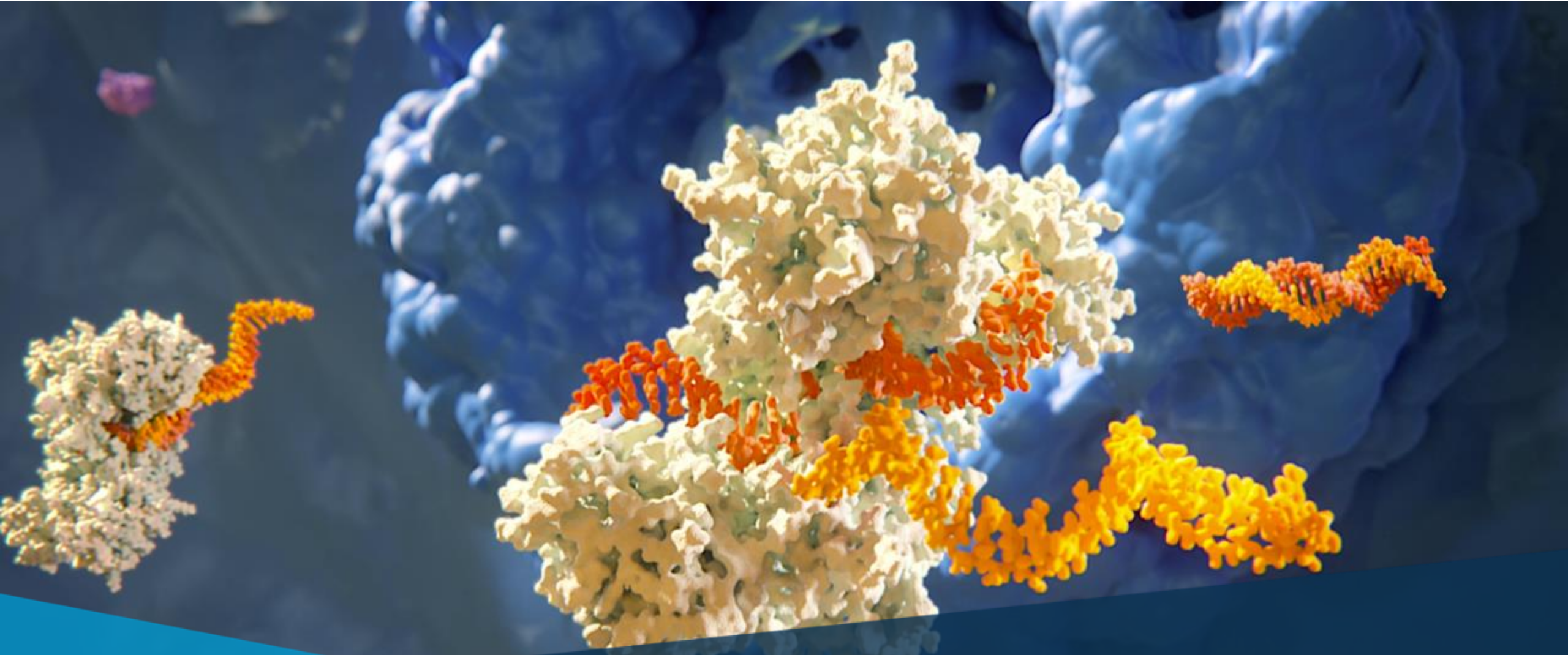

# Phase 3 Study, HELIOS-A, in hATTR Amyloidosis Patients Evaluating a Single Dose Regimen

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**October 5, 2022**

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# ATTR Amyloidosis

## Rare, Progressively Debilitating, and Fatal Disease

### Description

Caused by misfolded TTR protein that accumulates as amyloid deposits in multiple tissues including heart, nerves, and GI tract[1]

**Hereditary ATTR (hATTR) Amyloidosis**

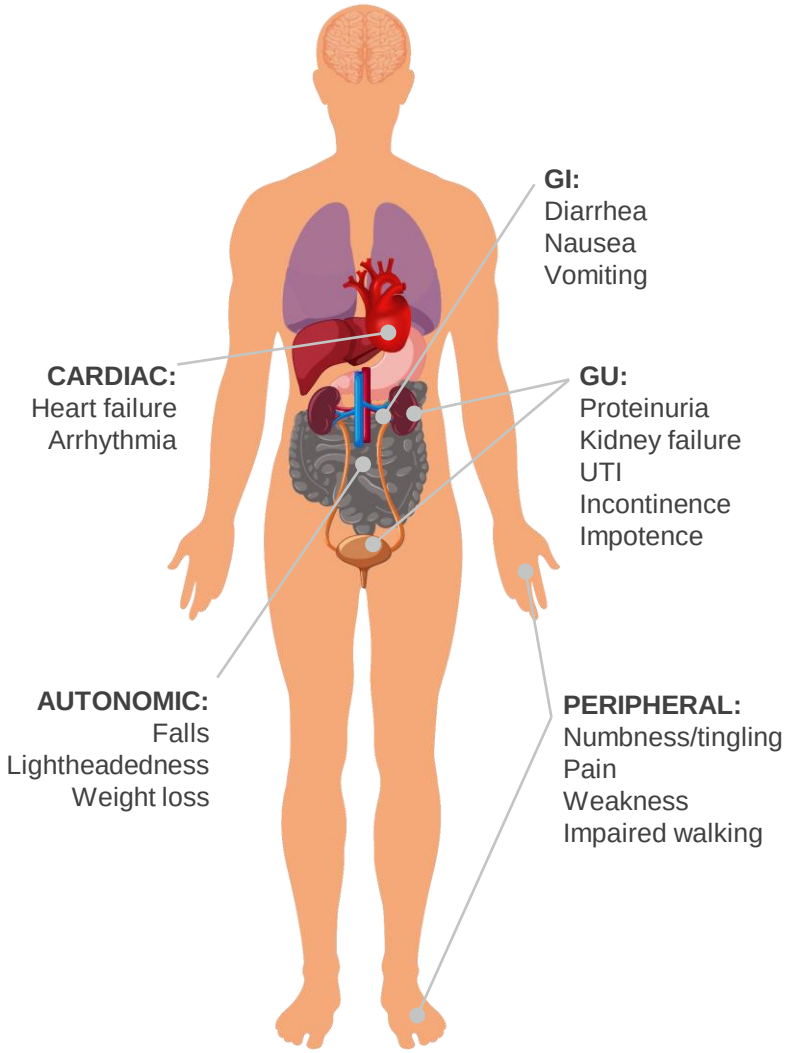
**~50,000**

**patients worldwide***

**Wild-Type ATTR (wtATTR) Amyloidosis**

**~200,000 – 300,000**

**patients worldwide**

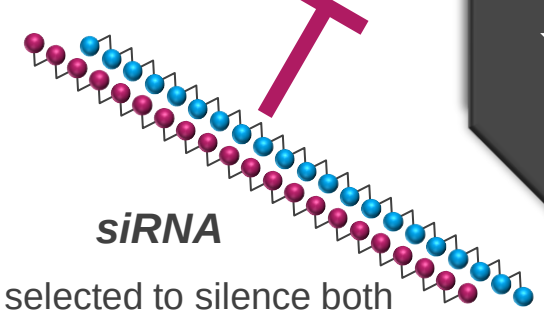



[1] Coelho T, et al. N Engl J Med. 2013;369(9):819-829

* Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012

# RNAi Therapeutic Hypothesis in ATTR Amyloidosis

## Silencing TTR Gene Expression to Address Underlying Cause of Disease



***siRNA***

Sequence selected to silence both mutant and wild-type TTR

Production of mutant and wild-type TTR in liver*

**Reduce**
circulating TTR

**Prevent or clear**
tissue amyloid deposits

**Halt or improve**
progressive manifestations of disease



* >95% of TTR in circulation produced in liver

# Patisiran: Clinical Development in hATTR Polyneuropathy

## Clinical development of patisiran - Phase 1 to Phase 3

✓ Phase 1: Healthy subjects

✓ Phase 2: hATTR-PN patients

✓ Phase 3: hATTR-PN patients

onpattro® (patisiran) lipid complex injection

**APOLLO Study**
225 hATTR-PN patients

**2:1 Randomization**

**Patisiran**
0.3 mg/kg
IV q3W
(N=148)

OR

**Placebo**
IV q3W
(N=77)

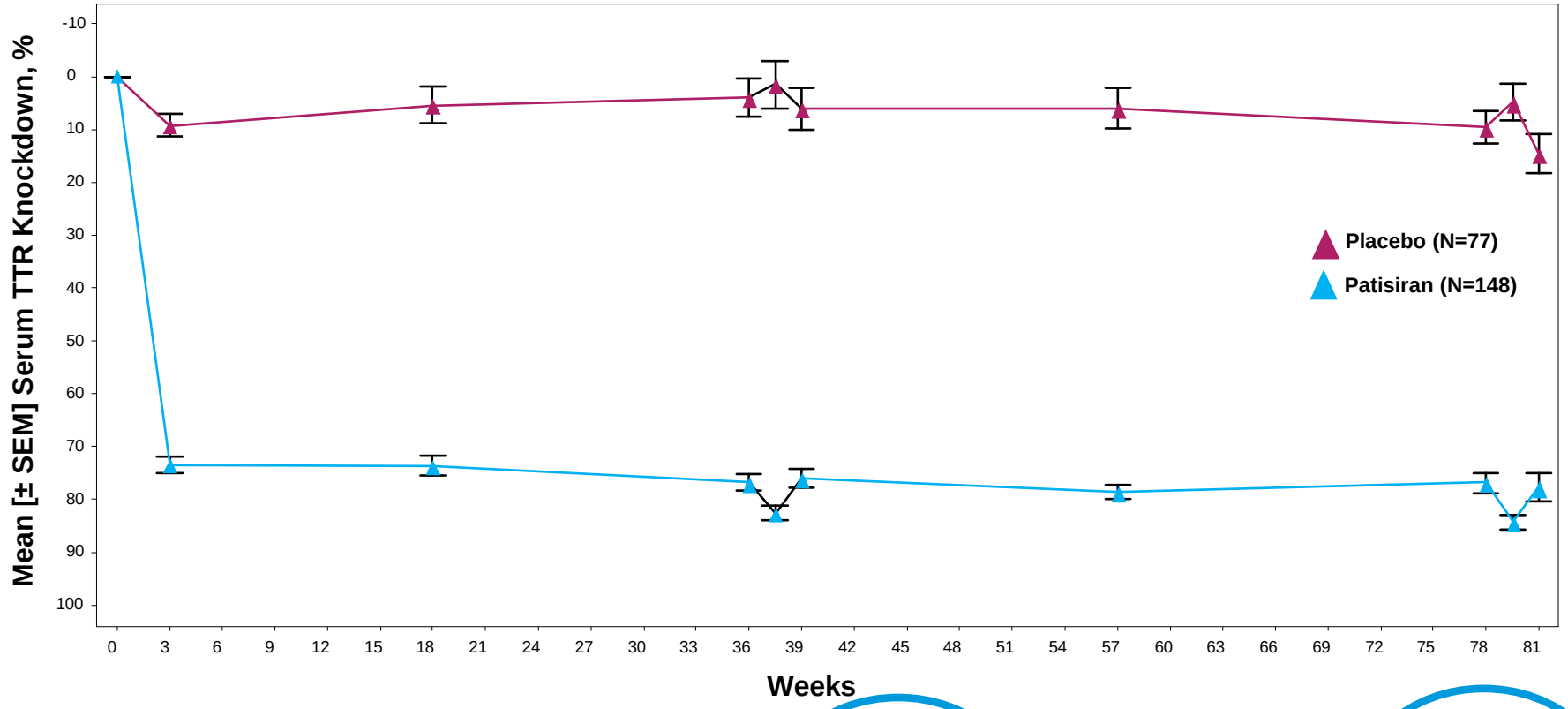
**Primary Endpoint**
Change in mNIS+7 from baseline at 18 months



hATTR-PN=hATTR amyloidosis patients with polyneuropathy; IV=Intravenous; q3W=Once every 3 weeks

# APOLLO Study: Serum TTR Reduction

## Sustained serum TTR reduction with patisiran treatment

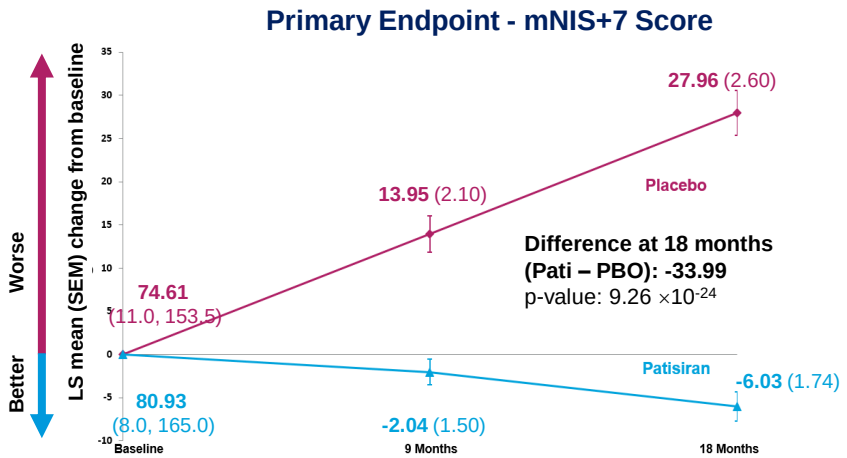


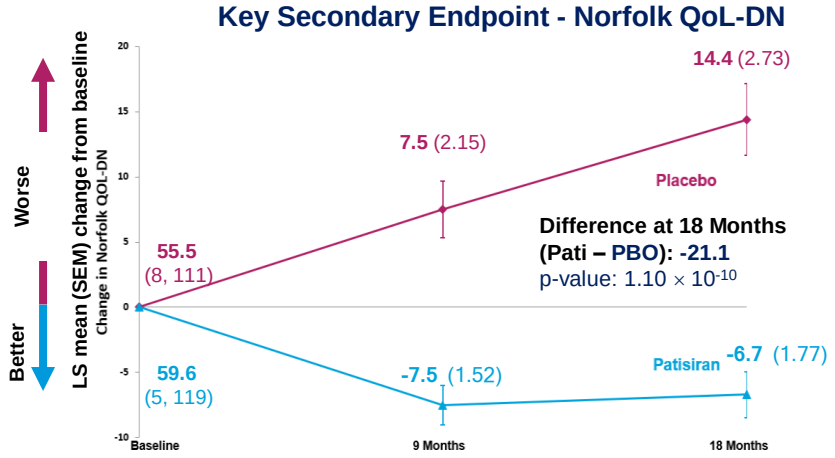

| TTR Change | Change from baseline at 9 months | | Change from baseline at 18 months | |
|---|---|---|---|---|
| | Placebo (N=77) | Patisiran (N=148) | Placebo (N=77) | Patisiran (N=148) |
| Mean (SEM) Serum TTR Knockdown | 1.5% (4.47) | 82.6% (1.36) | 4.8% (3.38) | 84.3% (1.48) |

SEM=Standard error of the mean; Adams et al., EU-ATTR Meeting, Nov 2017

# APOLLO - Key Efficacy Data

## Clinically and statistically-significant improvements in neuropathy and quality of life compared to placebo at 18 months



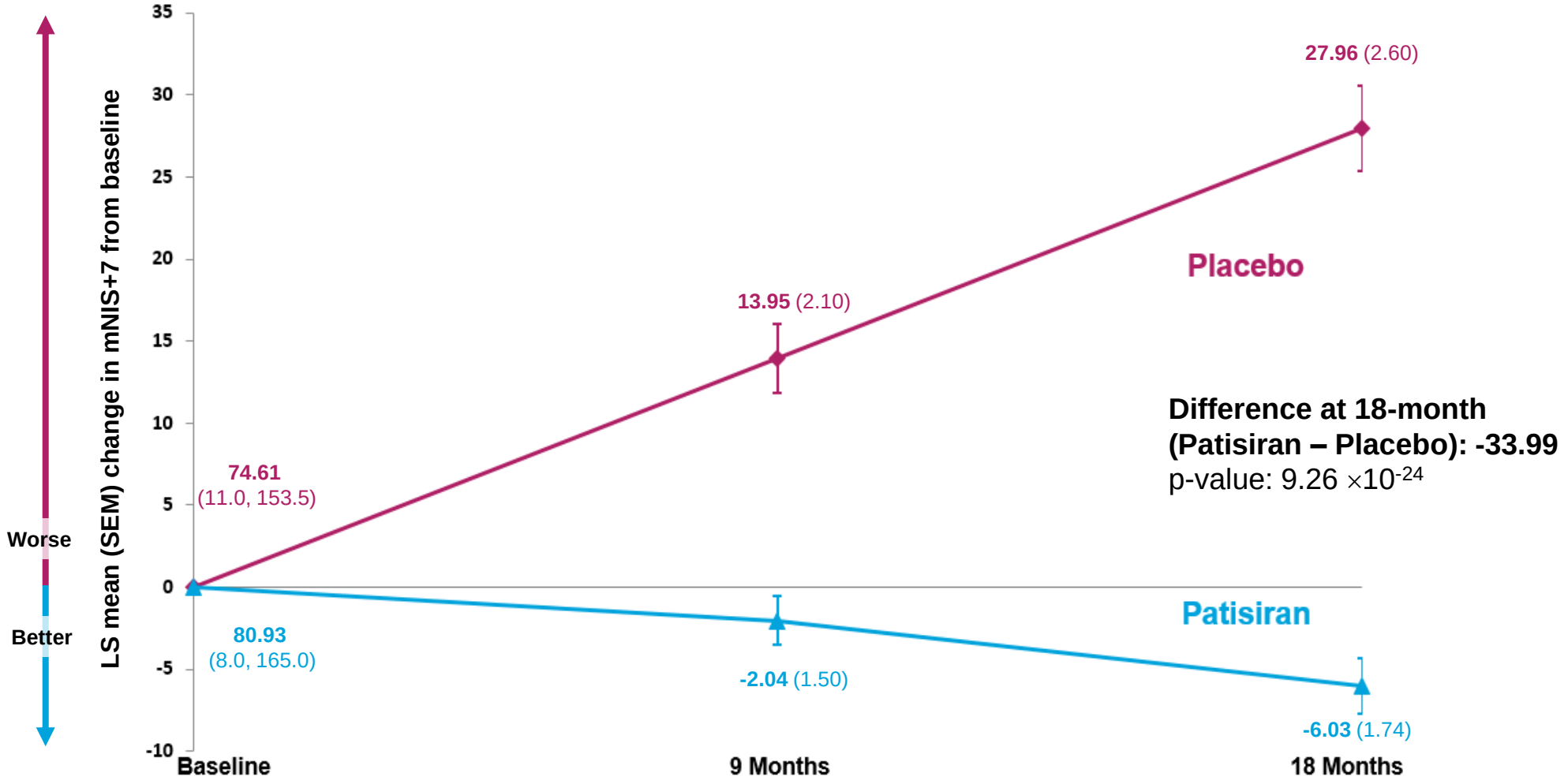

**All other secondary endpoints which all directly assess key clinical outcomes showed statistically significant ($p < 0.001$) improvement compared to placebo at 18 months**

- Improved motor strength (NIS-Weakness)
- Reduced disability (Rasch-built Overall Disability Scale, R-ODS)
- Faster gait speed (10 meter walk test)
- Improved nutritional status (modified body mass index, mBMI)
- Reduced autonomic symptoms (COMPASS 31)

MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; Pati, patisiran; PBO, placebo; CFB, change from baseline
mNIS+7 reference range: 0-304 points

# APOLLO Study: mNIS+7 Change From Baseline

## Significant clinical effect of patisiran in hATTR-PN patients




SEM=Standard error of the mean; Adams et al., EU-ATTR Meeting, Nov 2017

# Vutrisiran a Subcutaneous Therapeutic for hATTR

## Patisiran

Approved RNAi Therapeutic
for Treatment of Polyneuropathy of hATTR Amyloidosis

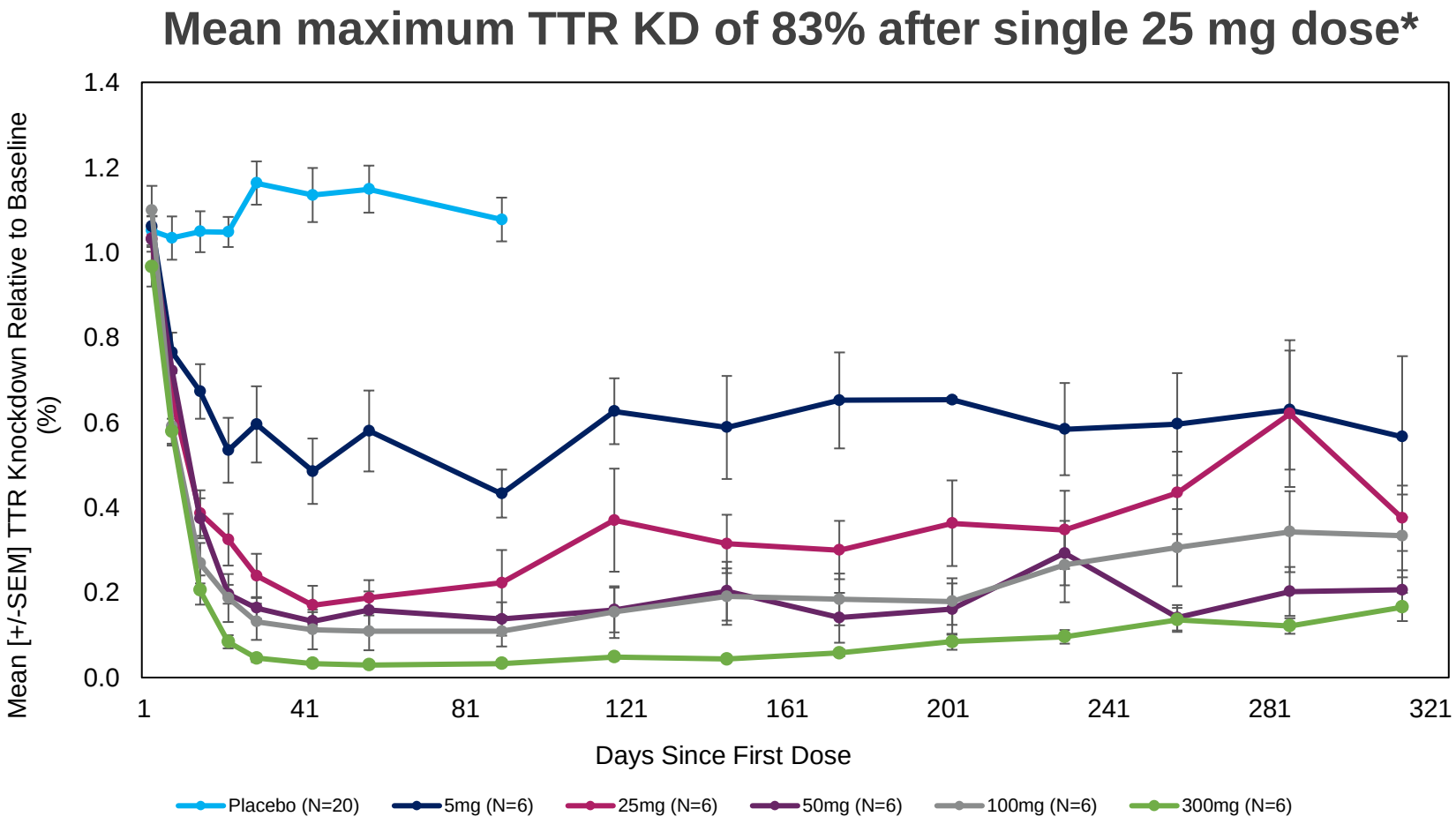
- RNAi therapeutic targeting TTR mRNA, formulated in a lipid nanoparticle
- IV administration, once every 3 weeks (pre-medication required)
- Approved, based on data from the pivotal APOLLO phase 3 study

## Vutrisiran

- RNAi therapeutic targeting TTR mRNA, covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable specific delivery of siRNA to hepatocytes
- Subcutaneous administration
- Potential for less frequent dosing

# Vutrisiran: Serum TTR Reduction

## Dose dependent TTR reduction over a wide range of single SC dose levels




- All doses well tolerated; increase in ALT (>3xULN) observed at 200 mg dose level in one subject

SEM= Standard error of the mean; * Taubel J, et al. Phase 1 Study of ALN-TTRsc02, a Subcutaneously Administered Investigational RNAi Therapeutic for the Treatment of Transthyretin-Mediated Amyloidosis. ISA 2018: XVIIth International Symposium of Amyloidosis; Kumamoto, Japan; March 2018 (poster)

# Leveraging Model Based Analysis For Vutrisiran Development

## Development questions for vutrisiran after phase 1 study

1. Can a similar magnitude of TTR reduction as patisiran be achieved with multiple dosing of vutrisiran?

2. Can we skip the phase 2 study and go directly from single dose study in healthy volunteers to multiple-dose pivotal phase 3 study in patients?

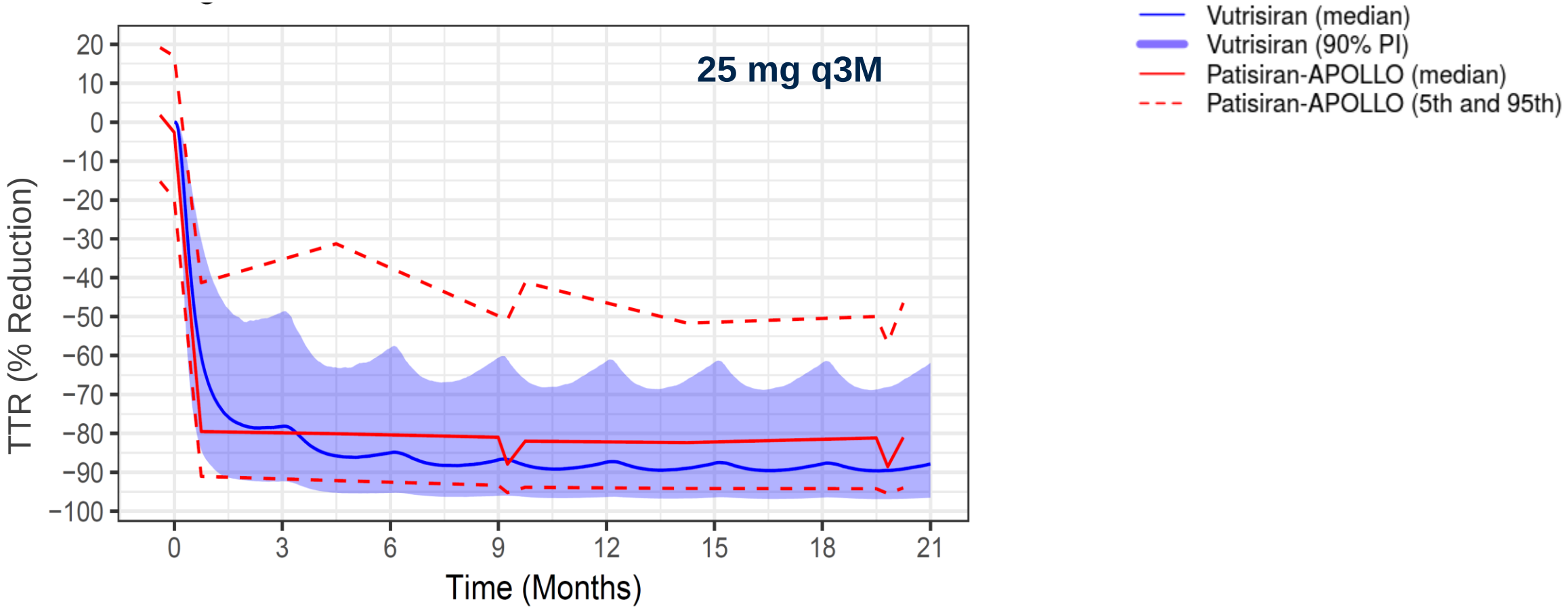
3. What is the optimal dose and dosing frequency for the phase 3 study?

4. Can we use a 9-month endpoint for mNIS+7?

# Phase 3 Model Predictions: Serum TTR Reduction

## 85% TTR reduction predicted with 25 mg q3M vutrisiran

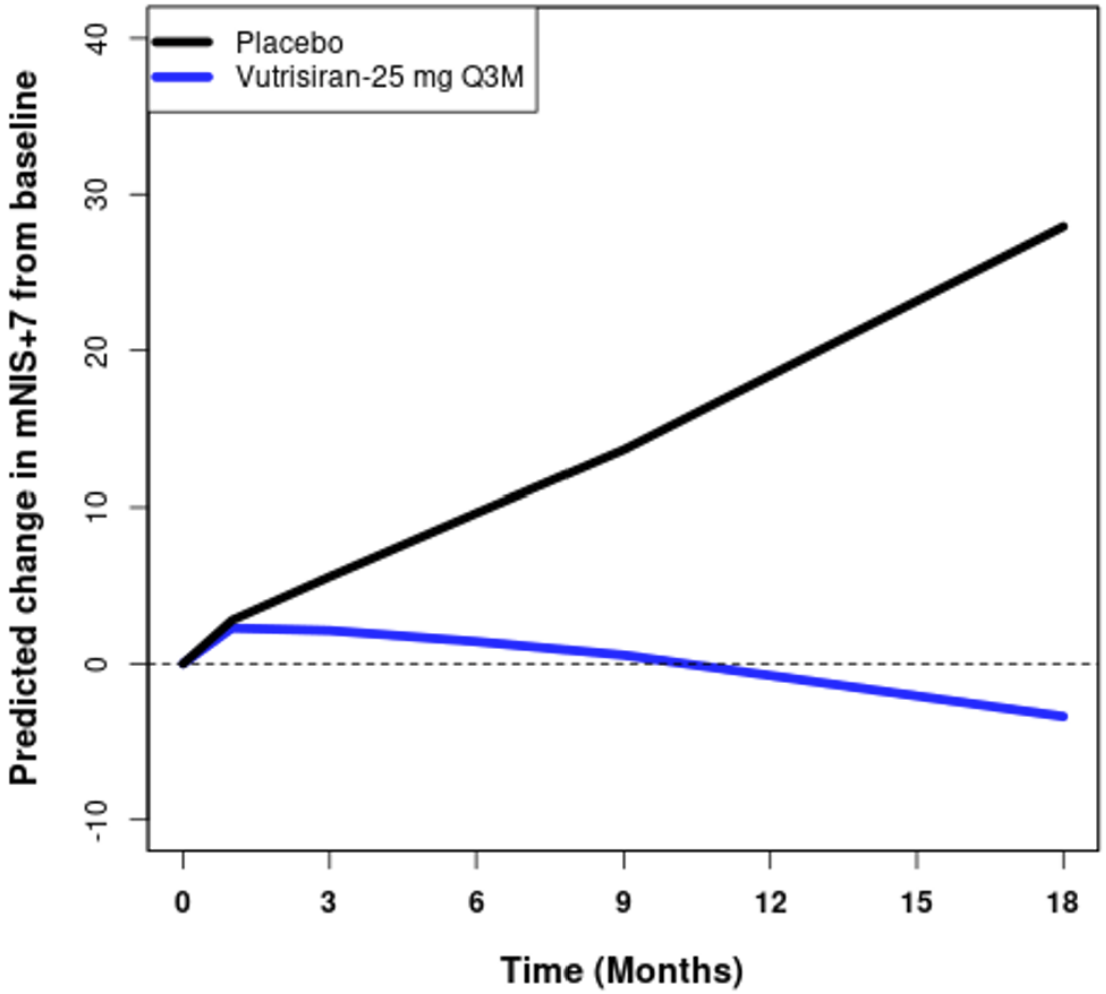
TTR lowering slightly better than patisiran




 q3M=Once every 3 months; PI=Prediction interval.

# Phase 3 Model Predictions: mNIS+7

## Vutrisiran 25 mg q3M predicted to be similar to patisiran




- Model predicted halting or reversal of disease progression (ΔmNIS+7 ≤ 0) at month-9 with 25 mg q3M vutrisiran
- mNIS+7 decrease of 4 points from baseline predicted at month-18 with 25 mg q3M vutrisiran



q3M=Once every 3 months

# Decision to Proceed to Phase 3

## Regulatory Agencies accepted model-based rationale to accelerate development

- FDA, EMA and PMDA approved acceleration from single dose in healthy volunteers to pivotal long-term phase 3 study in hATTR amyloidosis patients with polyneuropathy

- Agreed with proposed phase 3 vutrisiran dosing regimen of 25 mg (fixed dose) administered q3M

# Vutrisiran: Clinical Development in hATTR-PN

✓ Phase 1: Healthy subjects → Skip Phase 2 → Phase 3: HELIOS-A hATTR-PN patients

**Efficacy Assessments vs. APOLLO placebo arm**

**Primary Endpoint at M9**
- Change from baseline in mNIS+7*

**Secondary Endpoints at M9**
- Change from baseline in Norfolk QOL-DN*
- 10-meter walk test

**Exploratory Endpoints at M9 (select)**
- mBMI
- R-ODS
- NT-proBNP
- Serum TTR

**Secondary Endpoints at M18**
- Change from baseline in the following parameters:
  - mNIS+7
  - Norfolk QOL-DN
  - 10MWT
  - mBMI
  - R-ODS
- % reduction in serum TTR levels vutrisiran compared to within-study patisiran through 18M (non-inferiority)

**Vutrisiran** 25 mg SC q3M (N=122)

OR

**Patisiran** 0.3 mg/kg IV q3W (N=42)

**Primary Endpoint** Change in mNIS+7 from baseline at 9 months

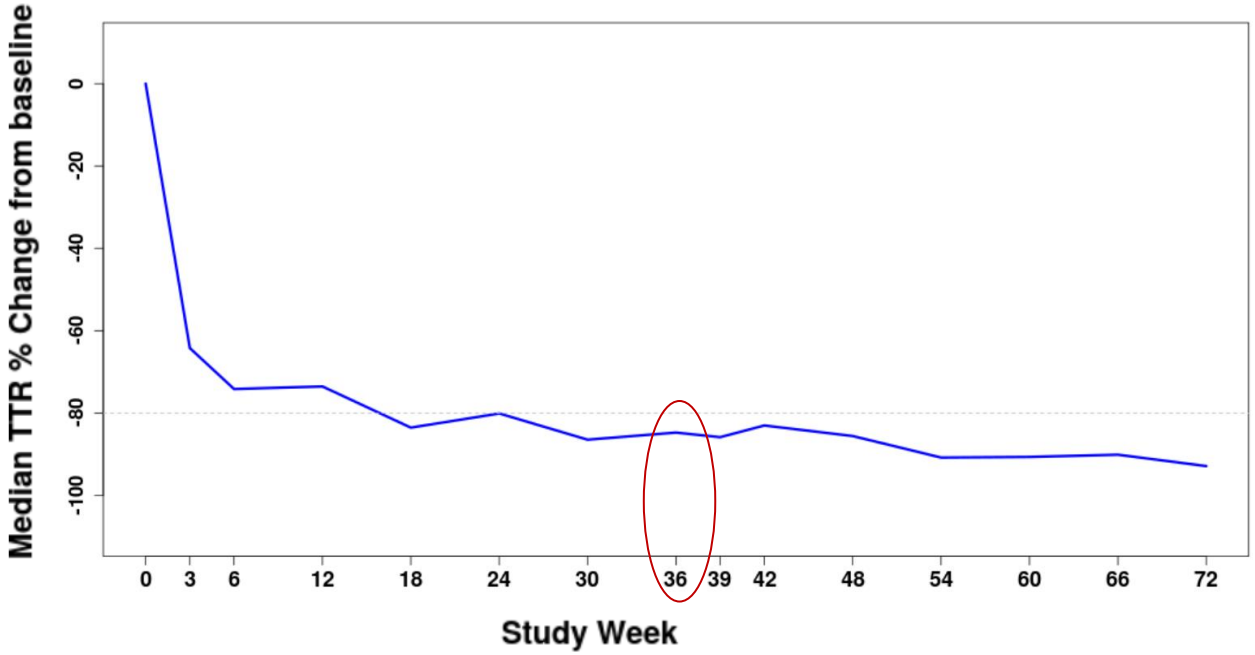


SC=subcutaneous; IV=Intravenous; q3M=Once every 3 months; q3W=Once every 3 weeks; patisiran is reference comparator

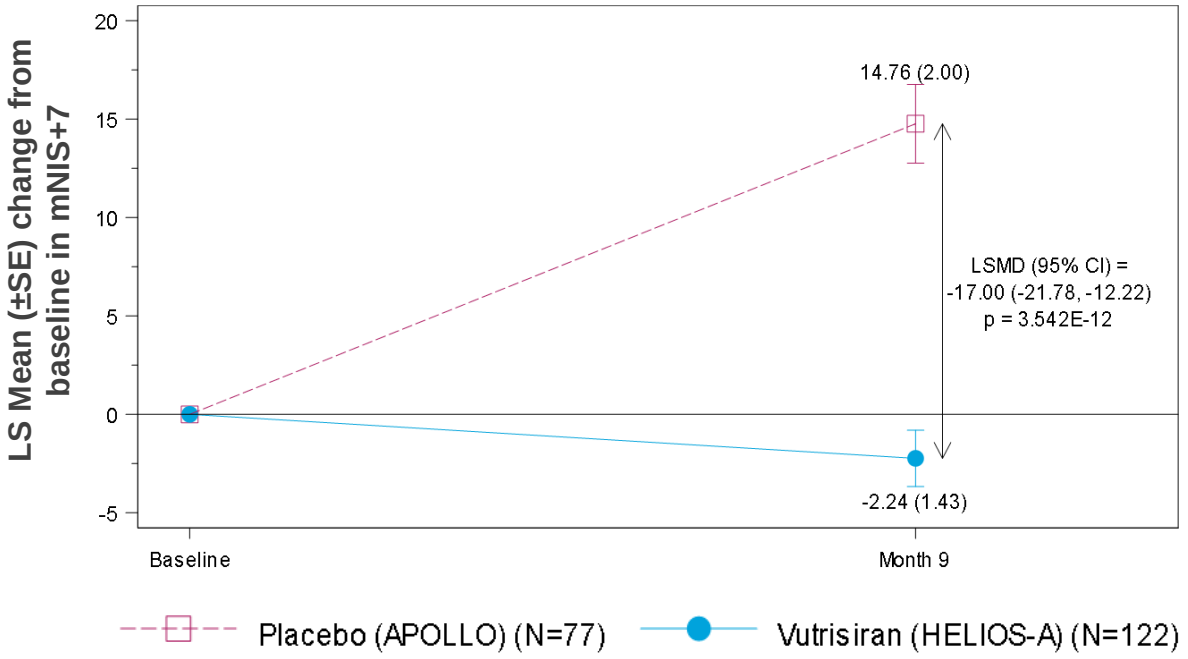
# HELIOS-A Primary Analysis Results at Month 9

## Observed data is in agreement with model predictions for TTR, mNIS+7 and safety

TTR Reduction = 84.8%




Δ mNIS+7 = -2.24




- No clinically relevant ALT elevation (> 3x ULN) with vutrisiran



LS=Least squares; SE=Standard error of the mean; LSMD=Least squares mean difference; CI=Confidence interval

# HELIOS-A Met Primary and Secondary Endpoints at Month 9

| Change from Baseline Endpoint | APOLLO Placebo (N=77) LS mean (95% CI) | Vutrisiran (N=122) LS mean (95% CI) | Vutrisiran – Placebo LS mean difference (95% CI) | P-value |
|---|---|---|---|---|
| mNIS+7 | 14.8 (10.8, 18.7) | -2.2 (-5.0, 0.6) | -17.0 (-21.8, -12.2) | $3.5 \times 10^{-12}$ |
| Norfolk QOL-DN total score | 12.9 (8.5, 17.3) | -3.3 (-6.6, -0.1) | -16.2 (-21.7, -10.8) | $5.4 \times 10^{-09}$ |
| 10-MWT (m/s) | -0.133 (-0.182, -0.083) | -0.001 (-0.038, 0.036) | 0.131 (0.070, 0.193) | $3.1 \times 10^{-05}$ |
| mBMI (exploratory)* | -60.2 (-80.1, -40.4) | 7.6 (-7.9, 23.0) | 67.8 (43.0, 92.6) | $8.5 \times 10^{-08}$ |

- All sensitivity analyses demonstrated consistent estimate of treatment effect of vutrisiran compared to placebo (APOLLO) on mNIS+7 and Norfolk QOL at Month 9
- Evidence of reversal of polyneuropathy manifestations
  - Majority of patients showed improvement in mNIS+7 and Norfolk QOL relative to baseline

*At Month 9, the vutrisiran group showed improvement in nutritional status as assessed by mBMI compared to the placebo group, nominal p value.

For APOLLO results, see Slide 25 and Slide 26

# Month 18 HELIOS-A results

- Statistical significance ($p \leq 0.05$) achieved for all Month 18 clinical efficacy endpoints per the prespecified multiple comparisons procedure
- Non-inferiority of vutrisiran (versus within study patisiran) was declared in Trough TTR percent reduction

| Endpoint (Superiority) | Placebo (N=77) LS mean (95% CI) | Vutrisiran (N=122) LS mean (95% CI) | Vutrisiran – Placebo LS mean difference (95% CI) | P-value |
|---|---|---|---|---|
| **mNIS+7** | 28.09 (23.58, 32.59) | -0.46 (-3.61, 2.69) | -28.55 (-34.00, -23.10) | 6.505E-20 |
| **Norfolk QoL-DN** | 19.8 (14.7, 24.9) | -1.2 (-4.8, 2.4) | -21.0 (-27.1, -14.9) | 1.844E-10 |
| **10-MWT** | -0.264 (-0.334, -0.194) | -0.024 (-0.075, 0.026) | 0.239 (0.154, 0.325) | 1.207E-07 |
| **mBMI** | -115.7 (-142.2, -89.1) | 25.0 (6.3, 43.8) | 140.7 (108.4, 172.9) | 4.159E-15 |
| **R-ODS** | -9.9 (-11.5, -8.3) | -1.5 (-2.6, -0.3) | 8.4 (6.5, 10.4) | 3.541E-15 |

| Endpoint (Non-inferiority) | Vutrisiran (N=120) HL median[1] | Patisiran (N=40) HL median[1] | Vutrisiran – Patisiran HL median difference[2] (95% CI) | Noninferiority (95% lower CI > -10%) |
|---|---|---|---|---|
| **Trough TTR percent reduction** | 84.67 | 80.60 | 5.28 (1.17, 9.25) | Yes |

- Vutrisiran demonstrated an acceptable safety profile
  Adverse events were consistent with the underlying disease; informed by observations on the placebo arm of APOLLO

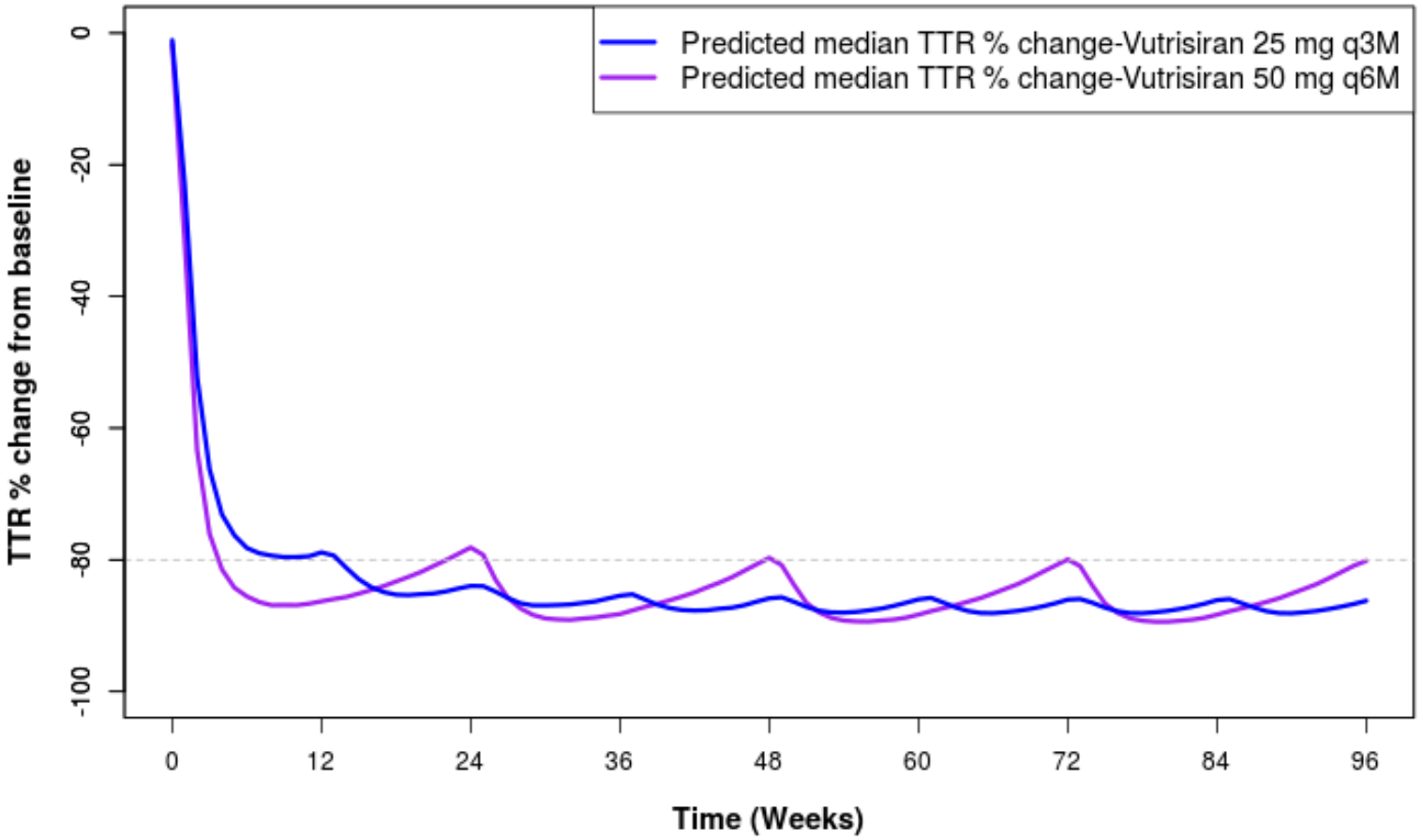


1. Hodges-Lehmann 1-sample medians; 2 Hodges-Lehmann 2-sample median difference.

# Vutrisiran is fifth approved RNAi therapeutic

# Evaluation of Alternate Dosing Regimen

## Modeling performed to evaluate feasibility of reduced dosing frequency (q6M vs q3M)




- Modeling supports extension of dosing interval from 3 months to 6 months
- Similar average TTR reduction predicted with 50 mg q6M and 25 mg q3M



q3M=Once every 3 months; q6M=Once every 6 months

# Summary

- A model-based analysis was used to predict pharmacodynamics (TTR) and clinical efficacy (mNIS+7) after different dosing regimens of vutrisiran.
- Based on simulation results, 25 mg q3M regimen was identified as the optimal Phase 3 dose.
- Facilitated a well-informed decision and regulatory acceptance of dose selection for HELIOS-A (Phase 3) study.
- Observed pharmacodynamic, clinical efficacy and safety results from HELIOS-A were in agreement with model predictions.
- A model-based analysis led to significant savings in time and resources during development (skipped Phase 2 study) and enabled faster access of vutrisiran to patients.