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

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ABSTRACT - POSTER #S318WIP

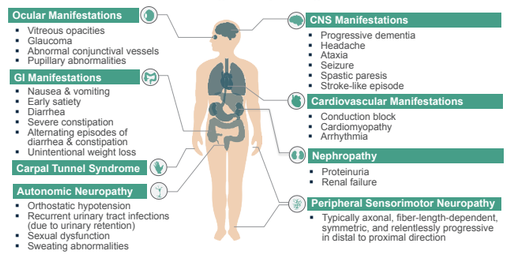
Transthyretin (TTR) transports vitamin A and thyroxine to peripheral tissues. In patients with hereditary TTR amyloid polyneuropathy (hATTR-PN), a point mutation in the TTR gene destabilizes TTR protein to induce deposition of amyloid in organs including peripheral and autonomic nerves. Amyloid deposition eventually leads to multi-organ failure, with life expectancy 5-15 years from symptom onset. Inotersen is a generation 2+ antisense oligonucleotide (ASO) inhibitor of TTR protein production.

We conducted a world-wide randomized, double-blind, placebo-controlled phase 3 study of inotersen in patients with hATTR-PN (NEURO-TTR, NCT01737398). Eligible patients were adults who had Stage I (ambulant) or Stage II (ambulant with assistance) disease. The primary endpoints were change from baseline in the composite modified Neuropathy Impairment Score+7 (mNIS+7) and patient reported Norfolk Quality of Life Diabetic-Neuropathy score. 172 patients were randomized (2:1) and received 300 mg weekly SC doses of inotersen, or placebo. Eighty percent of patients completed the 15-month treatment period. Inotersen-treated patients achieved statistically significant benefit compared to placebo for both primary endpoints. Key safety findings were thrombocytopenia and renal dysfunction. More than 95% who completed treatment have participated in the open-label extension study.

INTRODUCTION

- Transthyretin (TTR) is a 55 kDa protein composed of 4 identical subunits, primarily synthesized in the liver and secreted into the plasma, and is a transporter of thyroxine (T4) and retinol (vitamin A)
- Hereditary transthyretin amyloidosis (hATTR) is a rare systemic autosomal dominant disorder caused by mutations in the TTR gene with an estimated 50,000 patients world-wide
  - TTR mutations destabilize the normal tetrameric structure of TTR to cause dissociation into free monomers that form amyloid deposits in multiple organs
  - It is now appreciated that hATTR is a single systemic disease presenting with a wide spectrum of manifestations with a high percentage of patients with both nerve and heart involvement
- Major clinical manifestations of hATTR are intractable peripheral sensorimotor and autonomic neuropathy and cardiomyopathy
  - Sensory and motor neuropathy are length dependent, first presenting in the lower extremities
  - Amyloid deposits in the heart lead to restrictive cardiomyopathy and heart failure
  - Gastrointestinal symptoms of diarrhea and/or profound constipation often follow, reflecting autonomic dysfunction
  - Motor neuropathy results in mobility impairment that ultimately advances to requiring the full time use of a wheelchair
  - Some patients develop renal deposits, often with microalbuminuria as the initial presentation which can progress to renal failure
- The mean life expectancy is 3-15 years
  - Poorer prognosis is associated with cardiomyopathy involvement
- The most common causes of death are malnutrition and cachexia, renal failure, or cardiac disease

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

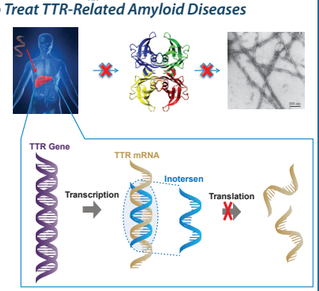


Adapted from: Conceição I et al. *J Peripher Nerv Syst*. 2016;21(1):5-9.

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

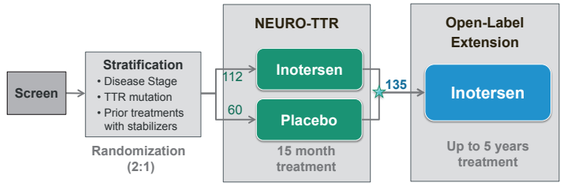
An RNA-Targeting Approach to Treat TTR-Related Amyloid Diseases

- 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



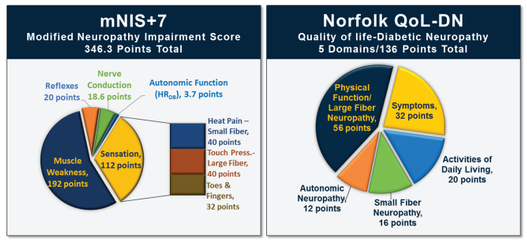
PIVOTAL PHASE 3 OBJECTIVES & STUDY DESIGN

World-wide randomized placebo-controlled phase 3 study
Patients with Stage 1 or Stage 2 hATTR
300 mg weekly, subcutaneous doses inotersen, or placebo, for 15 months

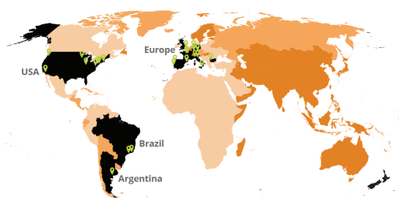


Two Primary Endpoint Assessments

Measure Motor, Sensory, and Autonomic Neuropathy



Ten Countries - 24 Sites



Argentina, Brazil, New Zealand
France, Germany, Italy
Portugal, Spain
United Kingdom
United States

Study Objective	To evaluate the clinical efficacy and safety of inotersen as compared to placebo in patients with TTR amyloid polyneuropathy (hATTR-PN)
Study Participants	**Key Inclusion Criteria** • hATTR-PN Stage 1 (ambulant) or Stage 2 (ambulant with assistance) • NIS score 10-130 inclusive • Positive amyloid biopsy • TTR variant by genotyping • Age 18-82 **Key Exclusion Criteria** • *NYHA ≥ 3* • *Previous liver transplant*
Stratification Factors	• Stage 1 vs. Stage 2 • V30M TTR mutation vs. non-V30M TTR mutation • Prior treatment with either tafamidis or diflunisal vs. no known prior treatment
Primary Endpoints	• Composite Neuropathy Impairment Score (mNIS+7) • Norfolk Quality of Life –Diabetic Neuropathy (QoL-DN)

PHASE 3 CLINICAL STUDY FINDINGS

Baseline Demographics and Disease Characteristics Represent a Diverse hATTR Patient Population

Characteristic	Placebo	Inotersen	Total
N	60	112	172
Age (yrs), mean (SD)	59.5 (14.05)	59.0 (12.53)	59.2 (13.04)
Male sex, n (%)	41 (68.3)	77 (68.8)	118 (68.6)
Race, n (%)			
White	53 (88.3)	105 (93.8)	158 (91.9)
Asian	3 (5.0)	1 (0.9)	4 (2.3)
Black	1 (1.7)	3 (2.7)	4 (2.3)
Other or multiple	3 (5.0)	3 (2.7)	6 (3.5)
Region, n (%)			
Europe	23 (38.3)	37 (33.0)	60 (34.9)
North America	26 (43.3)	56 (50.0)	82 (47.7)
South America/Australasia	11 (18.3)	19 (17.0)	30 (17.4)
Stratification Factors			
Val30Met TTR genotype, n (%)	32 (53.3)	58 (51.8)	90 (52.3)
Disease Stage 1, n (%)	39 (65.0)	74 (66.1)	113 (65.7)
Previous Use of Stabilizers, n (%)	33 (55.0)	61 (54.5)	94 (54.7)
CM-ECHO Set, n (%)	33 (55.0)	75 (67.0)	108 (62.7)

Inotersen Produced Significant Benefit in Both Primary 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

*Difference in least squares mean change from baseline between treatment groups. Values in parentheses are the 95% confidence intervals. †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 Both Primary Efficacy Endpoints for Key Stratification Subgroups at Week 66

Change From Baseline	Statistical Significance Inotersen 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

Safety Findings

Key safety findings of thrombocytopenia and renal events were monitorable and manageable

Thrombocytopenia

- Three serious adverse events (all inotersen treated)
  - Two patients fully recovered; one patient died due to intracranial hemorrhage and low platelet levels
- One additional patient treated with inotersen discontinued due to non-serious thrombocytopenia

Renal Events

- Five patients discontinued due to a renal event
  - One placebo-treated patient
  - Two inotersen-treated patients due to pre-existing renal disease
  - Two inotersen-treated patients due to treatment emergent renal SAEs

Enhanced platelet & renal monitoring has proven effective since implementation

- All five SAEs described above occurred prior to full implementation of enhanced monitoring

SUMMARY OF FINDINGS

- Both primary endpoints (mNIS+7 and Norfolk QoL-DN) demonstrated clinically and statistically significant benefit 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
- Significant improvement was also achieved in key stratification subgroups within the diverse NEURO-TTR study population
- 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 the study participated in the open-label extension study
  - Key safety findings of thrombocytopenia and renal events were monitorable & manageable

CONCLUSIONS

- Both primary endpoints were met by inotersen in the randomized placebo-controlled phase 3 study, NEURO-TTR
- Benefit demonstrated across a diverse hATTR population
- Inotersen demonstrated an acceptable safety and tolerability profile for hATTR, a severe and fatal disease with few treatment options
- The results from this pivotal phase 3 study support a highly favorable benefit-risk profile for patients with hATTR
- Marketing authorization submissions are planned for Q4, 2017

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DISCLOSURES & ACKNOWLEDGEMENTS

Disclosures

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