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# Eplontersen: NEURO-TTRansform Results

April 25, 2023

Nasdaq: IONS

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# Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen), TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen), eplontersen, olezarsen, donidalorsen, ION363, pelacarsen, bepirovirsen, Ionis' technologies, and Ionis' other products in development. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2022, which is on file with the SEC. Copies of this and other documents are available at www.ionispharma.com.

In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.





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# Agenda

| Topic | Speaker |
| --- | --- |
| Welcome | Wade Walke, Ph.D. |
| Introduction | Brett Monia, Ph.D. |
| ATTR & Eplontersen Program Overview | Eugene Schneider, M.D. |
| NEURO-TTRansform Week-35 and Week-66 Data | Sami Khella, M.D. |
| ATTR Cardiomyopathy & CARDIO-TTRansform | Sam Tsimikas, M.D. |
| Commercial Readiness | Onaiza Cadoret |
| Concluding Remarks | Brett Monia, Ph.D. |
| Q&A | |



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# Introduction

Brett Monia, Ph.D.
Chief Executive Officer

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# Eplontersen: Well Positioned to Address Underserved, Global ATTRv-PN Market[1,2]

**Met co-primary and all secondary endpoints**

- Met all co-primary and secondary endpoints at week-35 and 66
- Substantial number of patients improved in measures of neuropathy progression and quality of life compared to baseline

**Favorable safety and tolerability**

- Favorable safety and tolerability profile comparable to placebo
- Safety and tolerability consistent with LICA platform

**Next steps: regulatory & commercial**

- Preparing to launch in the U.S.; PDUFA December 22, 2023
- Preparing for additional oUS regulatory submissions this year



1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval.

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# ATTR & Eplontersen Program Overview

Eugene Schneider, M.D.
Executive Vice President, Chief Clinical Development Officer

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# Eplontersen's Development Program is Designed to Deliver Robust Dataset Supporting Treatment for ATTR

## ATTRv POLYNEUROPATHY


- Met co-primary + secondary endpoints in Phase 3 with favorable safety and tolerability
- **NDA accepted, PDUFA date of December 22, 2023**
- **On track for oUS submissions in 2023**

## ATTR CARDIOMYOPATHY


- Most comprehensive ATTR-CM study to date
- Positioned to deliver most robust data in broad patient population
- **Full enrollment expected in 2023**
- **On track for data in H1:2025**

## ATTR


- Open-label extension studies in patients with ATTRv-PN and ATTR-CM enrolling
- Imaging sub-studies in ATTR-CM to assess the effects on cardiac structure and function underway
- Additional profile-enhancing studies planned



1. Timing expectations and peak sales estimates are based on current assumptions and are subject to change.

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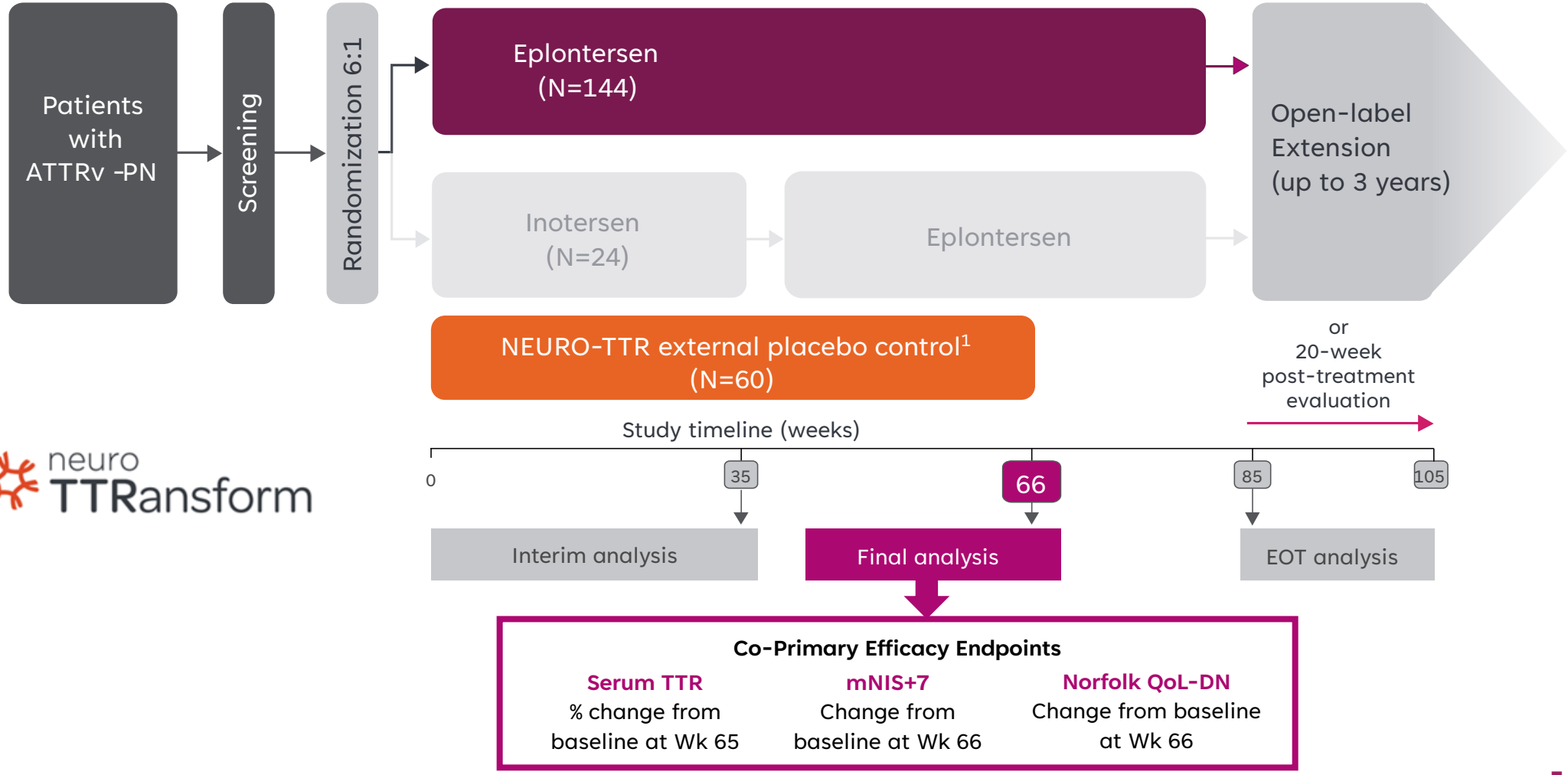
# NEURO-TTRansform Study Designed to Demonstrate Benefit in Patients with ATTRv-PN

- A multicenter, open-label study in 168 patients with hereditary TTR amyloid polyneuropathy (ATTRv-PN)




[1]Benson et al, *N Engl J Med* (2018) 379:22-3 1. Figure adapted from Coelho et al, *Neurol Ther* (2021) 10:375-89.


8

# Co-Primary Endpoints of NEURO-TTRansform

## Serum TTR

### TTR Concentration

- % change from baseline
  - Measured just prior to subsequent eplontersen dose

## Composite Neuropathy Impairment Score

### mNIS+7[3]

- 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[2]

## Neuropathy QoL Instrument[1]

### Norfolk QoL-DN[3]

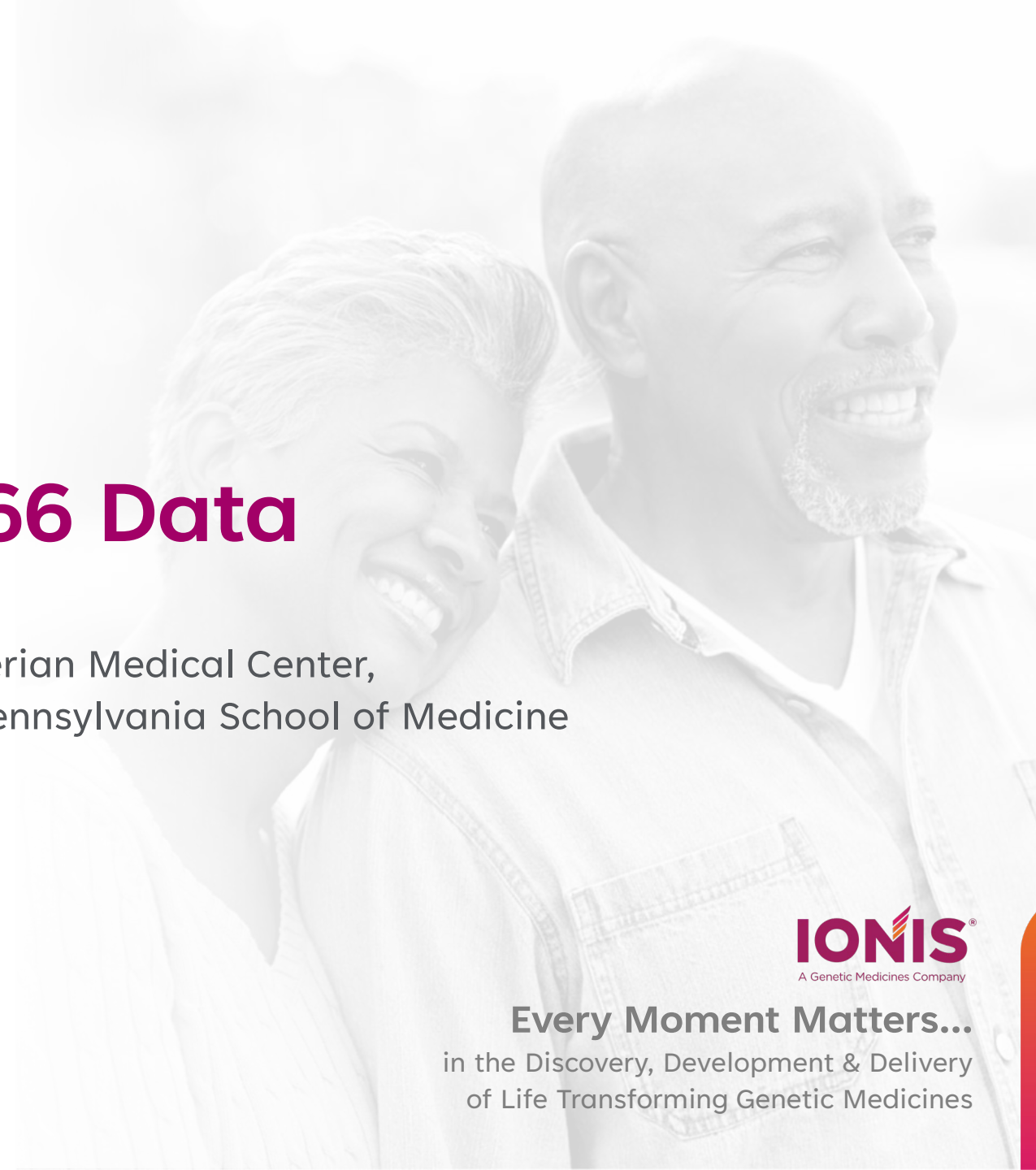
- Sum of 5 Domains:
  - Physical functioning/large fiber neuropathy
  - Activities of daily living
  - Symptoms
  - Small fiber neuropathy
  - Autonomic neuropathy



1. Secondary endpoint at week-35 interim analysis. 2. HRdb, heart rate response to deep breathing. 3. Total Score, change from baseline at week-35 and week-66.

# NEURO-TTRansform
# Week-35 and Week-66 Data

Sami Khella, M.D.
Chief, Department of Neurology, Penn Presbyterian Medical Center,
Professor of Clinical Neurology, University of Pennsylvania School of Medicine



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# TTR Amyloidosis (ATTR) Remains an Area of High Unmet Need

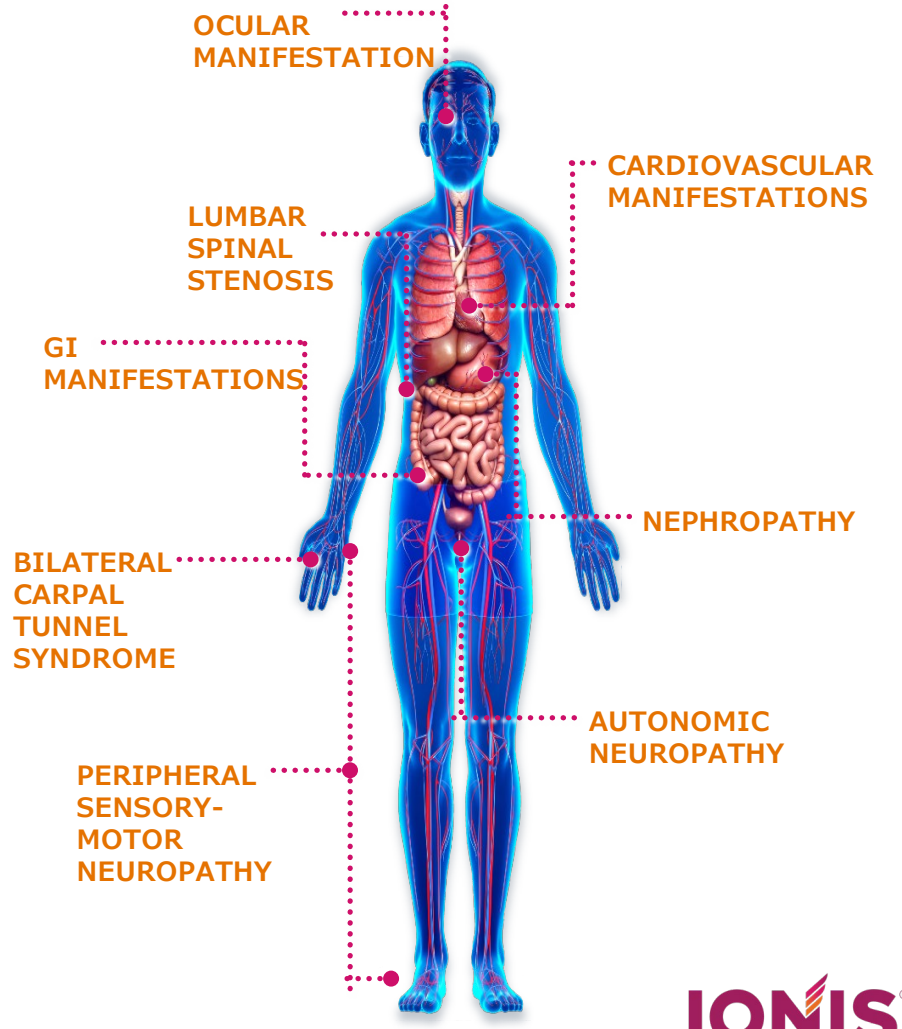
## ATTR

- ATTR is a systemic, progressive and fatal disease
- ATTR is caused by accumulation of misfolded protein that can occur in multiple tissues, including heart, nerves and GI tract
- Patients experience a rapid loss of independence and quality of life before succumbing to their disease

**~40K ATTRv polyneuropathy patients worldwide[1]**

~10K ATTRv-PN

~30K ATTRv-Mixed




Source: amyloidosis.org (https://amyloidosis.org/facts/familial/; https://amyloidosis.org/facts/wild-type/

NOTE: For illustrative purposes only. 1. Conceição I et al. *J Peripher Nerv Syst* (2016) 21:5-9. 2. Ando Y et al. *Orphanet J Rare Dis*. (2013) 8:31.
1. Market data on file



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# Baseline Characteristics

| Baseline Characteristics | 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 | 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] n (%) | | |
| 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**, n (%) | | |
| 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) |

***Baseline demographics and clinical characteristics were generally well balanced between groups with few minor differences***



mNIS+7 maximum 346 points; Norfolk QoL-DN maximum 136 points.

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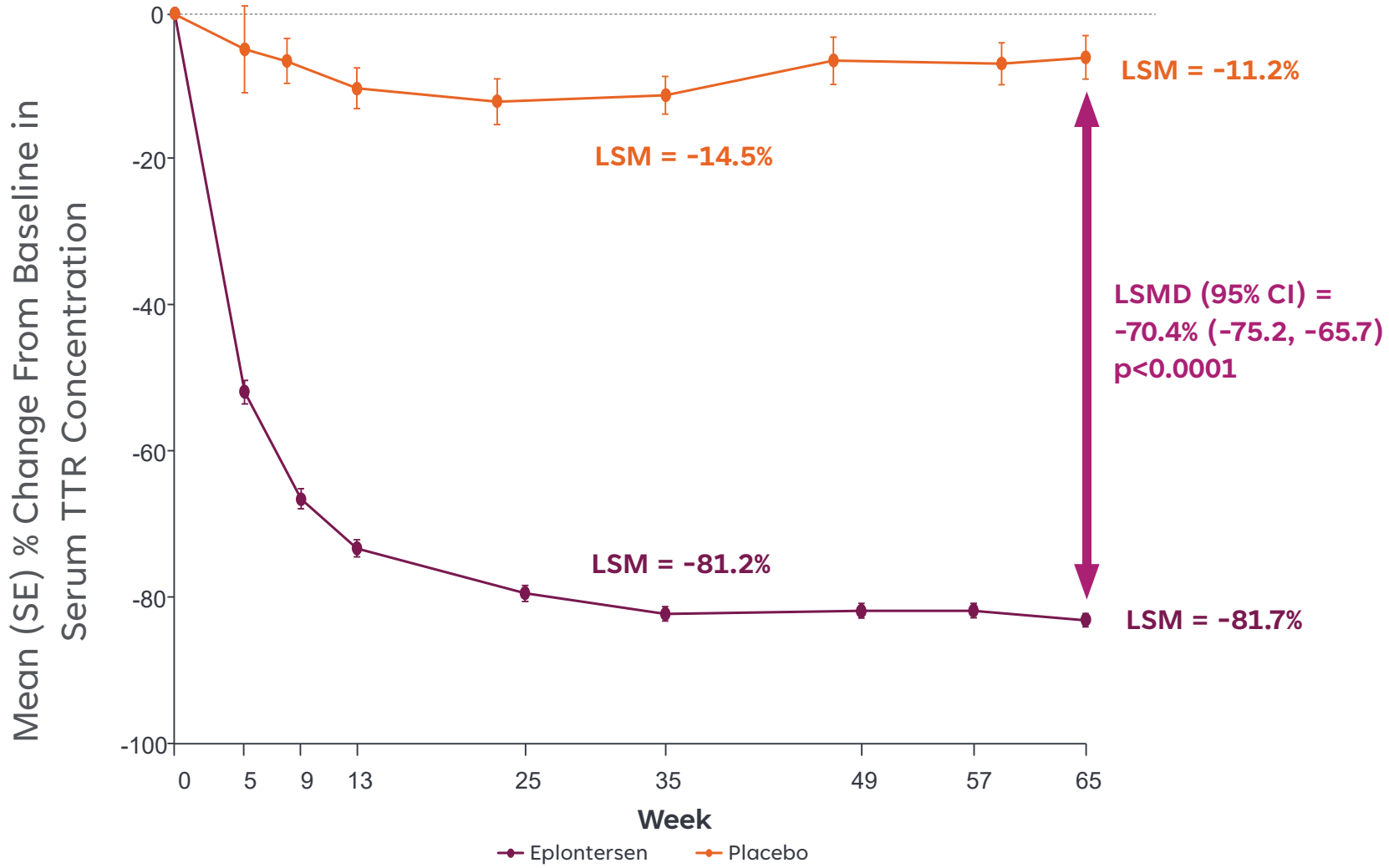
# Eplontersen Treatment Resulted in Significant and Sustained Reductions in Serum TTR Concentration Compared to Placebo




The statistical analysis of percent change from baseline is based on a mixed effects model with repeated measures (MMRM) adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V30M variant, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction.



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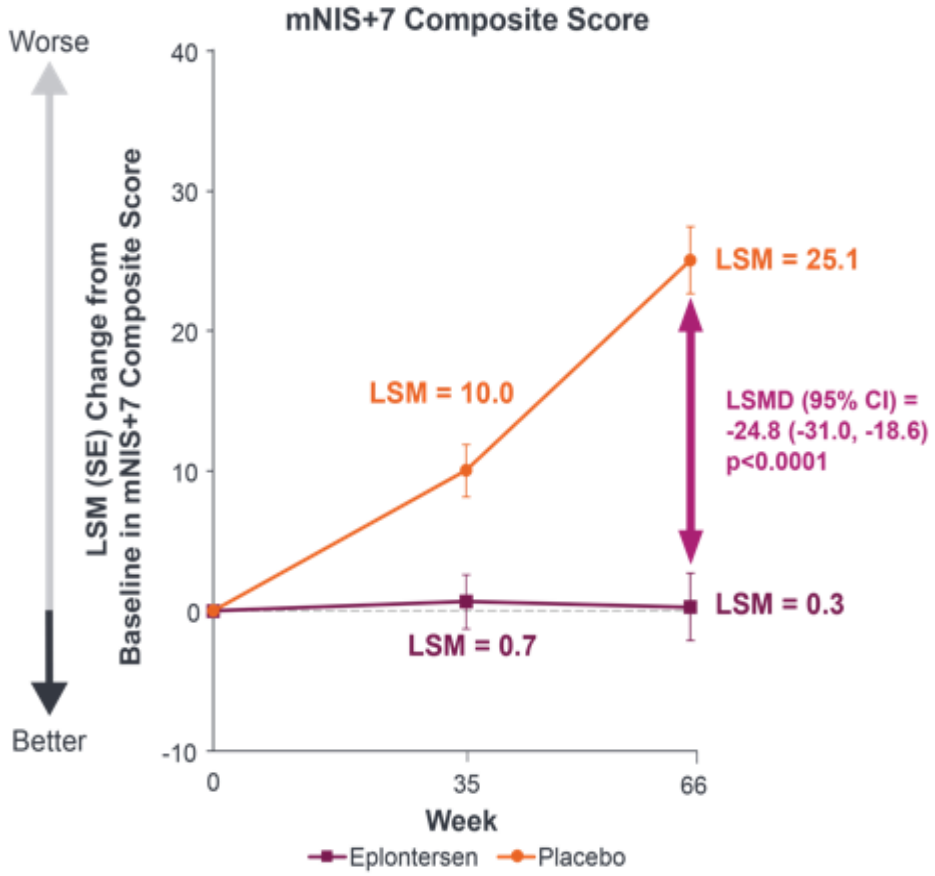
# Eplontersen Halted Neuropathy Progression With the Majority of Patients Improving Compared to Baseline




- **53%** of treated patients showed **improvement** in neuropathy at week-66 compared to baseline[1]
- Eplontersen treatment effect was **consistent** across:
  - Prespecified **subgroups**; and
  - mNIS+7 **components**

The statistical analysis of change from baseline is based on a mixed effects model with repeated measures (MMRM) adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V30M variant, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction.

1. Responder rates, defined as study completers, were 53.1% for mNIS+7 in the eplontersen group and 19.2% in the external placebo group. Overall, 47.2% of patients treated with eplontersen improved from baseline in mNIS+7; in the external placebo group, 16.7% improved.



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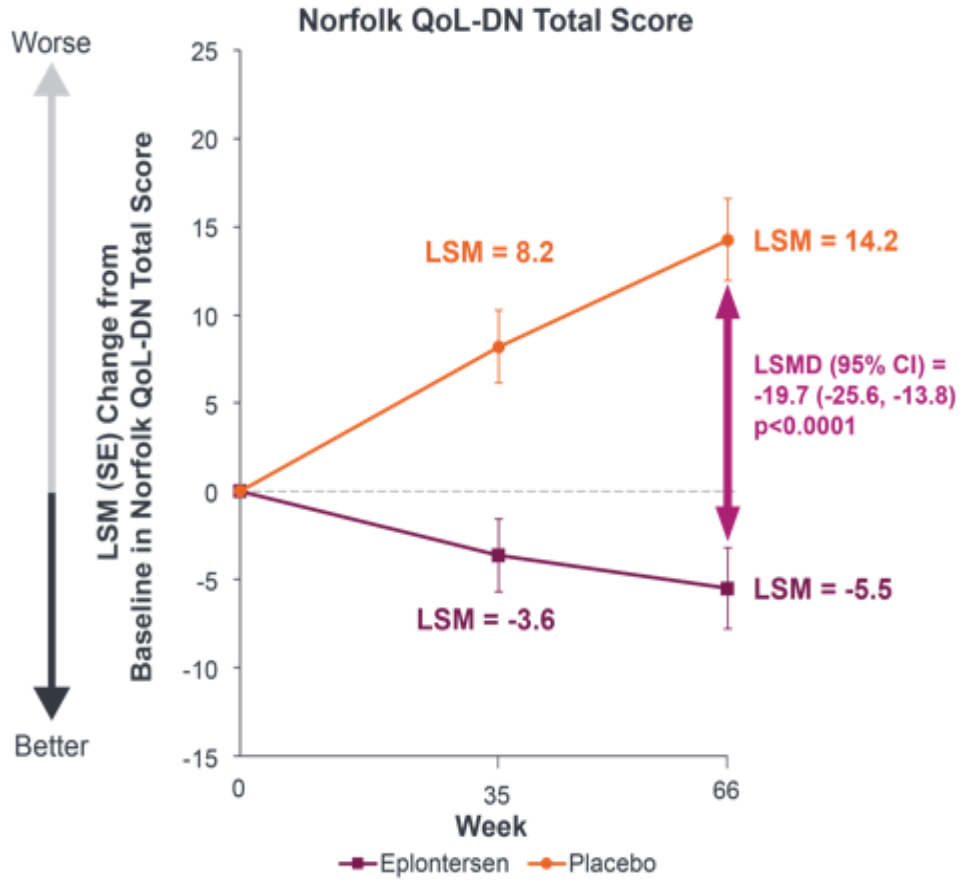
# Eplontersen Showed Continued Improvement in Quality of Life




- **65%** of treated patients showed **improvement** in QoL at week-66 compared to baseline[1]
- Eplontersen treatment effect was **consistent** across:
  - Prespecified **subgroups**; and
  - Norfolk QoL **domains**

The statistical analysis of change from baseline is based on a mixed effects model with repeated measures (MMRM) adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V30M variant, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction.

1. Responder rates, defined as study completers, were 64.8% for Norfolk QoL-DN in the eplontersen group and 23.1% in the external placebo group. Overall, 57.6% of patients treated with eplontersen improved from baseline in Norfolk QoL-DN; in the external placebo group, 20.0% improved.



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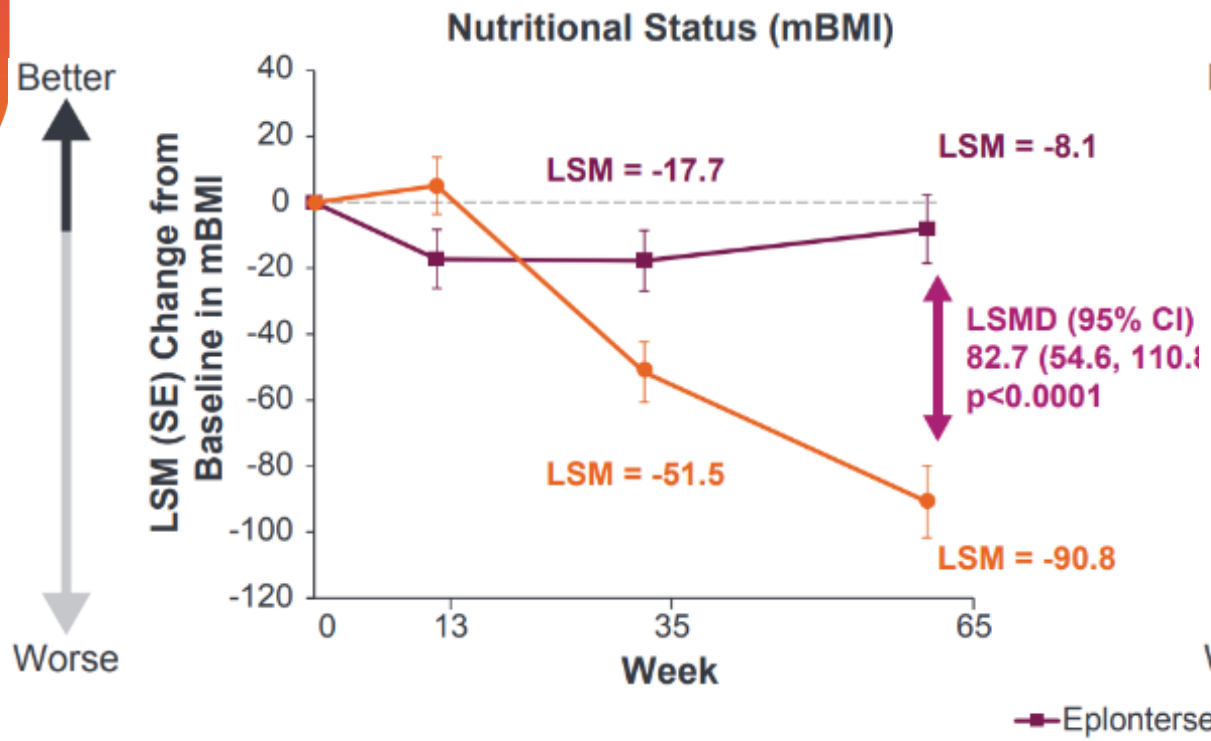
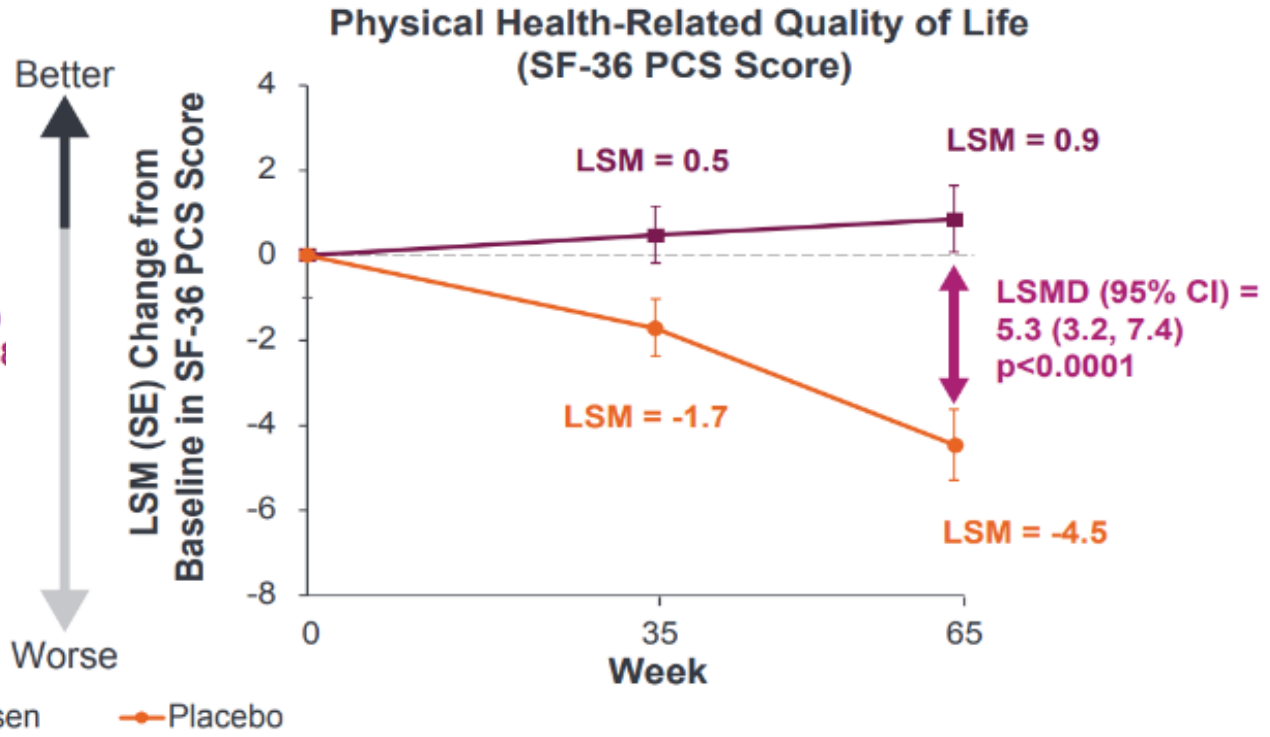
# Eplontersen Achieved Statistical and Clinical Significance for All Secondary Endpoints at Week-66 Compared to Placebo




**Nutritional status measured by mBMI remained relatively stable with eplontersen and decreased with placebo**

**Physical health measured by SF-36 PCS score remained stable with eplontersen and decreased with placebo**

Additionally:

- Symptom severity measured by NSC score remained stable with eplontersen and increased with placebo
- Disability/mobility measured by PND score improved or remained stable with eplontersen to a greater extent compared to placebo



CI, confidence interval; LSMD, least-squares mean difference; mBMI, modified body mass index; PCS, Physical Component Summary; SF-36, 36-item Short Form Survey. 1 mBMI, calculated as BMI (kg/m2) × serum albumin (g/L), assesses nutritional status, with higher scores indicative of better nutritional status.

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# Favorable Safety and Tolerability Profile

- Eplontersen and placebo had comparable rates of TEAEs, including those related to study drug and leading to treatment discontinuation
- No TEAEs of special interest led to study drug discontinuation
- No SAEs were related to study drug
- 2 deaths occurred in the eplontersen group prior to the interim analysis, both related to known sequelae of ATTR amyloidosis[1-5] and neither assessed as study drug–related

| Incidence, n (%) | Placebo | Eplontersen |
|---|---|---|
| N | 60 | 144 |
| Any TEAE | 60 (100) | 140 (97.2) |
| Related to study drug | 23 (38.3) | 53 (36.8) |
| Leading to study drug discontinuation | 2 (3.3) | 5 (3.5) |
| TEAE of special interest | 12 (20.0) | 41 (28.5) |
| Ocular events potentially related to Vit A deficiency | 9 (15.0) | 39 (27.1) |
| Thrombocytopenia | 1 (1.7) | 3 (2.1) |
| Glomerulonephritis | 2 (3.3) | 0 |
| Other TEAE of interest | 47 (78.3) | 87 (60.4) |
| Any serious TEAE | 12 (20.0) | 21 (14.6) |
| Related to study drug | 1 (1.7) | 0 |
| Fatal TEAE | 0 | 2 (1.4) |
| Related to study drug | 0 | 0 |



[1]Cavallaro et al, *Neurology* (2016) 87:750-1; [2]Yamada et al, *Prog Mol Biol Transl Sci* (2012) 107:41-78; [3]Yamashita et al, *Neurology* (2008) 70:123-28; [4]Ellie et al, *Neurology* (2001) 57:135-7; [5]Porcari et al, *Cardiovasc Res* (2023) 118:3517-35.

# Summary of Positive NEURO-TTRansform Results

- In patients with ATTRv-PN, eplontersen treatment resulted in clinically and statistically significant benefits through Week 66 compared with placebo
  - Sustained reduction in serum TTR concentration
  - Halted progression of neuropathy impairment
  - Improved patient quality of life
- Substantial number of patients improved in measures of neuropathy progression and quality of life compared with baseline
- These findings are further supported by statistically significant improvements in all secondary endpoints at Week 66 compared with placebo
- Eplontersen was well tolerated and demonstrated an acceptable safety profile

***Data generated to date reinforce eplontersen's potential to be an important medicine for the thousands of patients living with this debilitating and fatal disease***



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# ATTR Cardiomyopathy & CARDIO-TTRansform

Sam Tsimikas, M.D.
Senior Vice President, Global Cardiovascular Development

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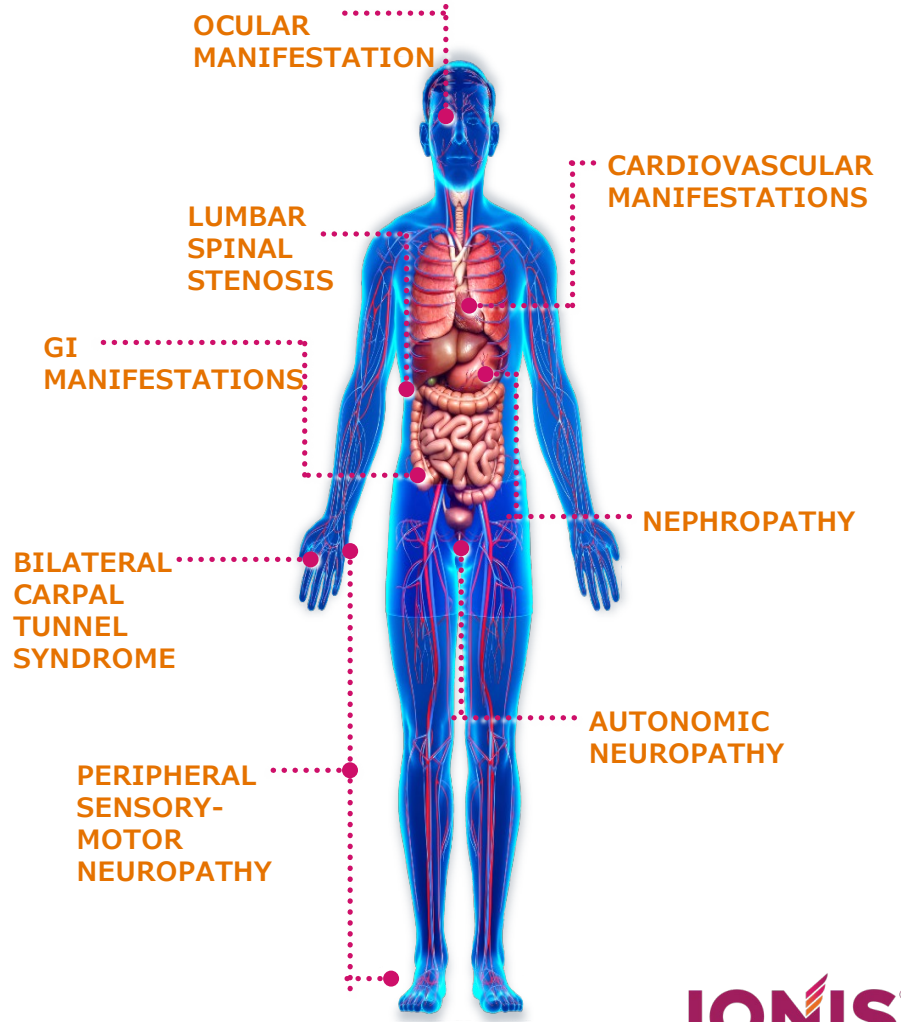
# ATTR Cardiomyopathy

- ATTR cardiomyopathy is caused by the accumulation of misfolded protein in the cardiac muscle
- Patients experience ongoing debilitating heart damage resulting in progressive heart failure resulting in death within three to five years from disease onset[4]

**Global Patient Population**

| | Indication | Patients |
|---|---|---|
| | ATTR | ~500K |
| Cardio | wtATTR | 300K-500K |
| Cardio | ATTRv-CM | 10K |
| Polyneuro | ATTRv-Mixed | 30K |
| Polyneuro | ATTRv-PN | 10K |






GI, gastrointestinal. 1. Conceição I et al. *J Peripher Nerv Syst*. 2016;21:5-9. 2. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31. 3. Gertz MA. *Am J Manag Care*. 2017;23:S107-S112. 4. Maurer MS et al. *Circulation*. 2017;135:1357-1377.

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# CARDIO-TTRansform

## Phase 3 Study in Patients with ATTR Cardiomyopathy

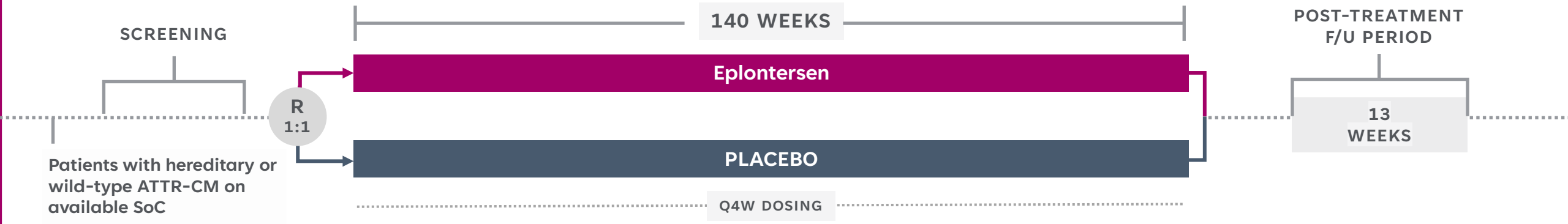
### DESIGN

A global, randomized, double-blind, placebo-controlled study in up to ~1,400 patients with hereditary or wild-type TTR amyloid cardiomyopathy

Imaging sub-studies in ATTR-CM to assess the effects on cardiac structure and function

### PRIMARY ENDPOINT

Cardiovascular death & frequency of cardiovascular clinical events at Week 140 (~32 months)




**On track for full enrollment in 2023 and data in H1:2025[1]**

1. Timing expectations are based on current assumptions and are subject to change

# Commercial Readiness

Onaiza Cadoret

EVP, Chief Global Product Strategy and Operations Officer

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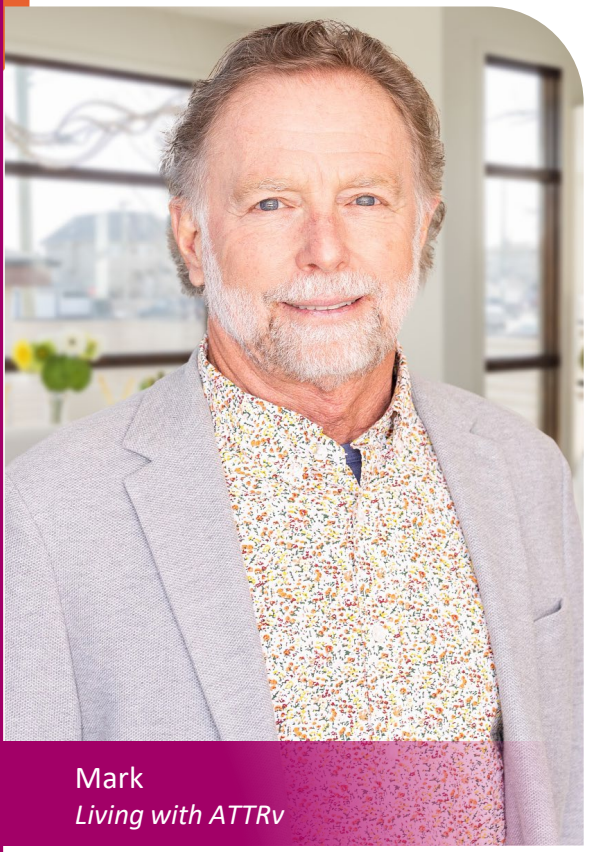
# Eplontersen: An Important Potential Treatment For A Largely Underserved Patient Population[1,2,3]



Mark
*Living with ATTRv*

## Eplontersen

Potential to provide benefit with **at-home** auto-injector administration for **global ATTR population**

First Potential Approval: **2023**

Estimated Peak sales: **Multibillion**

**Global Patient Segments**
Expanding Patient Population

| | Indication | Patients |
|---|---|---|
| | ATTR | ~500K |
| Cardio | wtATTR | 300K-500K |
| Cardio | ATTRv-CM | 10K |
| Polyneuro | ATTRv-Mixed | 30K |
| Polyneuro | ATTRv-PN | 10K |

1. ATTRv-PN potential approval this year. 2. Market data on file 3. Peak sales estimates are based on current assumptions and are subject to change.



Source: amyloidosis.org (https://amyloidosis.org/facts/familial/; https://amyloidosis.org/facts/wild-type/ NOTE: For illustrative purposes only. 1. Conceição I et al. J Peripher Nerv Syst. 2016;21:5-9. 2. Ando Y et al. Orphanet J Rare Dis. 2013;8:31.

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# Uniquely Positioned to Bring Eplontersen for ATTR to Patients in Need [1,2,3]

IONIS® + AstraZeneca

Deep expertise in ATTR, patient identification tools, and rare disease marketing

Vast global-scale and heritage in commercializing CVD medicines

**Shared strategy to bring eplontersen to patients with ATTR around the globe**

**ATTR represents an estimated >$10B market opportunity worldwide[4]**



1. Market data on file 2. Timing expectations and global peak sales estimates are based on current assumptions and are subject to change. 3. Assuming approval
4. Estimated global peak sales includes ATTRv-PN and ATTR-CM.

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# Closing Remarks

Brett Monia, Ph.D.
Chief Executive Officer

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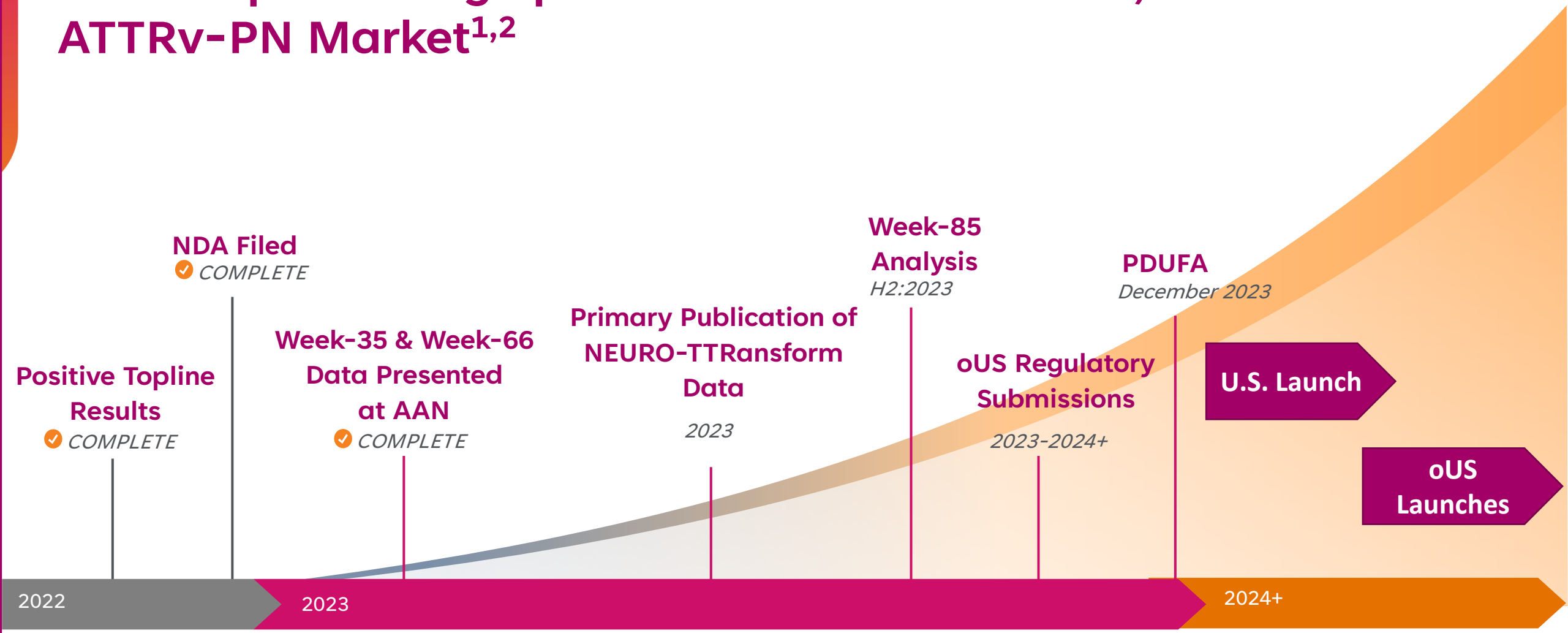
# Eplontersen: Well Positioned to Address Global, Underserved ATTRv-PN Market[1,2]

- Halted neuropathy progression and improved quality of life with favorable safety profile
- Simple at-home self-administration with autoinjector
- Uniquely poised to deliver benefit to largely untapped patient population



1. Timing expectations based on current assumptions and subject to change 2. Assuming approval.

# Next Steps to Bring Eplontersen to Underserved, Global ATTRv-PN Market[1,2]






1. Timing expectations based on current assumptions and subject to change 2. Assuming approval.

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# Q&A

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