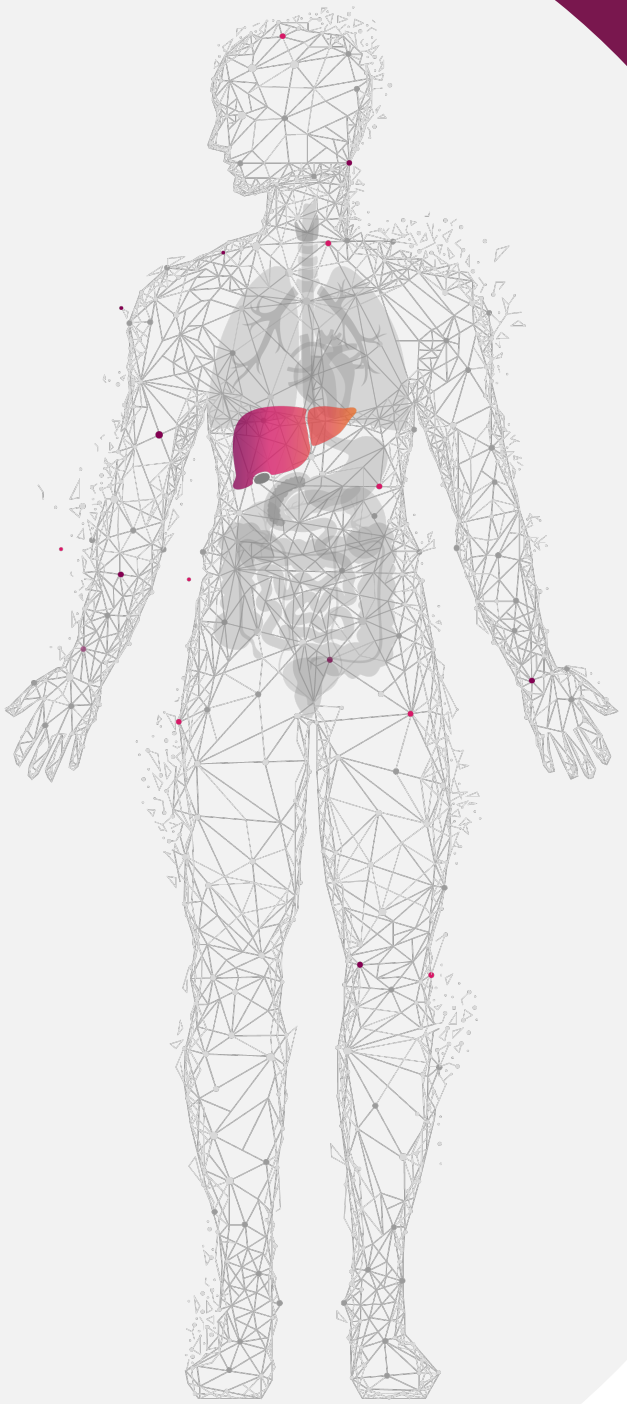

Eplontersen in ATTR-polyneuropathy: results from the Week 35 interim analysis of NEURO-TTRansform

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Background

- Hereditary transthyretin (TTR) amyloidosis (ATTRv) is a rare, severe, progressive, debilitating, and ultimately fatal disease caused by systemic accumulation of TTR amyloid fibrils in multiple organ systems[1]

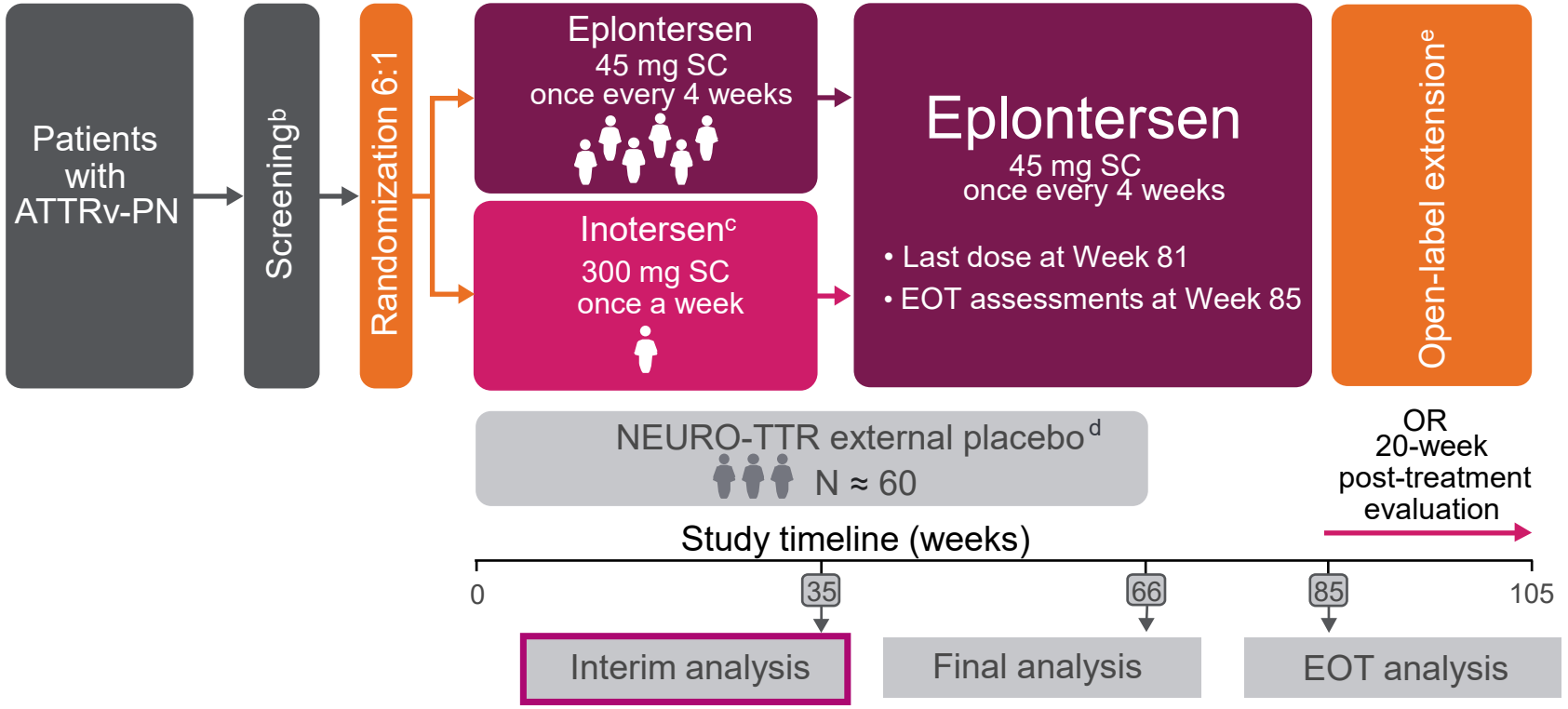
- Eplontersen (ION-682884) is an investigational ligand-conjugated antisense (LICA) oligonucleotide designed to degrade hepatic *TTR* mRNA and inhibit TTR protein synthesis[2]
  - Eplontersen is conjugated to a triantennary *N*-acetyl galactosamine ligand to support receptor-mediated hepatocyte uptake

- **Objective**: To evaluate the effects of eplontersen at the Week 35 interim time point in patients with ATTRv polyneuropathy (ATTRv-PN) enrolled in the ongoing phase 3, international, open-label NEURO-TTRansform study (NCT04136184, EudraCT 2019-001698-10)

[1]Ando et al, *Orphanet J Rare Dis*, 8:31, 2013. [2]Coelho et al, *Neurol Ther*, 10:375-89, 2021.

NEURO-TTRansform Study Design

- Key inclusion criteria:
  - Adult patients
    - 18–82 years
  - ATTRv-PN defined by:
    - Coutinho Stage 1–2[a]
    - Documented genetic mutation in the *TTR* gene
    - Signs/symptoms consistent with polyneuropathy (NIS ≥ 10 and ≤ 130)



Eplontersen, also known as IONIS-TTR-L_{Rx} and AKCEA-TTR-L_{Rx}.
ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; EOT, end of treatment; NIS, Neuropathy Impairment Score; SC, subcutaneous; TTR, transthyretin.
[a]Stage 1 (ambulatory without assistance) or Stage 2 (ambulatory with assistance). [b]The screening period is ≤ 6 weeks (or ≤ 10 weeks if genetic testing is required). [c]The inotersen reference group was intended to confirm sufficiently comparable disease progression and treatment response patterns between NEURO-TTR[1] (NCT01737398) and NEURO-TTRansform. [d]Placebo arm of the NEURO-TTR study[1]. [e]Patients not participating in the open-label extension will enter a 20-week post-treatment evaluation after completing end-of-treatment assessments.
[1]Benson et al, *N Engl J Med*, 379:22-31, 2018. Figure adapted from Coelho et al, *Neurol Ther*, 10:375-89, 2021.

See Poster P283 for Baseline Patient Characteristics and Demographics

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NEURO-TTRansform Patient Disposition at Week 35 Interim Analysis

	Inotersen (Ref arm)	Eplontersen
N	24	144
Patient Completed Week 35	20 (83.3%)	140 (97.2%)
Discontinued Study Treatment (includes after Week 35)	4 (16.7%)	6 (4.2%)
Voluntary withdrawal	0	1 (0.7%)
Treatment discontinuation due to COVID-19	0	0

- The interim analysis evaluates efficacy and safety with different time cuts
  - Efficacy includes data up to Week 35
  - Safety includes all data available at interim, including data collected beyond Week 35

Baseline Characteristics
Eplontersen Arm and External Placebo

Baseline Characteristics	External Placebo	Eplontersen
N	60	144
Age, mean years (SD)	59.5 (14.0)	53.0 (15.0)
Male, n (%)	41 (68.3%)	100 (69.4%)
Race, n (%)		
White	53 (88.3%)	112 (78.3%)
Asian	3 (5.0%)	22 (15.4%)
Black or African American	1 (1.7%)	5 (3.5%)
Other/Multiple	3 (5.0%)	4 (2.8%)
Region, n (%)		
Europe	23 (38.3%)	54 (37.5%)
North America	26 (43.3%)	21 (14.6%)
So. America/Australasia	11 (18.3%)	69 (47.9%)
Previous Treatment, n (%)		
Tafamidis or Diflunisal	36 (60.0%)	100 (69.4%)

Baseline Characteristics	External Placebo	Eplontersen
N	60	144
Disease stage, n (%)		
Stage 1- mild	42 (70.0%)	115 (79.9%)
Stage 2- moderate (use aids)	18 (30.0%)	29 (20.1%)
PND Score[a]		
I (sensory, but can walk)	23 (38.3%)	56 (39.2%)
II (difficulty walking, no aids)	19 (31.7%)	61 (42.7%)
IIIA (1 walk stick or crutch)	15 (25.0%)	16 (11.2%)
IIIB (2 walk sticks or crutches)	3 (5.0%)	10 (7.0%)
TTR variant		
V30M	33 (55.0%)	85 (59.0%)
Non-V30M	27 (45.0%)	59 (41.0%)
mNIS+7, mean (SD)	74.8 (39.0)	81.3 (43.4)
Norfolk QoL-DN, mean (SD)	48.7 (26.7)	44.1 (26.6)

mNIS+7 maximum 346 points; Norfolk QoL-DN maximum 136 points.
[a]Data missing for one subject on eplontersen arm.

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Week 35 Interim Analysis

Co-Primary Endpoints

Serum TTR

TTR Concentration

- % change from baseline

Composite Neuropathy Impairment Score

mNIS+7[a]

- Measures:
  - Motor neuropathy
  - Sensory neuropathy
  - Autonomic neuropathy
- Includes:
  - Motor, reflex, and sensation deficits scored by neurologist
  - Nerve conduction tests
  - Full body quantitative sensation testing of small and large fibers
  - Autonomic deficit by HRdb

Key Secondary

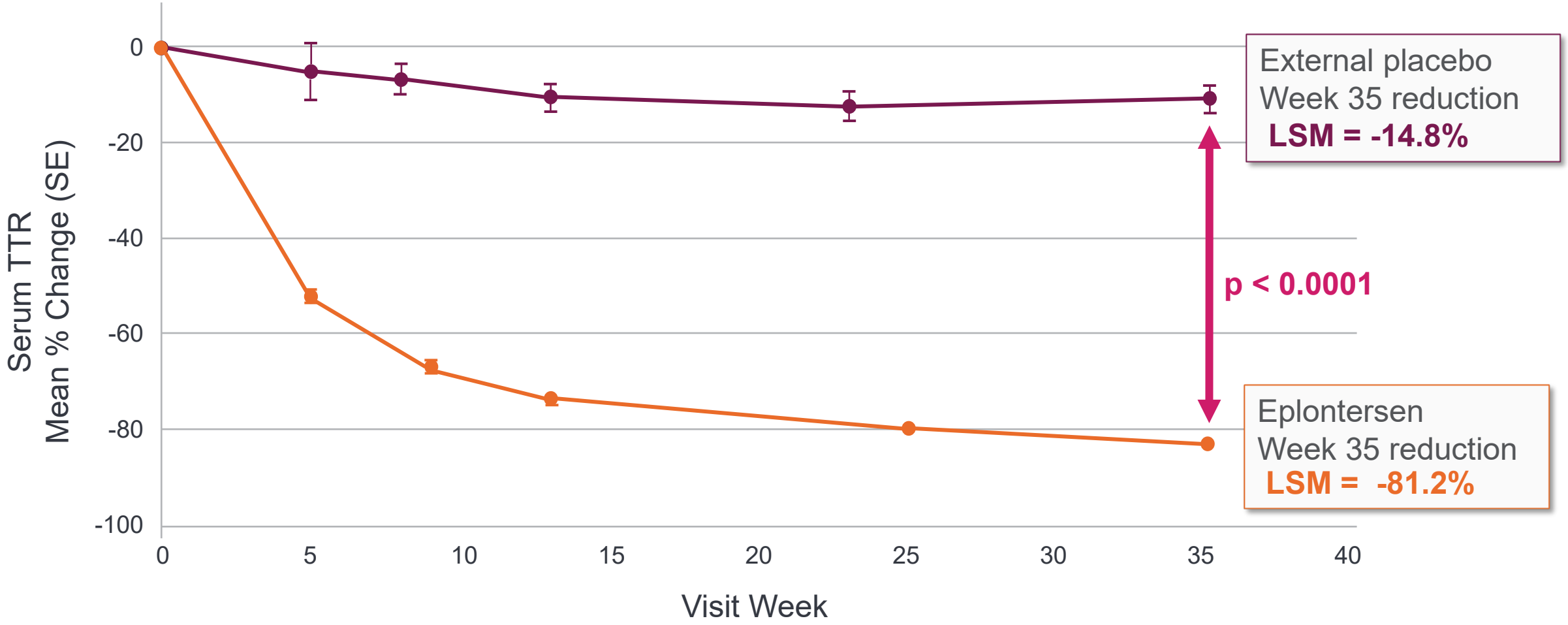
Neuropathy QoL Instrument

Norfolk QoL-DN[a]

- Sum of 5 Domains:
  - Physical functioning/large fiber neuropathy
  - Activities of daily living
  - Symptoms
  - Small fiber neuropathy
  - Autonomic neuropathy

HRdb, heart rate response to deep breathing.
[a]Total Score, change from baseline at Week 35.

Eplontersen Treatment Resulted in a Consistent and Significant Reduction in Serum TTR Levels Over Time



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Positive Results For Each Efficacy Endpoint at Week 35

Endpoint	P-value
Co-primary	
Serum TTR reduction	< 0.0001
Neuropathy impairment (mNIS+7)	< 0.0001
Key Secondary	
Quality of life (Norfolk QoL-DN)	< 0.0001

P-value for difference in least-squares mean change from baseline at Week 35

Eplontersen Treatment Effect Consistent Across Disease Stage, Mutation Type, and Previous Treatment

mNIS+7

Subgroup	P-value
Stage 1	< 0.01
Stage 2	< 0.01
V30M	< 0.01
Non-V30M	< 0.01
Previous Treatment	< 0.01
No Previous Treatment	< 0.01

Norfolk QoL-DN

Subgroup	P-value
Stage 1	< 0.01
Stage 2	< 0.01
V30M	< 0.01
Non-V30M	< 0.01
Previous Treatment	< 0.01
No Previous Treatment	n.s.

P-value for difference in least-squares mean change from baseline at Week 35

n.s., not significant.

Eplontersen Safety Profile Overall Favorable

- TEAEs related to study drug and study drug discontinuation rates were lower or similar for eplontersen compared to external placebo
- No TEAEs of special interest leading to drug discontinuation
- No hepatobiliary safety signals or Hy's Law cases
- Low 1.4% incidence of injection site reactions, and no flu-like reactions
- No SAEs assessed as drug-related
- 2 deaths in eplontersen arm
  - Neither assessed as drug-related
  - Known sequelae of TTR amyloidosis[1-4]

Incidence, n (%)	Placebo[a]	Eplontersen
N	60	144
Any TEAE	60 (100%)	134 (93.1%)
Related to study drug	23 (38.3%)	36 (25.0%)
Leading to study drug d/c	2 (3.3%)	5 (3.5%)
TEAE of special interest[b]	14 (23.3%)	22 (15.3%)
Ocular related to Vit A	12 (20.0%)	20 (13.9%)
Thrombocytopenia	1 (1.7%)	2 (1.4%)
Glomerulonephritis	1 (1.7%)	0
Other TEAE of interest[c]	48 (80.4%)	80 (55.6%)
Any Serious TEAE	13 (21.7%)	21 (14.6%)
Related to study drug	1 (1.7%)	0
Fatal TEAE[d]	0	2 (1.4%)
Related to study drug	0	0

Treatment emergent adverse event (TEAE) is defined as an adverse event that first occurred or worsened after the first dose of investigational product. d/c denotes discontinuation; SAE, serious adverse event. [a]External placebo cohort. [b]TEAEs of special interest include ocular adverse events related to vitamin A deficiency, thrombocytopenia, and glomerulonephritis. [c]Other TEAEs of interest include coagulation abnormalities, abnormal liver function, adverse events at the injection site, flu-like symptoms, CNS disorders, haemorrhages, cardiac disorders, or reduced thyroxine. [d]One patient with intracerebral hemorrhage in setting of normal platelet counts; one patient with arrhythmia in setting of known ATTR-CM.

[1]Cavallaro et al, *Neurology*, 87:750-1, 2016. [2]Yamada et al, *Prog Mol Biol Transl Sci*, 107:41-78, 2012. [3]Yamashita et al, *Neurology*, 70:123-8, 2008.
[4]Ellie et al, *Neurology*, 57:135-7, 2001.

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NEURO-TTRansform Interim Analysis

Met both co-primary endpoints & key secondary endpoint

- TTR and Neuropathic Impairment (mNIS+7)
- Quality of Life (Norfolk QoL-DN)

Eplontersen demonstrated a favorable safety and tolerability profile

- No specific safety concerns

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Disclosures

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TC: is a principal investigator for the NEURO-TTRansform trial (paid to institution) and has received financial support from Ionis and Akcea to attend scientific meetings. **WM:** reports no conflicts of interest. **NRD:** has consulted for Alnylam, Eidos, and Intellia and has lectured for Alnylam. **C-CC:** reports no conflicts of interest. **YP:** has lectured for Alnylam and Pfizer. **MCF:** has lectured and taken part in advisory boards to Pfizer, PTC, and Alnylam. **Y-CG:** reports no conflicts of interest. **JW:** has served as member of advisory boards and lecturer for Pfizer and Alnylam. **L-SR:** reports no conflicts of interest. **CRC:** reports no conflicts of interest. **PK:** is currently participating in the ION trial. **JLB:** has participated in an Ionis ad hoc advisory committee. **LO:** has received speaker honoraria from Pfizer, SOBI, and Alnylam. **FAB:** has received honoraria from Ionis for conducting clinical trials. **MW:** has received advisory board and speaker honoraria and financial support for conference attendance from Akcea, Alnylam, Pfizer, and SOBI. **IC:** is a principal investigator for the NEURO-TTRansform trial (paid to institution) and has received financial support from Ionis and Akcea as a speaker, consultant, and to attend scientific meetings. **SWJ, GB, MB, ES, and NJV:** are employed by Ionis. **MRG:** has received personal fees from Ionis/Akcea, Prothena, Sanofi, Janssen, Aptitude Health, Juno, Physicians Education Resource, AbbVie, Johnson & Johnson, Celgene, Research to Practice, and Sorrento; grants and personal fees from Ashfield; and development of educational materials from i3 Health. **YA:** reports no conflicts of interest. **JG:** has served as an expert advisor for Alnylam, Ionis, Intellia, Eidos, Pfizer, and ATTRalus. **SK:** is a consultant to Alnylam, Ionis, SOBI, Pfizer, and Eidos. **PJBD:** reports no conflicts of interest. **MWC:** is a principal investigator for the NEURO-TTRansform trial and is a consultant for Ionis.

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Study Drug

Eplontersen is an investigational drug and has not been approved by the FDA, EMA, or any other regulatory agency