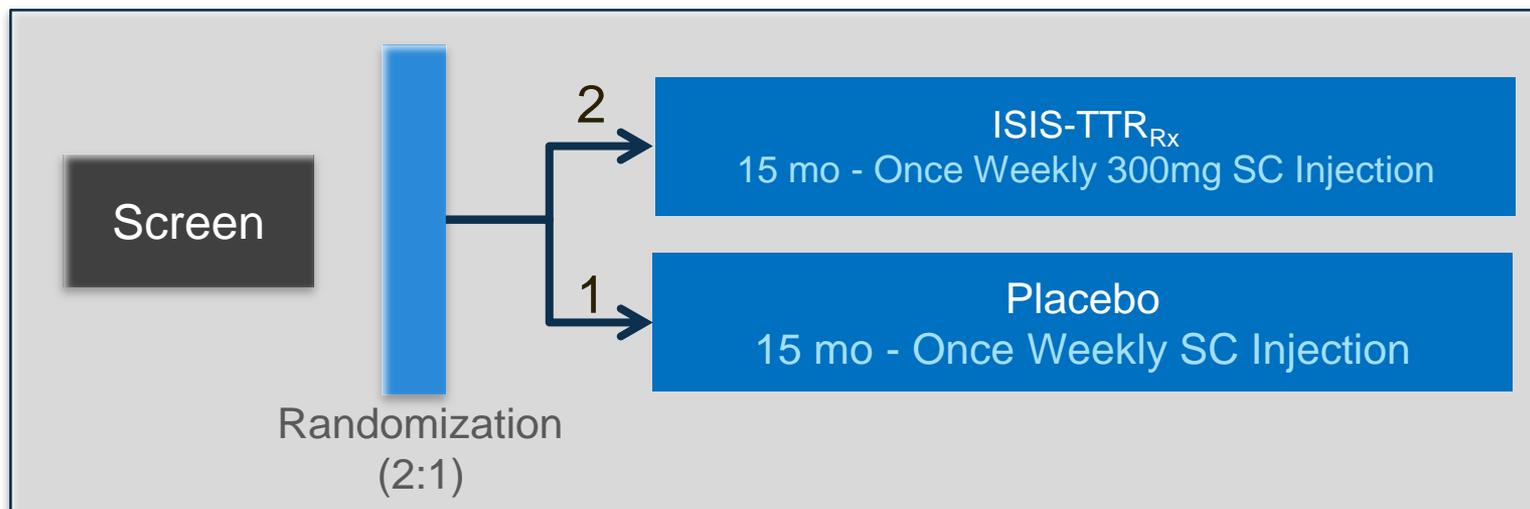
- ✓ Significant reductions in plasma TTR observed
- ✓ Phase 3 dose identified → 300mg

- **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



ISIS-TTR_{Rx} Phase 3 – In Progress

“The Isis Study”

Evaluate Efficacy

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

Evaluate Safety

- **Determine the safety of ISIS-TTR_{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

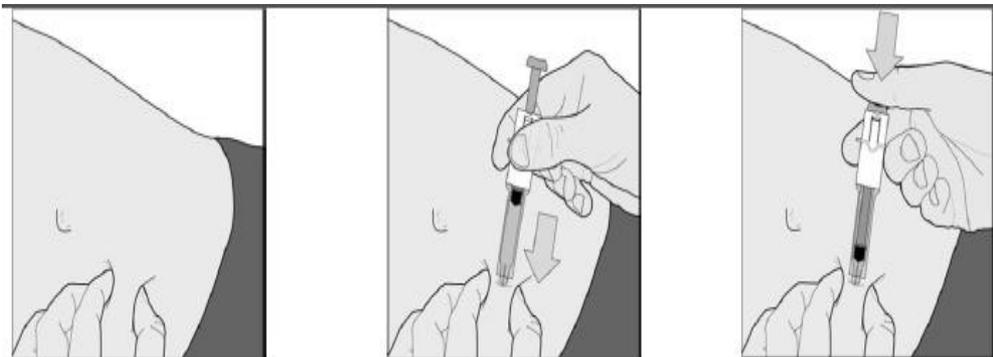
- **~195 TTR Amyloidosis Patients**

Treatment

- **15-month treatment period**
 - Weekly injections
- **Subcutaneous injections**
 - Both Placebo and ISIS-TTR_{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



ISIS-TTR_{Rx} Phase 3 Study

“The Isis Study”

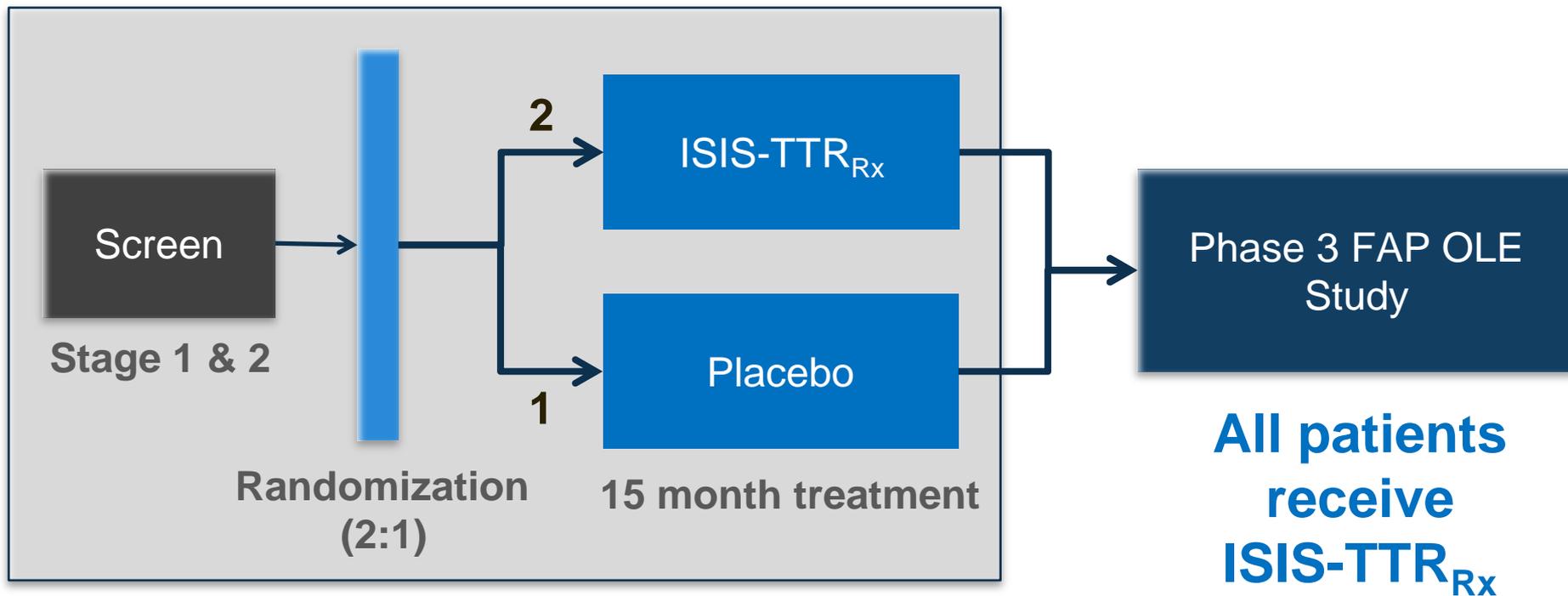


Patient Assistance

- 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_{Rx} FAP Open-Label Extension (OLE) Study

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Open-Label Extension (OLE) Study – In Progress

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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_{Rx} Phase 3 Global Study

Nine Participating Trial Sites in the United States



Steve Heitner
Portland, OR



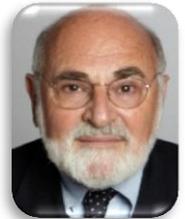
Morie Gertz
Rochester, MN



Thomas Brannagan
New York, NY



John Berk
Boston, MA



Peter Gorevic
New York, NY



Annabel Wang
Irvine, CA



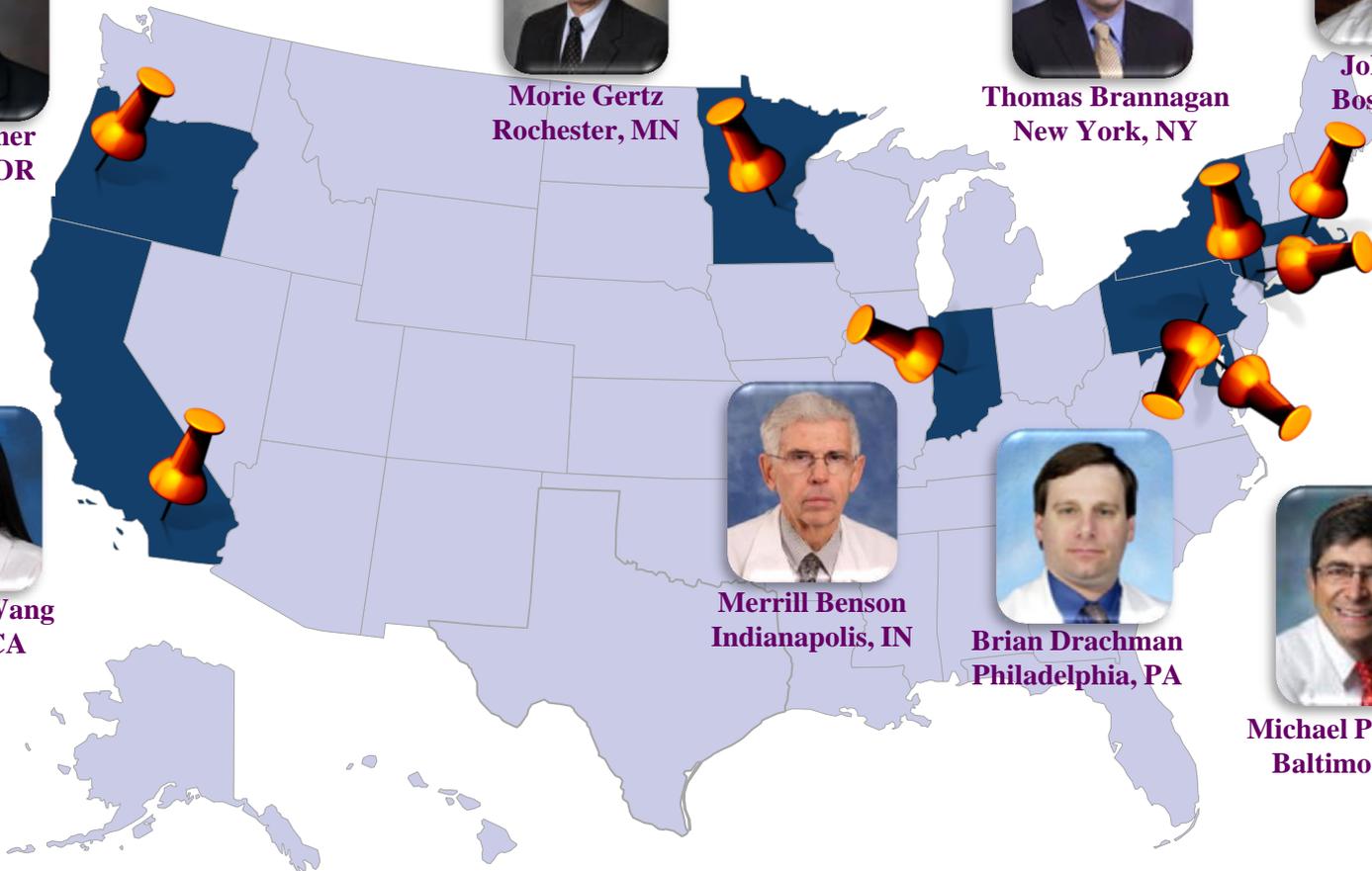
Merrill Benson
Indianapolis, IN



Brian Drachman
Philadelphia, PA



Michael Polydefkis
Baltimore, MD



US Trial Sites

Find Information on the ISIS TTR Amyloidosis Website

www.ttrstudy.com

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ISIS-TTR_{Rx}

TTR Amyloidosis / ISIS-TTR_{Rx} Clinical Trials / About Clinical Trials / About the Drug / Site Contacts



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-TTR_{Rx} in patients with Familial Amyloid Polyneuropathy (FAP), the form of TTR amyloidosis that causes nerve damage.



Interested in Knowing More?

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

Patient Volunteers Needed



Thank You

Patients and Families

Investigators and Site Staff

