Safety and Efficacy of Inotersen in Patients with Hereditary Transthyretin Amyloidosis with Polyneuropathy (NEURO-TTR)

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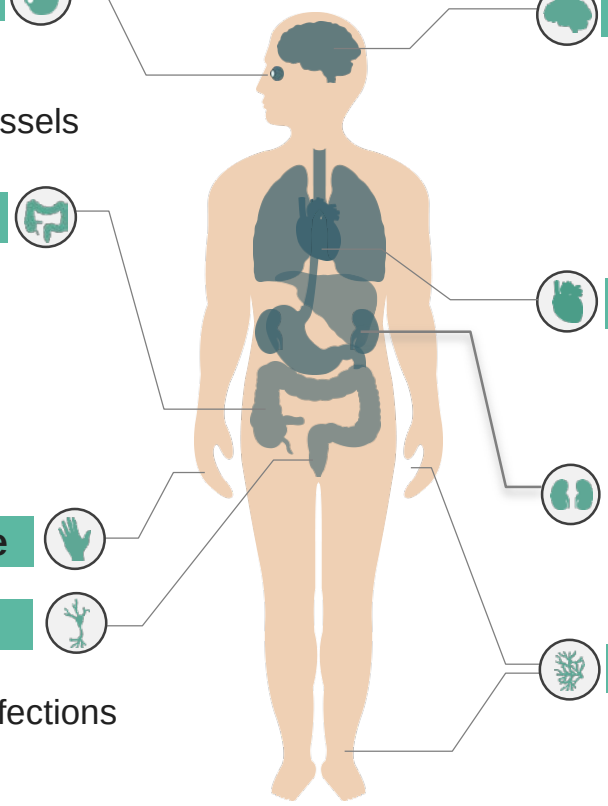
Disclosures

Dr. Wang is a study investigator

UNLABELED/UNAPPROVED USE: Inotersen is an investigational drug

NEURO-TTR was sponsored by Ionis Pharmaceuticals, Inc.
www.clinicaltrials.gov NCT01737398

TTR Amyloidosis is a Severe, Progressive and Fatal Disease Affecting Multiple Organs



Ocular Manifestations

- Vitreous opacities
- Glaucoma
- Abnormal conjunctival vessels
- Pupillary abnormalities

GI Manifestations

- Nausea & vomiting
- Early satiety
- Diarrhea
- Severe constipation
- Alternating episodes of diarrhea & constipation
- Unintentional weight loss

Carpal Tunnel Syndrome

Autonomic Neuropathy

- Orthostatic hypotension
- Recurrent urinary tract infections (due to urinary retention)
- Sexual dysfunction
- Sweating abnormalities

Cerebral Manifestations

- Progressive dementia
- Headache
- Ataxia
- Seizure
- Spastic paresis
- Stroke-like episode

Cardiovascular Manifestations

- Conduction block
- Cardiomyopathy
- Arrhythmia

Nephropathy

- Proteinuria
- Renal failure

Peripheral Sensorimotor Neuropathy

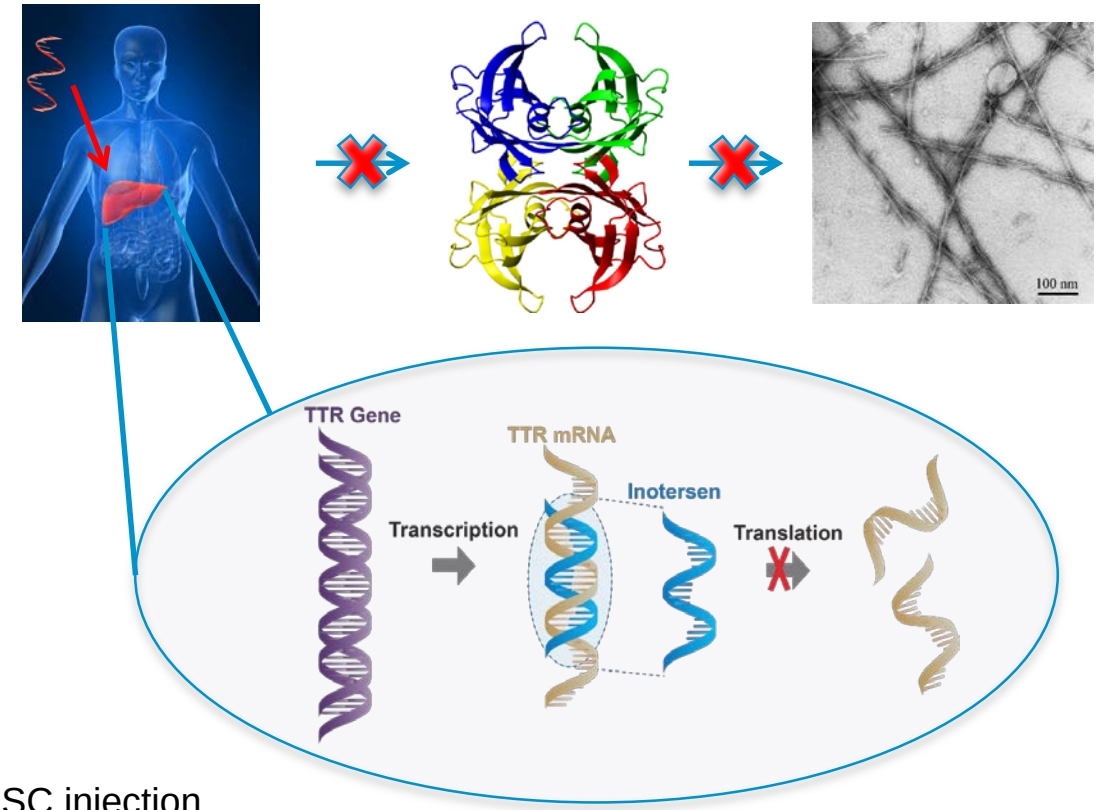
- Typically axonal, fiber-length-dependent, symmetric, and relentlessly progressive in distal to proximal direction

Adapted from: Conceição I et al. J Peripher Nerv Syst. 2016;21(1):5-9.

Inotersen (IONIS-TTR$_{Rx}$)

An RNA-Targeting Approach to Treat TTR-Related Amyloid Diseases

- Inotersen is a generation 2+ antisense oligonucleotide (ASO) inhibitor of transthyretin (TTR) protein production by the liver
- Binds wild-type and mutant TTR mRNAs to support RNase H1-mediated degradation of the target mRNA with consequent reduction of TTR protein synthesis



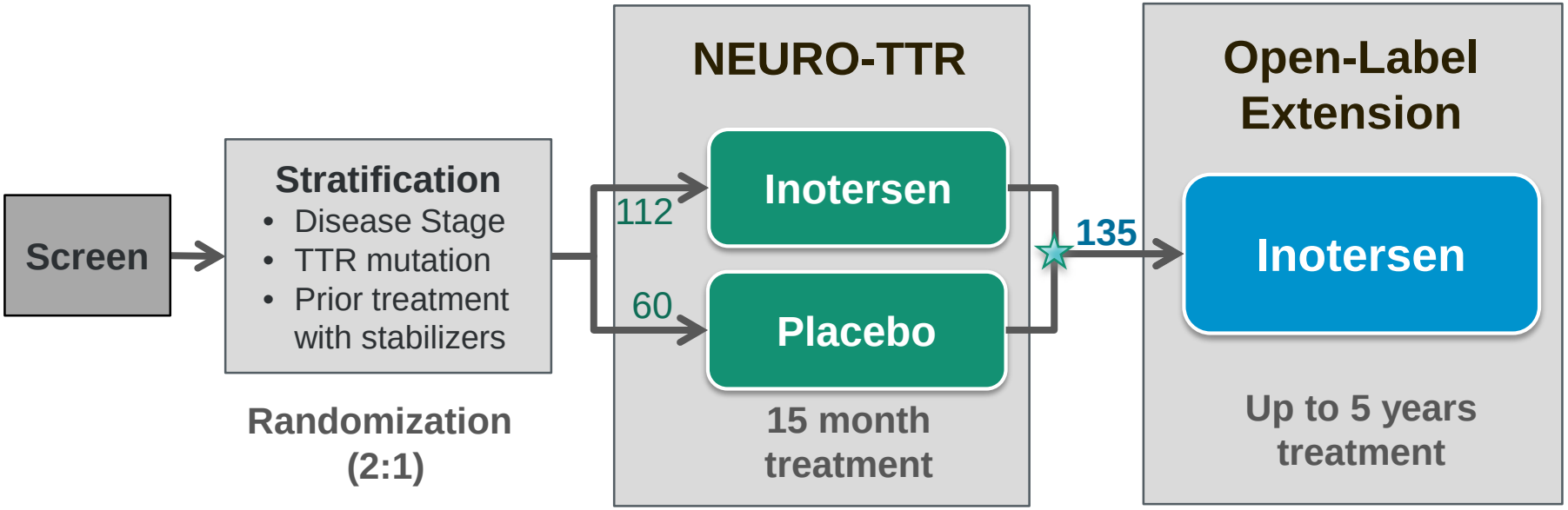
- Administered as a once-weekly SC injection
  - No premedication needed for administration
  - Long drug half-life provides consistent TTR reductions over time
- Convenient at home dosing

NEURO-TTR: A Phase 3 Study of Inotersen in Patients with Hereditary TTR Amyloid Polyneuropathy (hATTR-PN)

Eligibility: Patients with Stage 1 or Stage 2 hATTR-PN

Treatment: 300 mg weekly subcutaneous doses of inotersen, or placebo, for 15 months

Extension: Patients who completed NEURO-TTR were eligible for the open-label extension study in which all patients received inotersen



NEURO-TTR
polyNEUROpathy in TTR amyloidosis: assessment of antisense oligonucleotide therapy

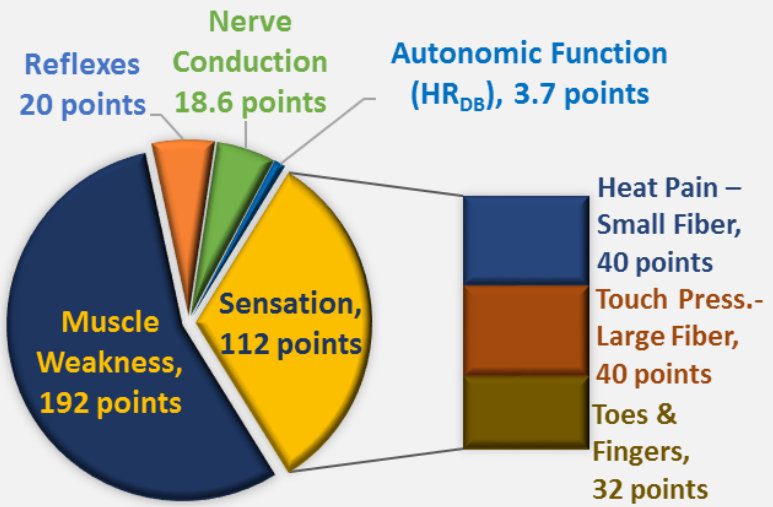
☆ Primary Efficacy Endpoints: Change from Baseline to Week 66 in the composite mNIS+7 score and Norfolk QOL-DN total score

Two Primary Endpoint Assessments

Measure motor, sensory, and autonomic neuropathy

mNIS+7

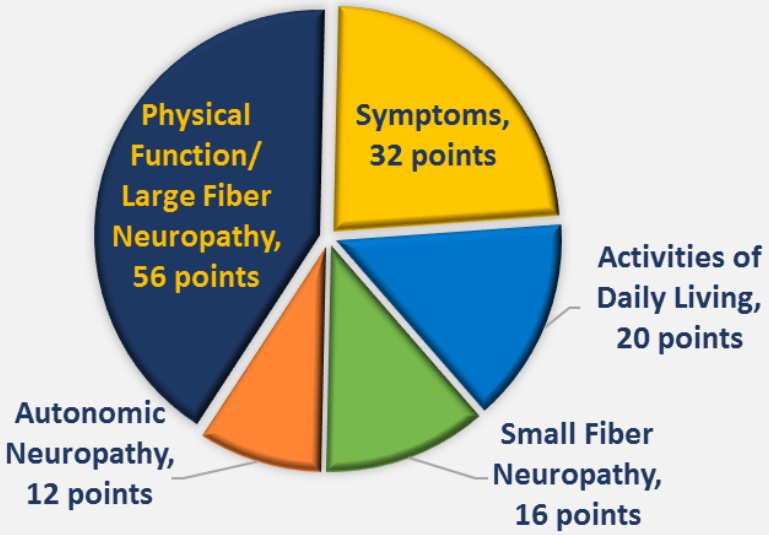
Modified Neuropathy Impairment Score
346.3 Points Total



Higher Score = Lower Function

Norfolk QoL-DN

Quality of life-Diabetic Neuropathy
5 Domains/136 Points Total



Higher Score = Poorer QoL

Vinik EJ, et al. J Peripher Nerv Syst. 2014

Inotersen Produced Significant Benefit in Both Primary Efficacy Endpoints

Analysis Change From Baseline	**Change from Baseline vs PBO*** Week 66	**Statistical Significance†** Week 66
mNIS+7	-19.73 (-26.43, -13.03)	p = 0.00000004
Norfolk QOL-DN	-11.68 (-18.29, -5.06)	p = 0.0006

Values in parentheses are the 95% confidence intervals. *Difference in least squares mean change from baseline between treatment groups. †Statistical significance for mNIS+7 (p=0.0005) and Norfolk QOL-DN (p=0.032) also achieved at Week 35.

Inotersen Produced Significant Benefit in Primary Efficacy Endpoints for Key Stratification Subgroups at Week 66

Change From Baseline	Statistical Significance (*vs* Placebo)	
Stratification	**mNIS+7**	**NORFOLK QOL-DN**
Val30Met	p < 0.001	p = 0.010
Non-Val30Met	p < 0.001	p = 0.025
Stage I Disease	p < 0.001	p = 0.019
Stage II Disease	p < 0.001	p = 0.008
Previous use of stabilizers	p < 0.001	p = 0.052
Treatment Naive	p < 0.001	p = 0.003

NEURO-TTR

polyNEUROpathy in TTR amyloidosis: assessment of antisense oligonucleotide therapy

Summary of Results

NEURO-TTR
polyNEUROpathy in TTR amyloidosis: assessment of antisense oligonucleotide therapy

Clinically and highly statistically significant benefit demonstrated in both mNIS+7 and Norfolk QOL-DN endpoints in favor of inotersen treatment

- Statistical significance, vs placebo, achieved as early as 8 months
- Quality of life results indicate that improvements in patients' neurological status is providing a meaningful impact on their well being

Inotersen was overall well tolerated and had an acceptable safety profile

- More than 80% of patients completed the study
- More than 95% of patients who completed NEURO-TTR enrolled in the open-label extension study
- Key safety findings of thrombocytopenia and renal events were monitorable & manageable

Benefit demonstrated across a diverse hATTR population

NEURO-TTR Investigators

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IONIS PHARMACEUTICALS