SAFETY AND EFFICACY OF INOTERSEN IN PATIENTS WITH HEREDITARY TRANSTHYRETIN AMYLOIDOSIS POLYNEUROPATHY (hATTR-PN)

Teresa Coelho, MD

Centro Hospitalar do Porto
Porto, Portugal

Disclosures

- Hospital Santo António was paid per protocol for clinical trials from FoldRx, Pfizer, Ionis Pharmaceuticals and Alnylam

- Dr. Coelho received financial support from Pfizer, Ionis Pharmaceuticals and Alnylam to attend scientific meetings

- Dr. Coelho integrates the speakers' bureau of Pfizer and received honoraria

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

Ocular Manifestations

- Vitreous opacities
- Glaucoma
- Abnormal conjunctival vessels
- Papillary 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
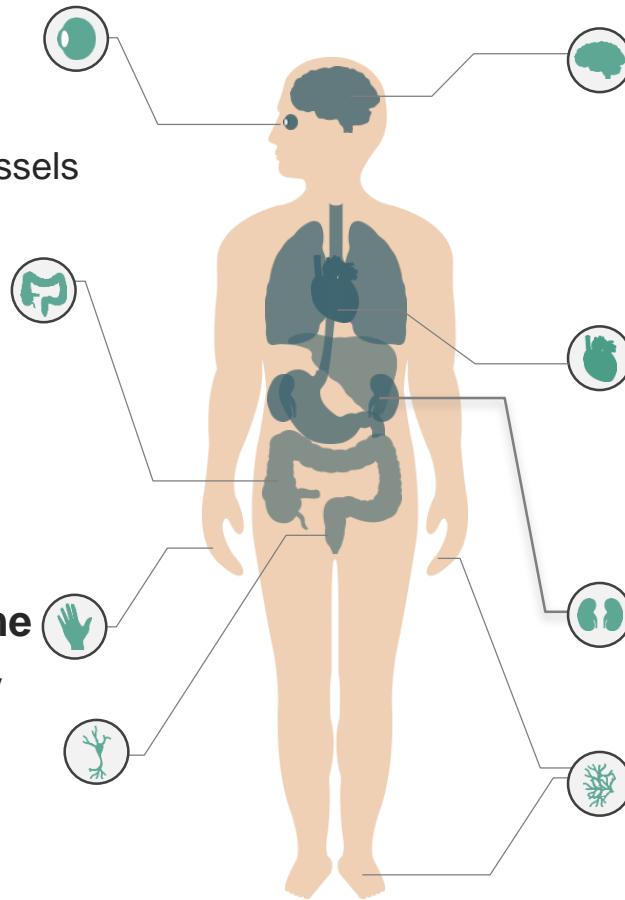
Cerebral Amyloid Angiopathy

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

Cardiovascular Manifestations

- Conduction blocks
- Cardiomyopathy
- Arrhythmia
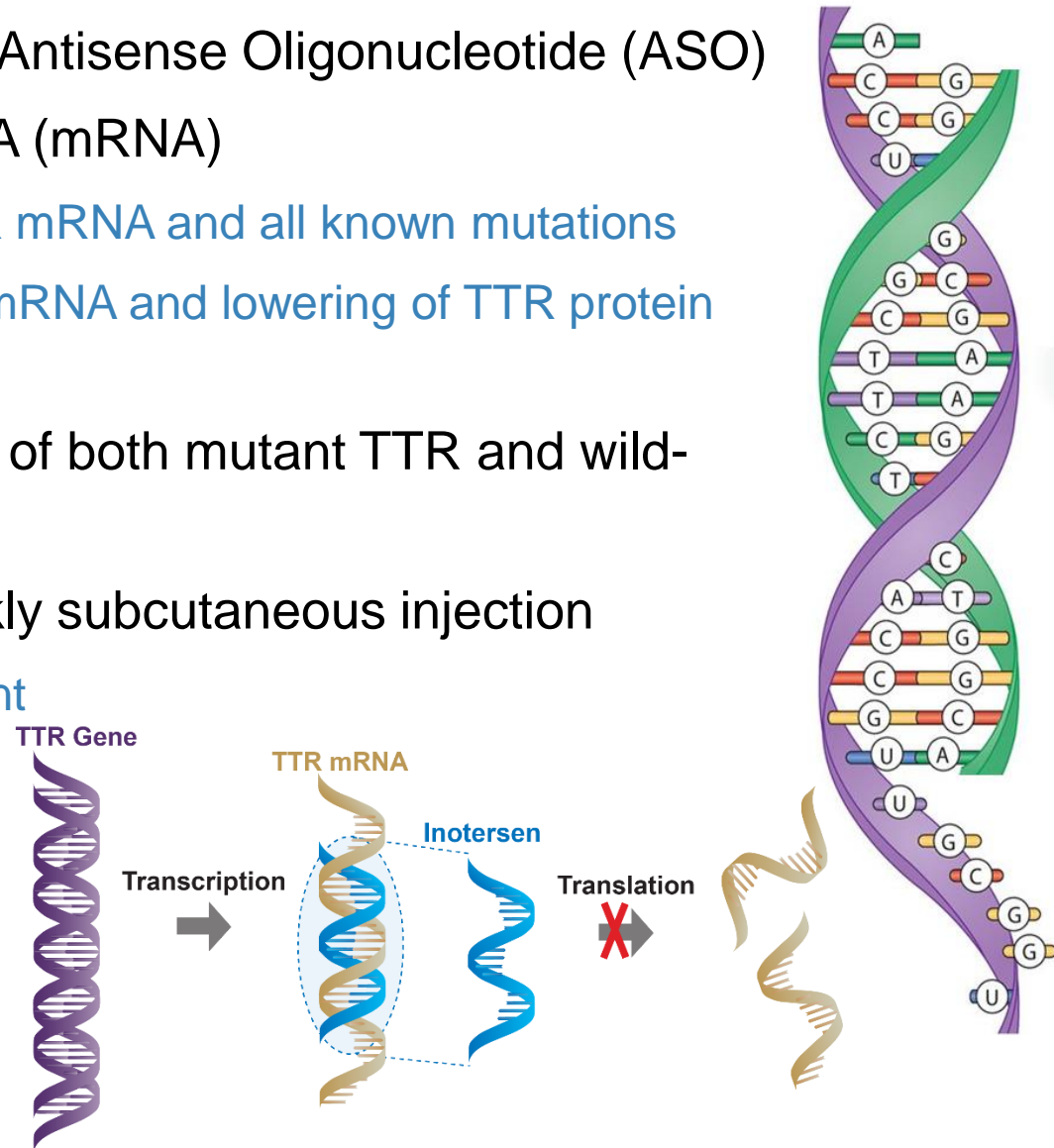
Nephropathy

- Proteinuria
- Renal failure

Peripheral sensory-motor neuropathy

- Typically axonal, fiber-length-dependent, symmetric, and relentlessly progressive in distal to proximal direction
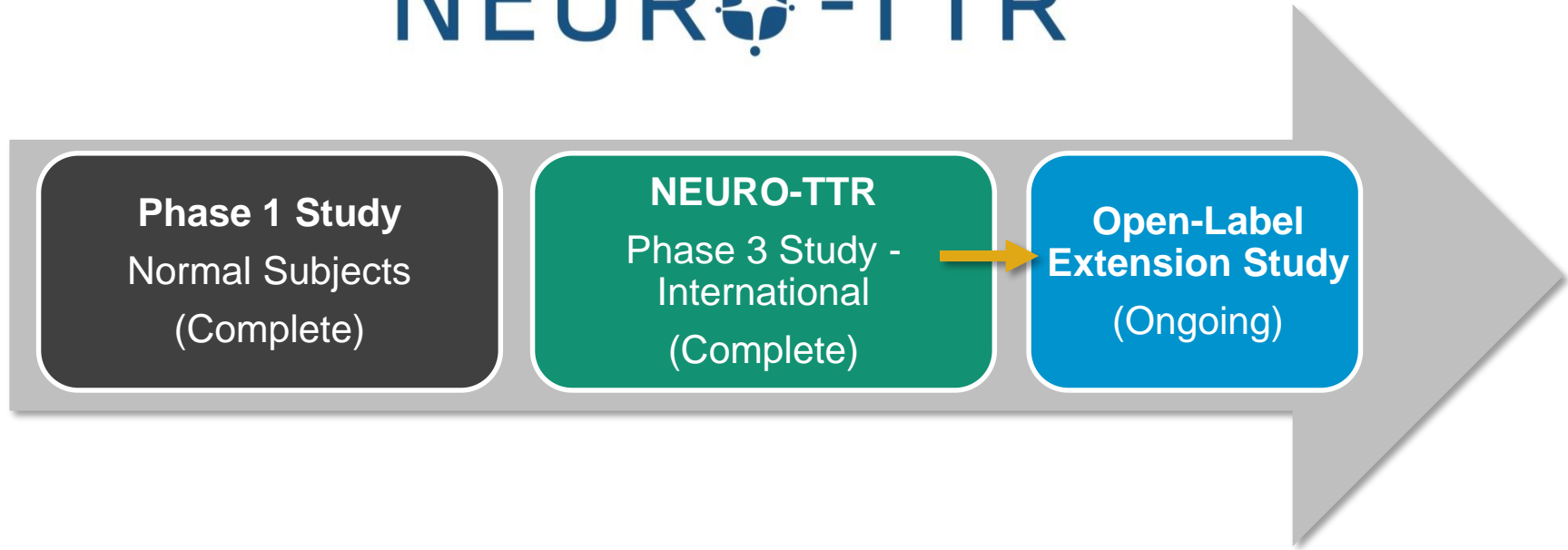
Inotersen (IONIS-TTR$_{Rx}$)
An RNA-Targeting Approach to Treat TTR-Related Amyloid Diseases

- Inotersen, a Generation 2.0+ Antisense Oligonucleotide (ASO)

- Binds to TTR messenger RNA (mRNA)
  - Binds to wild-type (normal) TTR mRNA and all known mutations
  - Results in degradation of TTR mRNA and lowering of TTR protein production

- Inotersen reduces production of both mutant TTR and wild-type TTR protein by the liver

- Administered as a once-weekly subcutaneous injection
  - Long half-life provides consistent TTR reductions over time
  - No premedication
 - Patients can self-administer at home

TTR Gene

TTR mRNA

Inotersen

Transcription

Translation

NEUR🔵-TTR

polyNEUROpathy in TTR amyloidosis:
assessment of antisense oligonucleotide therapy

NEUR🔵-TTR

Phase 1 Study
Normal Subjects
(Complete)

NEURO-TTR
Phase 3 Study - International
(Complete)

Open-Label Extension Study
(Ongoing)

NEURO-TTR is a 15-month treatment (300mg), placebo-controlled study in patients with Stage 1 and Stage 2 ATTR Polyneuropathy (hTTR-PN)

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

NEURO-TTR
polyNEUROpathy in TTR amyloidosis: assessment of antisense oligonucleotide therapy
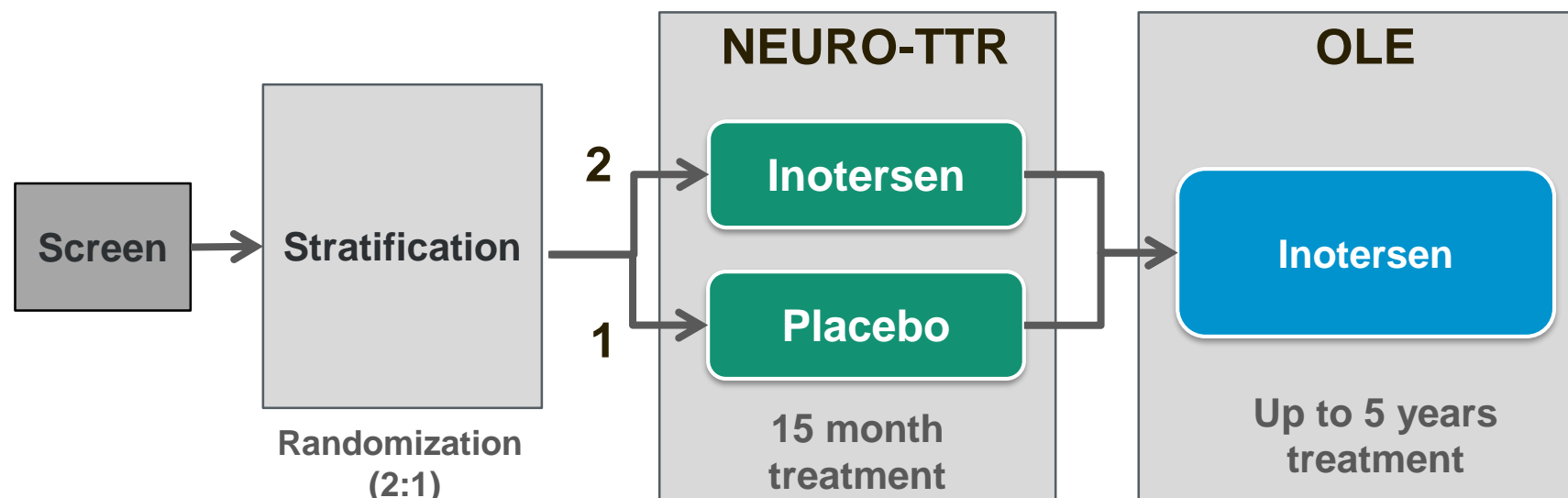
- <u>Stratification:</u>
  - Stage 1 vs. Stage 2
  - V30M TTR mutation vs. non-V30M TTR mutation
  - Previous treatment with either tafamidis or diflunisal vs. no known previous treatment
- <u>Primary endpoints:</u>
  - Modified Neuropathy Impairment Score +7 (mNIS+7)
  - Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN)

Two Primary Endpoints

Composite Neuropathy Impairment Score (mNIS+7)

Patient Reported Quality of Life (Norfolk QOL-DN)

NEURO-TTR

polyNEUROpathy in TTR amyloidosis:
assessment of antisense oligonucleotide therapy

mNIS+7	Norfolk Quality of Life
• Composite Neuropathy Impairment Score	• Neuropathy QOL Instrument
• Measures:	• Sum of 5 Domains
- Motor neuropathy	• Measures:
- Sensory neuropathy	- Total quality of life
- Autonomic neuropathy	- Physical functioning/large fiber neuropathy
• Includes:	- Activities of daily living
- Motor, reflex and sensation deficits scored by neurologist	- Symptoms
- Nerve conduction tests	- Small fiber neuropathy
- Full body quantitative sensation testing of small and large fibers	- Autonomic neuropathy
- Autonomic deficit by HRDB	

Baseline Demographics By Region
172 Patients Enrolled/Received Study Drug

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United States (n=82)

Mean Age:	65 yr (40-78)
Male:	74% (n=61)
Mean mNIS+7:	71 (11-175)
%V30M:	26% (n=21)
CM-Echo Set:	77% (n=63)
Txt (stabilizers) Naïve:	48% (n=39)
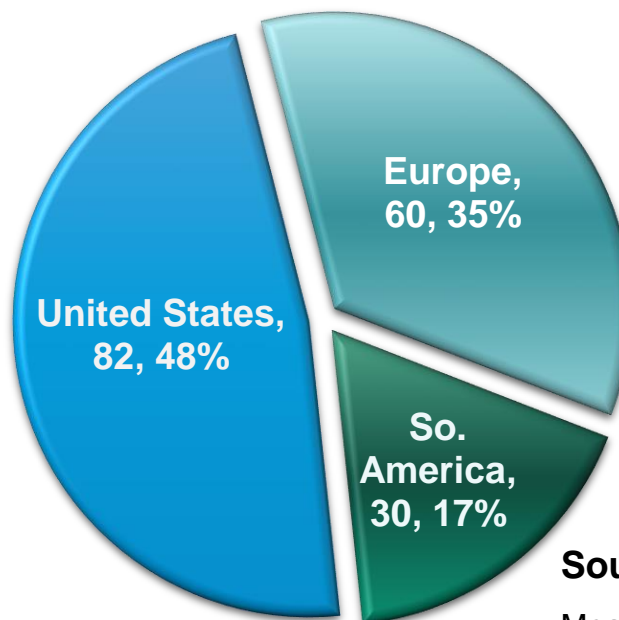
Europe (n=60)

Mean Age:	57 yr (27-81)
Male:	65% (n=39)
Mean mNIS+7:	88 (30-169)
%V30M:	67% (n=40)
CM-Echo Set:	57% (n=34)
Txt (stabilizers) Naïve:	22% (n=13)

South America/NZ (n=30)

Mean Age:	49 yr (28-73)
Male:	60% (n=18)
Mean mNIS+7:	76 (13-160)
%V30M:	93% (n=28)
CM-Echo Set:	37% (n=11)
Txt (stabilizers) Naïve:	70% (n=21)

Pie chart: United States, 82, 48%; Europe, 60, 35%; So. America, 30, 17%

Demographics (Total)	
Mean Age (yr)	59.2
Male	118 (68.6%)
Mean mNIS+7 (SD)	77.62 (37.63)
V30M	89 (51.7%)
Cardio-ECHO	108 (62.8%)
Prior Stabilizer Tx	99 (57.6%)

Twenty-Seven TTR Mutations Enrolled
52% Val30Met

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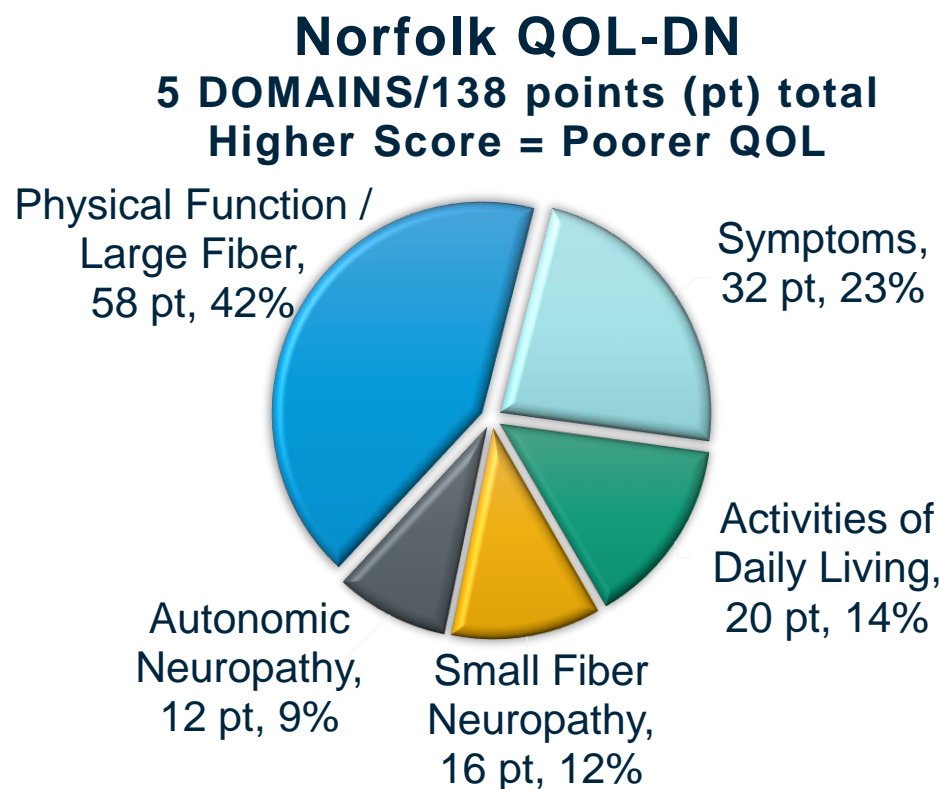assessment of antisense oligonucleotide therapy
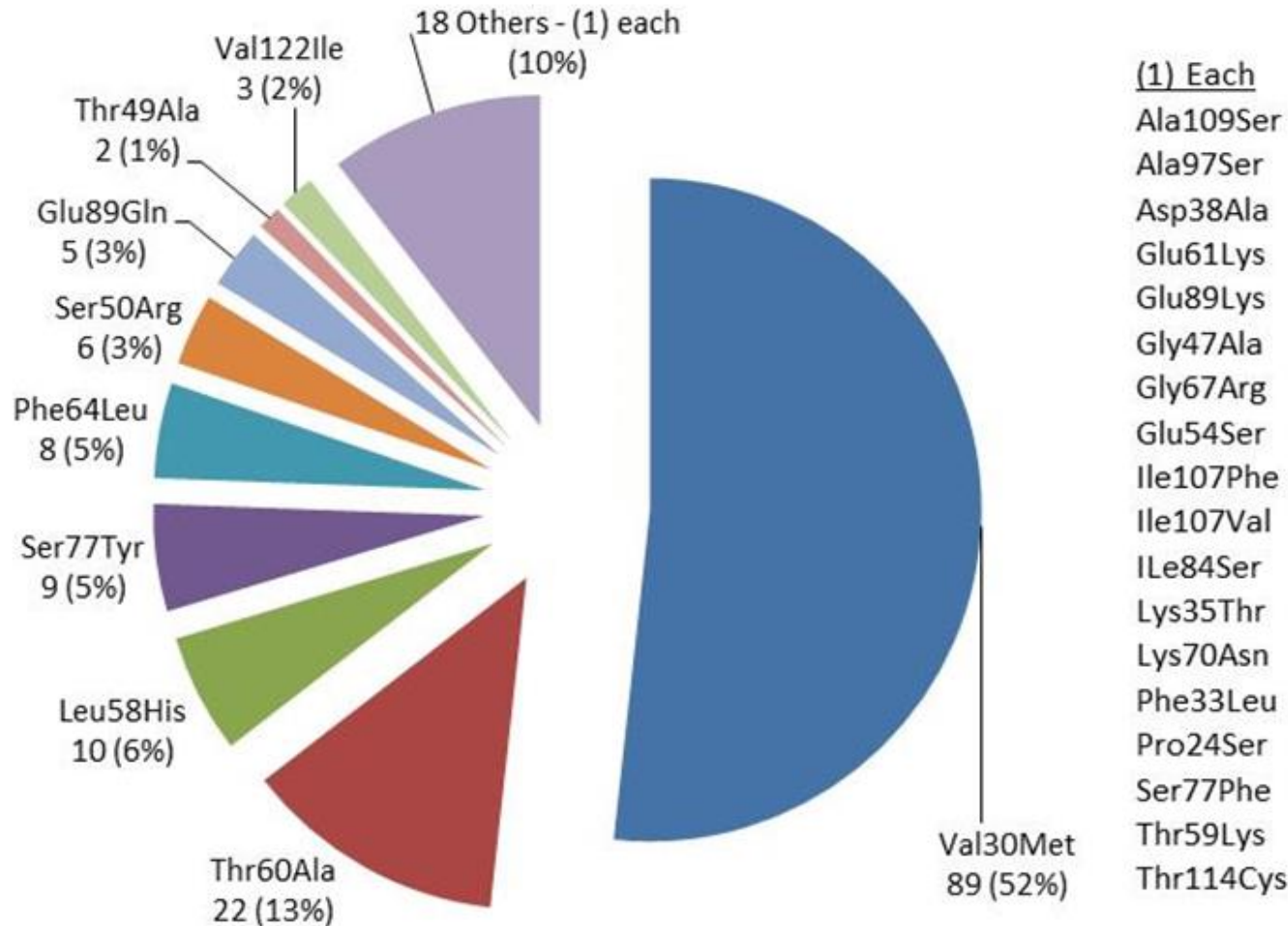
Inotersen Produced Significant Benefit in mNIS+7 Primary Endpoint

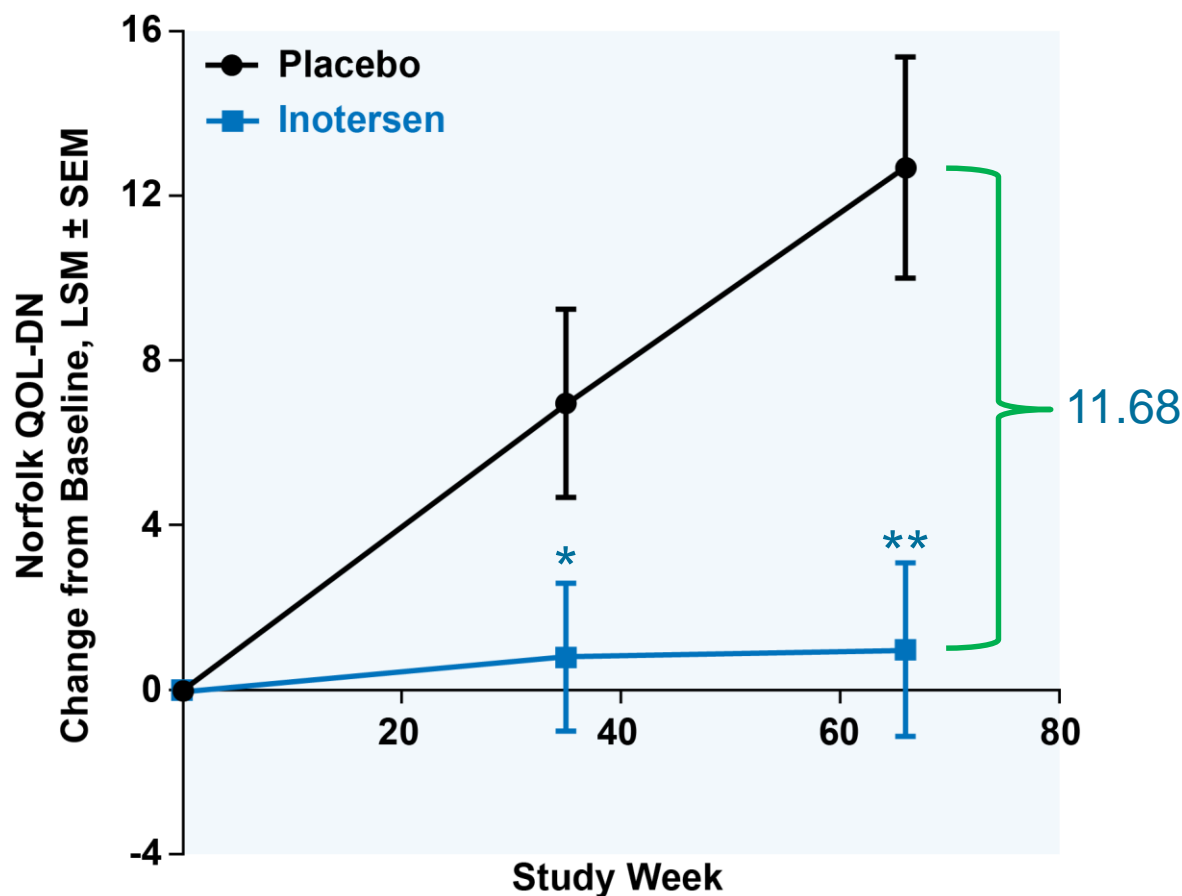| Analysis Change From Baseline	Statistical Significance at Month 8 Inotersen vs Placebo	Statistical Significance at Month 15 Inotersen vs Placebo
mNIS+7 (Full Analysis Set)	$p = 0.0005$	$p = 0.00000004$
Val30Met	$p = 0.021$	$p < 0.001$
Non-Val30Met	$p = 0.007$	$p < 0.001$
Stage I Disease	$p = 0.005$	$p < 0.001$
Stage II Disease	$p = 0.033$	$p < 0.001$
Previous use of stabilizers	$p = 0.005$	$p < 0.001$
Treatment Naive	$p = 0.031$	$p < 0.001$

Norfolk QOL-DN
A Patient Reported Outcome Measure

➢ Validated (*Vinik et al.)* Instrument for Assessment of QoL in patients with hTTR-PN

➢ Reliable Indicator of the Impact of Disease Severity on QoL

- QoL scores increase with duration of symptoms

- Steeper increase in scores observed earlier in the course of disease

- Significant correlations between each domain and other measures of neurological function

Norfolk QOL-DN
5 DOMAINS/138 points (pt) total
Higher Score = Poorer QOL

Physical Function / Large Fiber, 58 pt, 42%

Symptoms, 32 pt, 23%

Activities of Daily Living, 20 pt, 14%

Autonomic Neuropathy, 12 pt, 9%

Small Fiber Neuropathy, 16 pt, 12%

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

Inotersen Produced Significant Benefit in Norfolk QOL-DN Primary Endpoint

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Analysis Change From Baseline	Statistical Significance at Month 8 Inotersen vs Placebo	Statistical Significance at Month 15 Inotersen vs Placebo
Norfolk QOL-DN (Full Analysis)	p = 0.032	p = 0.0006
Val30Met	p = 0.028	p = 0.010
Non-Val30Met	p = 0.441	p = 0.025
Stage I Disease	p = 0.291	p = 0.019
Stage II Disease	p = 0.029	p = 0.008
Previous use of stabilizers	p = 0.065	p = 0.052
Treatment Naive	p = 0.254	p = 0.003

Inotersen Produced Substantial and Highly Significant Benefit in the Norfolk QOL-DN Primary Endpoint

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LSM = Least Squares Mean

*p = 0.032
**p = 0.0006

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NEURO-TTR Top-line Safety Summary

- The key safety findings identified were thrombocytopenia and renal dysfunction (as previously identified)

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 Dysfunction

- Five patients discontinued due to a renal event
  - Four inotersen-treated patients: 2 met renal stopping rule and 2 experienced renal SAEs that led to discontinuation
  - One placebo-treated patient met renal stopping rule

- **Enhanced renal & platelet monitoring has proven effective since implementation**
  - All five SAEs described above (3 thrombocytopenia SAEs and 2 renal SAEs) occurred before enhanced monitoring was fully implemented

Summary of Topline Results

- Both co-primary endpoints (mNIS+7 and Norfolk QOL-DN) showed robust and highly statistically significant benefit with treatment vs. placebo in patients with hTTR-PN

  - Results indicate an association between patients' perception of benefit and clinical measurements

  - Efficacy observed across mutations (V30M/non-V30M), disease stage (Stage 1/Stage 2) and +/- TTR stabilizers

- Safety issues have been identified & appear monitorable & manageable
  - Platelet and renal monitoring appears effective

  - More than 80% of patients completed the study

  - More than 95% of patients who completed the study participated in the open-label extension study

- A detailed review of efficacy and safety from the study is ongoing

Acknowledgements