Patisiran Pharmacokinetics (PK), Pharmacodynamics (PD), and Exposure-Response (E-R) Relationship in Patients with Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

Xiaoping (Amy) Zhang, *Varun Goel, Husain Attarwala, and Gabriel Robbie*

Alnylam Pharmaceuticals, Cambridge, USA

17 June 2018 | 4th Congress of the European Academy of Neurology | Lisbon, Portugal

Background and Objectives

Hereditary ATTR (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, life-threatening disease caused by mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and GI tract[1-3]

Patisiran

- Lipid nanoparticle (LNP) formulation of siRNA (ALN-18328) targeting hepatic production of wild type (wt) and mutant TTR
- LNP is composed of ALN-18328, 2 novel lipid excipients (DLin-MC3-DMA and PEG_{2000}-C-DMG) and 2 approved lipid excipients (DSPC and cholesterol)[4,5]
- APOLLO is a global phase 3 study evaluating clinical efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD) and antidrug antibody (ADA) of patisiran.[6]

Objectives of Analyses

- To characterize the PK of ALN-18328, DLin-MC3-DMA and PEG_{2000}-C-DMG following patisiran 0.3 mg/kg q3w dosing over 18 months
- To assess the pharmacodynamic effect of patisiran on serum TTR
- To explore the relationship between PK exposures and TTR lowering, efficacy and safety
- To evaluate the incidence of ADA and its impact on PK, PD, efficacy and safety

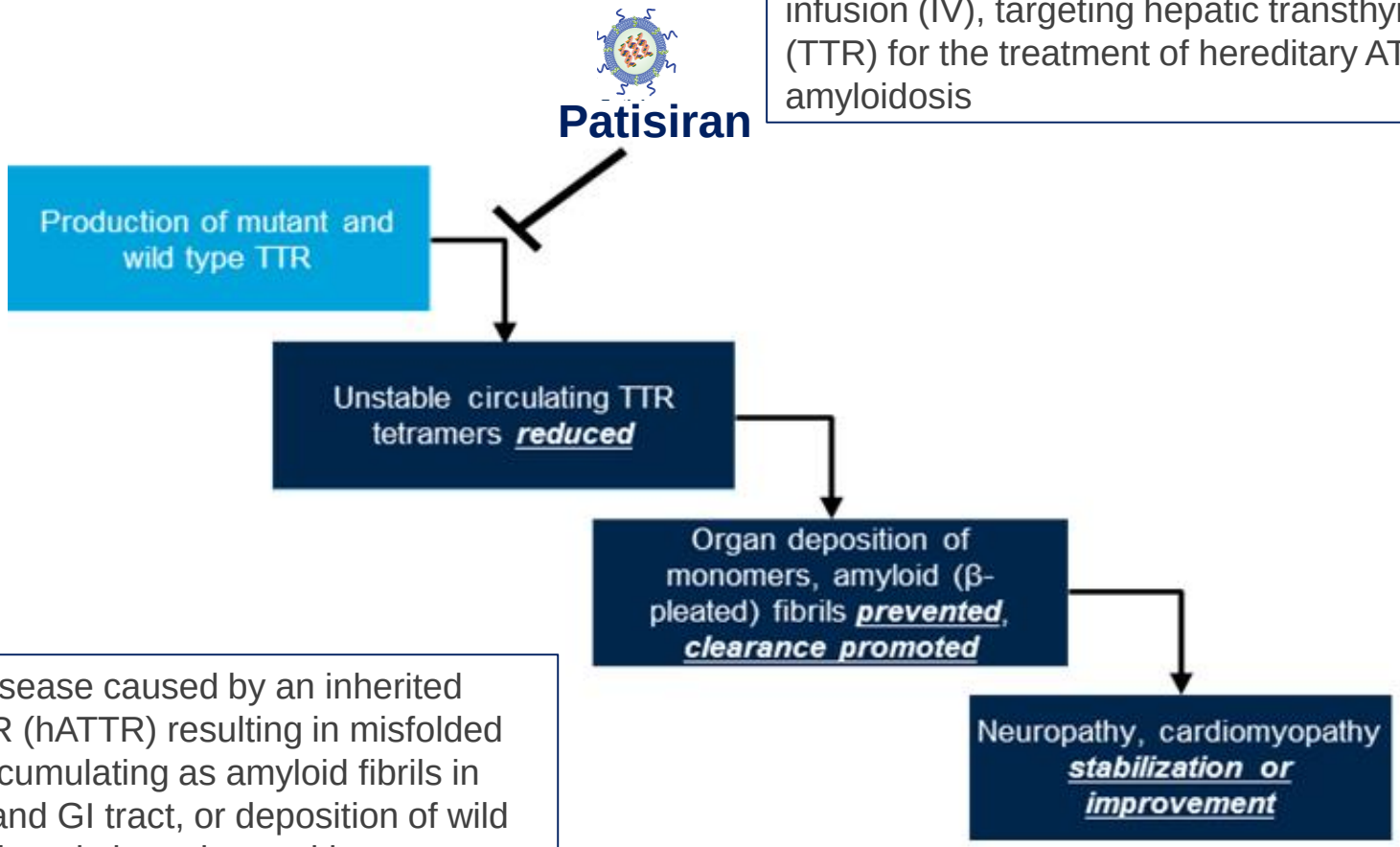
1. Hanna M. Curr Heart Fail Rep. 2014;11(1):50-57; 2. Mohty D et al. Arch Cardiovasc Dis. 2013;106(10):528-540; 3. Adams D et al. Neurology. 2015;85(8):675-682; 4. Cullis, P.R. and M.J. Hope, Mol Ther, 2017. 25(7): 1467-1475; 5. Mui, B.L., et al., Mol Ther Nucleic Acids, 2013. 2: e139, doi:10.1038/mtna.2013.66; 6. D Adams, A Gonzalez-Duarte, et al. EU ATTR conference in Paris, 02 November 2017.

Alnylam PHARMACEUTICALS

Background

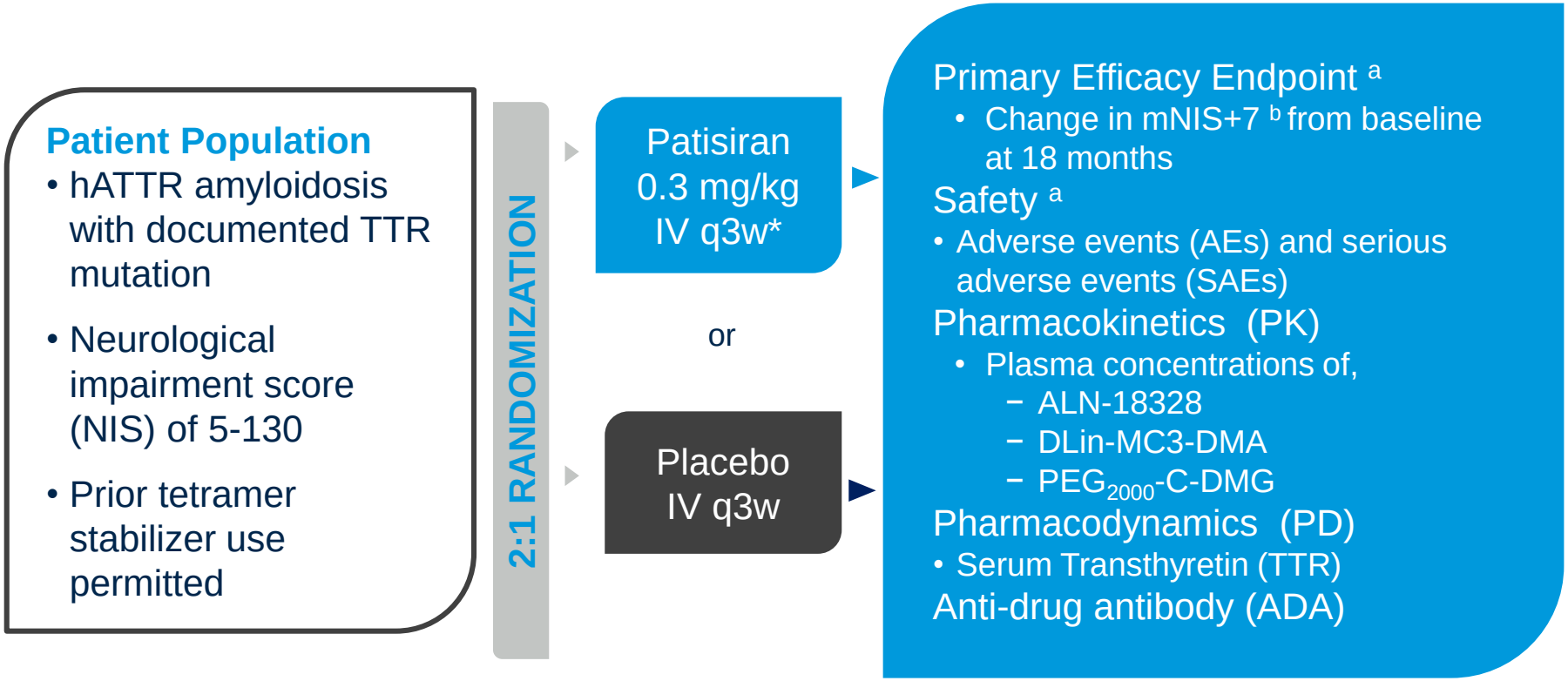
Therapeutic Hypothesis

Patisiran is an investigational RNAi therapeutic administered by intravenous infusion (IV), targeting hepatic transthyretin (TTR) for the treatment of hereditary ATTR amyloidosis



Multi-system disease caused by an inherited mutation in TTR (hATTR) resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and GI tract, or deposition of wild type (wt) transthyretin in patients without a pathogenic mutation (wtATTR)

Patisiran Phase 3 APOLLO Study Design



ClinicalTrials.gov Identifier: NCT01960348

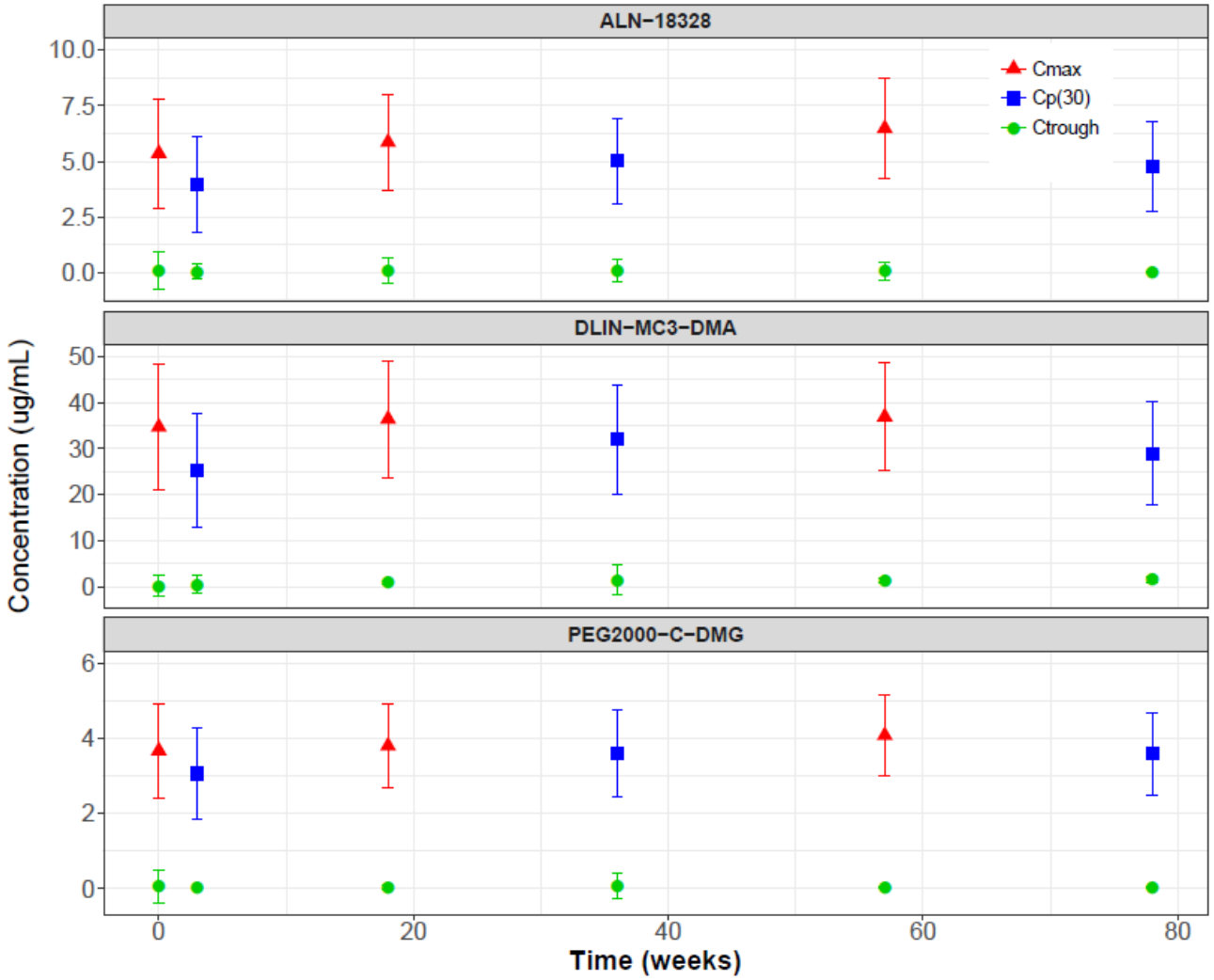
* Maximum dose was capped at 30 mg
[a] Results for efficacy and safety were presented at EU ATTR conference in Paris, 02 November 2017, by A Adams, A Gonzalez-Duarte, et al.
[b] mNIS+7, Modified Neuropathy Impairment Score +7

Methods

- PK parameters:
  - End of infusion (C_{max}), 30 minutes post end of infusion ($C_{p(30min)}$), pre-dose (C_{trough})
- Analysis subgroups:
  - Age (<65 and ≥65 y), sex (male/female), renal function (normal, mild and moderate impairment)[a], hepatic function (normal and mild impairment)[b], V30M mutation (Yes/No), race (Caucasian/Non-Caucasian), body weight category (< 100 kg and ≥ 100 kg)
- PK exposure-response (E-R) analyses:
  - Steady state PK exposures were divided by 4 quartiles:
    - ≤ 25, >25 to ≤50, > 50 to ≤75 and > 75 to ≤100%
  - Comparison of following parameters across 4 PK exposure quartiles for ALN-18328 :
    - TTR reduction from baseline (%) (over 18-months)
    - mNIS+7 change from baseline (at month 18)
  - Comparison of following parameters across 4 PK exposure quartiles for all 3 analytes
    - Incidence of AEs or SAEs
- ADA
  - Incidence of ADA
  - Comparison of PK, PD, efficacy and safety by ADA status

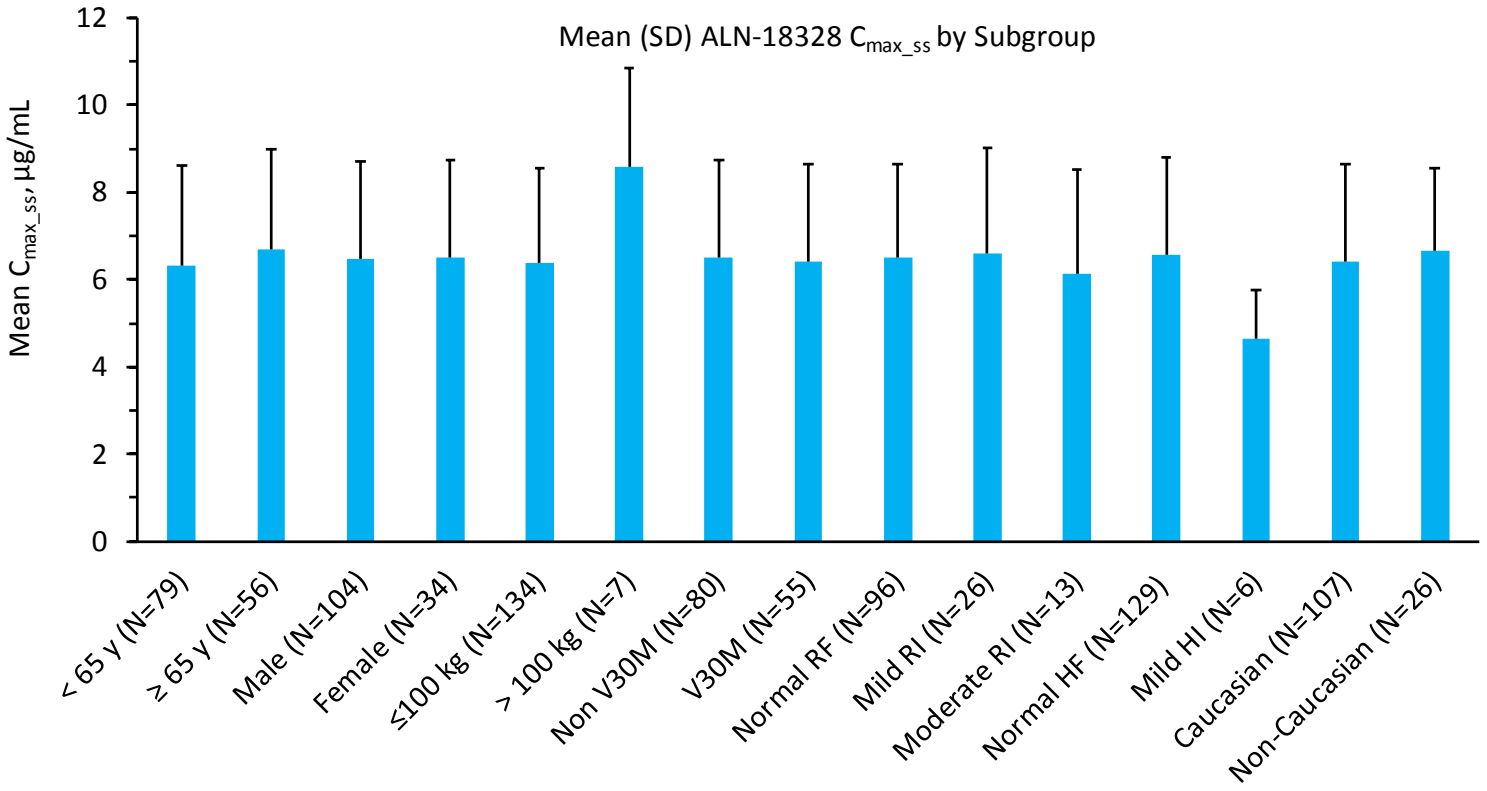
[a] Renal impairment subgroups: normal renal function: estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73m^2; mild renal impairment: eGFR ≥60 to <90 mL/min/1.73m^2; 1 moderate renal impairment: eGFR ≥30 to <60 mL/min/1.73m^2 (FDA Guidance for industry: Pharmacokinetics in patients with impaired renal function. 2010)
[B] Hepatic impairment subgroups: Normal hepatic function: Bilirubin (BIL) ≤ upper limit of normal (ULN) and serum aspartate transaminase (AST) ≤ULN; mild hepatic impairment: BIL ≤ ULN and AST >ULN or ULN <BIL ≤1.5 x ULN. (Patel H, et al. Journal of Clinical Oncology. 2004;22(14_suppl):6051)

Pharmacokinetic Results



- **Patisiran exhibited linear and time-independent PK with chronic dosing of 0.3 mg q3w over 18 months**
- **Plasma concentrations of all 3 analytes were stable with minimal to no accumulation over 18 months of q3w dosing**

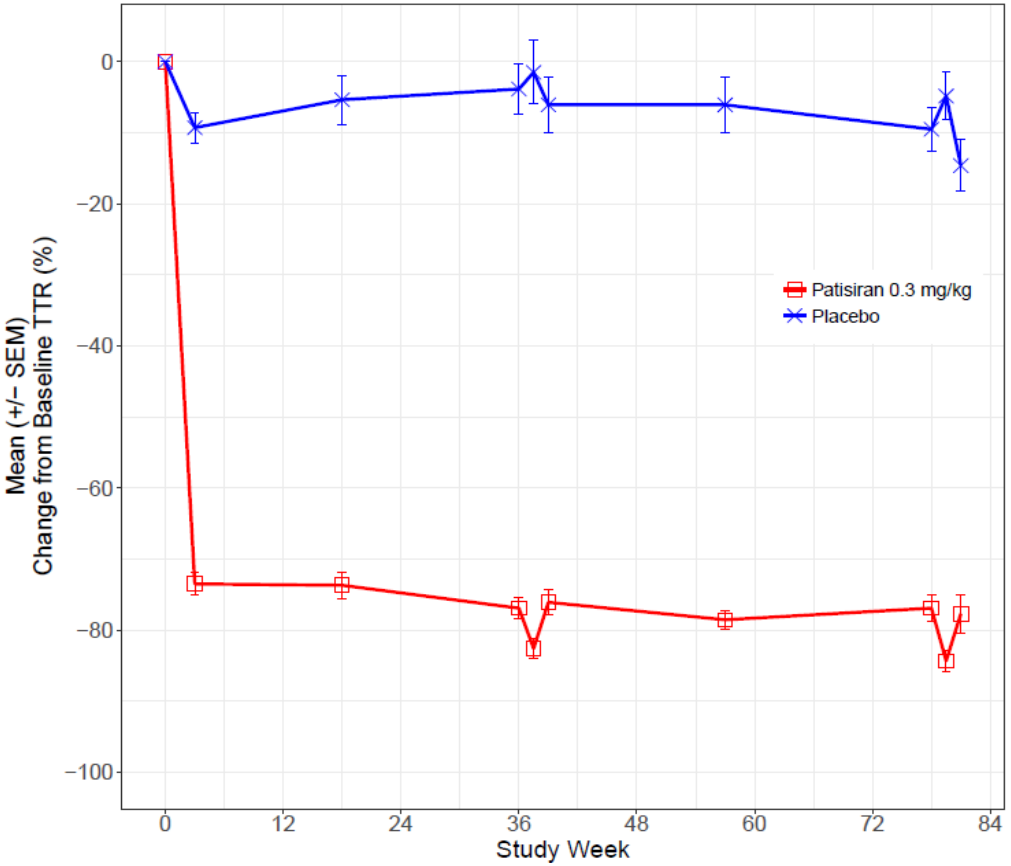
Pharmacokinetic Subgroup Analyses Results



HF: Hepatic function
HI: Hepatic impairment
RF: Renal function
RI: Renal impairment

- Similar and consistent steady state PK exposures were observed across all subgroups for the 3 analytes

Pharmacodynamic Results



- **Serum TTR reduction after the first dose was similar to long term reduction indicating rapid onset of effect**
- **TTR reduction was sustained over 18 months with q3w dosing**
- **Median reduction at month 18 was 84.3% [a]**
- **Serum TTR reduction was similar across all subgroups (See Slide 5)**

[a] D Adams, A Gonzalez-Duarte, et al. "Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy: Results from the Phase 3 APOLLO Study". Presented at EU ATTR conference in Paris, 02 November 2017

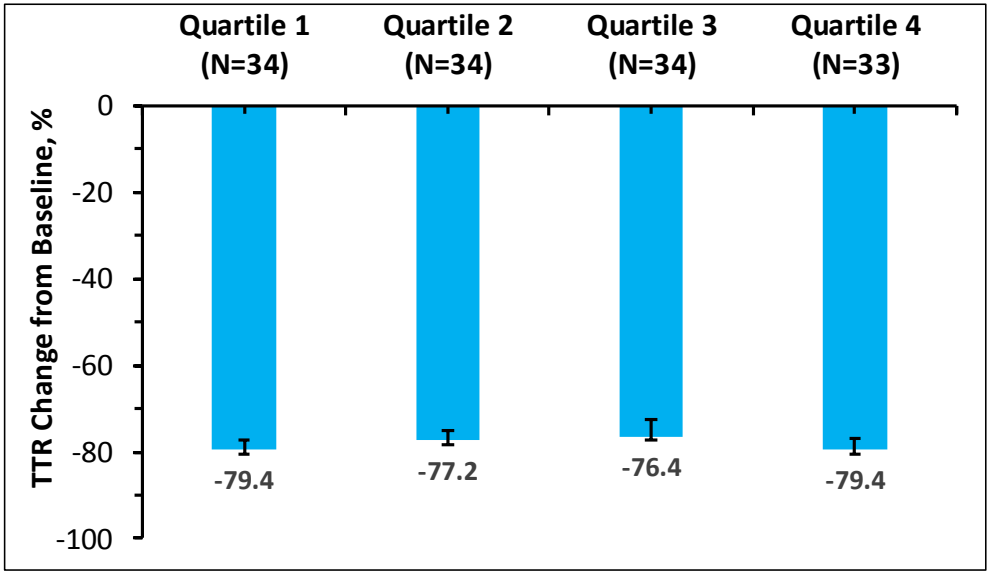
Alnylam PHARMACEUTICALS

PK Exposure-Response Analyses

Mean ALN-18328 C_{max_ss} Values (µg/mL)

Quartile 1	Quartile 2	Quartile 3	Quartile 4
3.69	5.63	7.25	9.43

TTR Change from Baseline (%) by ALN-18328 PK Exposure (C_{max_ss} Range)



Mean (±SEM) is presented

- **Similar TTR lowering (%) seen across ALN-18328 PK exposure range**
- **Similar efficacy (mNIS+7 change from baseline) seen across ALN-18328 PK exposure range**
- **No trend in incidence of AEs or SAEs across PK exposures of ALN-18328, DLin-MC3-DMA and PEG_{2000}-C-DMG**

[a] D Adams, A Gonzalez-Duarte, et al. "Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy: Results from the Phase 3 APOLLO Study". Presented at EU ATTR conference in Paris, 02 November 2017

Alnylam PHARMACEUTICALS

ADA Results

- Incidence of ADA in placebo (1.3%) and patisiran (3.4%) treated patients was low
  - ADA titer was low (ranged from 40 to 80)
  - ADA generally developed by Week 3 and was transient
  - None of the patients were ADA positive after Week 36

- No impact of ADA on,
  - PK exposures of ALN-18328, DLin-MC3-DMA, and PEG_{2000}-C-DMG
  - Serum TTR reduction
  - mNIS+7 change from baseline
  - Safety profiles

Summary

- Patisiran PK exposures were stable following chronic dosing over 18 months
- Plasma PK exposures and serum TTR lowering were similar in all patient subgroups
- Serum TTR lowering or clinical efficacy (mNIS+7 change from baseline) were similar across PK exposure range in patients
- No trend was seen in either incidence of AEs or SAEs across PK exposures of ALN-18328, DLin-MC3-DMA or PEG_{2000}-C-DMG
- Incidence of ADA in patisiran treated patients was low (3.4%), transient and did not impact PK, PD, efficacy and safety profiles
- Patisiran 0.3 mg/kg q3w is appropriate for a broad range of hATTR amyloidosis patients