Population Pharmacokinetic (PK) / Pharmacodynamic (PD) Model of Serum Transthyretin (TTR) Following Patisiran Administration in Healthy Volunteers and Patients with Hereditary TTR-Mediated (hATTR) Amyloidosis

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Background and Rationale

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

Analysis Objective

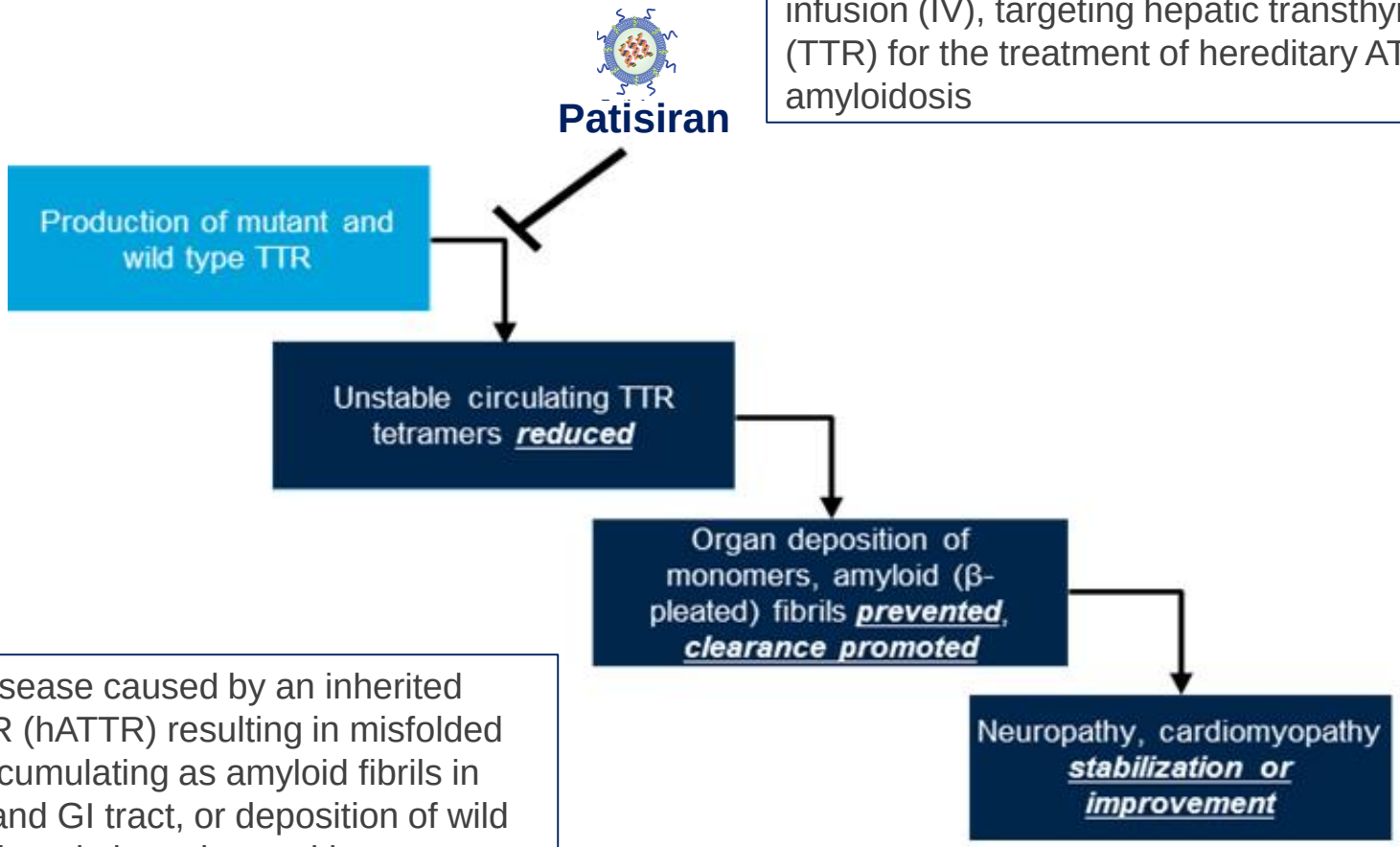
- Evaluate the relationship between plasma ALN-18328 (siRNA) levels and serum TTR levels following patisiran administration in healthy adults and hATTR amyloidosis patients

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

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)

Methods

Features of Pharmacokinetic (PK)/ Pharmacodynamic (PD) Dataset

- PK/PD data were pooled from five clinical studies from healthy volunteers and patients (n=283)
- Pooled dataset has both placebo and patisiran treated patients receiving single and multiple dosing up to 24 months
- Range of patisiran dose levels studied is 0.01 mg/kg – 0.5 mg/kg
- Serum TTR and plasma ALN-18328 levels were collected up to 24 months

Methods

- Non-linear mixed effects modeling was used to quantify the PK/PD relationship
- Impact of the following covariates were evaluated in the PK/PD model
  - **Baseline TTR levels**
  - **Mild and moderate renal function**
  - **Mild hepatic impairment**
  - **Race (Caucasian versus non-Caucasian)**
  - **Sex**
  - **Baseline age**
  - **Baseline body weight**
  - **TTR mutation (V30M versus non-V30M mutations)**
  - **Healthy volunteers versus hATTR amyloidosis patients**
  - **Concomitant administration of tetramer stabilizers**

Pooled Clinical Studies

The following studies were included in the analysis:

- ALN-TTR02-001: Phase1 randomized, single-blind, placebo controlled single ascending dose (SAD) study in healthy volunteers (N=17; 13 received patisiran and 4 received placebo)
- ALN-TTR02-005: Phase 1, randomized, double-blind, placebo controlled SAD study in Japanese healthy volunteers (N=12; 9 received patisiran and 3 received placebo)
- ALN-TTR02-002: A Phase 2, open-label, multi-dose, dose escalation trial in patients with TTR mediated polyneuropathy (N=29; all patients received patisiran)
- ALN-TTR02-003: A Phase2, multicenter, open-label extension study in patients with TTR mediated polyneuropathy previously treated with patisiran (N=27; all patients received 0.3 mg/kg patisiran every three weeks (q3W) for 2 years)
- APOLLO (ALN-TTR02-004): A Phase 3 multicenter, multinational, randomized, double-blind, placebo-controlled study in patients with TTR mediated polyneuropathy (N=225; 148 received 0.3 mg/kg patisiran q3W and 77 received placebo for 18 months)

Results

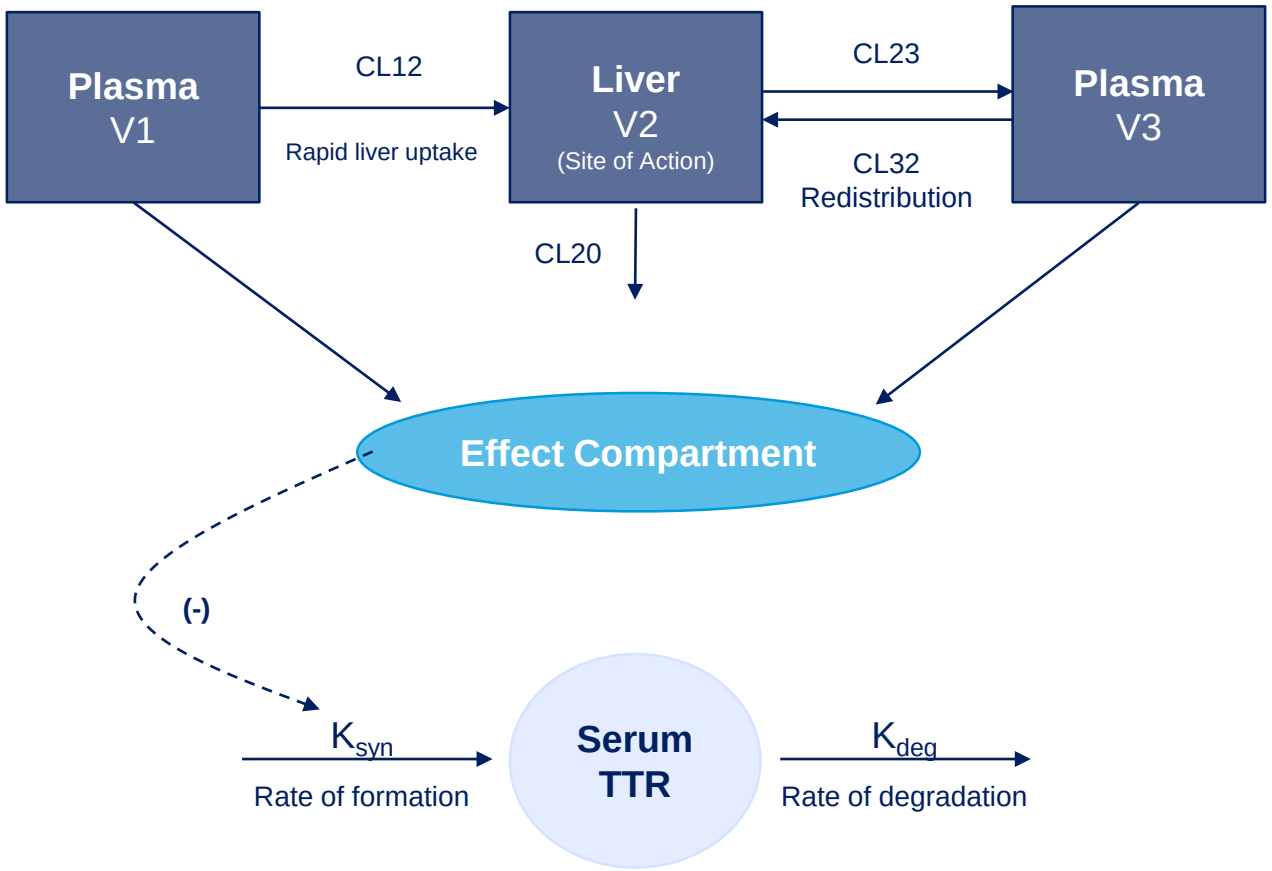
Baseline Demographics of the Pooled PK/PD Dataset

	Descriptive Statistics	Patisiran (n=199)	Placebo (n=84)
Serum TTR (µg/mL)	Median [Min, Max]	215.1 [52.3, 411]	201.7 [58.5, 371]
Age (years)	Median [Min, Max]	60.0 [21, 83]	62.0 [21, 80]
Body Weight (kg)	Median [Min, Max]	68.00 [36.2, 110.3]	68.00 [40.8, 110.2]
Sex	Male	150 (75.4%)	65 (77.4%)
	Female	49 (24.6%)	19 (22.6%)
Race	Caucasian	153 (76.9%)	53 (63.1%)
	Non-Caucasian	46 (23.1%)	31 (36.9%)
Hepatic Function	Normal	183 (92.0%)	81 (96.4%)
	Mild HI	15 (7.5%)	3 (3.6%)
	Moderate HI	1 (0.5%)	0 (0.0%)
Renal Function	Normal	142 (71.4%)	55 (65.5%)
	Mild	39 (19.6%)	24 (28.6%)
	Moderate	18 (9.0%)	5 (6.0%)
TTR Genotype	None	22 (11.1%)	7 (8.3%)
	V30M	78 (39.2%)	40 (47.6%)
	Non V30M	99 (49.7%)	37 (44.0%)
TTR Stabilizer on Treatment	Yes	18 (9.0%)	1 (1.2%)
	No	181 (91.0%)	83 (98.8%)

hATTR= hereditary amyloid transthyretin; LNP= lipid nanoparticles; NA= not applicable; SD= standard deviation; TTR = transthyretin
HI = hepatic impairment; N = number of subjects; V30M= valine to methionine mutation at position 30 in human TTR gene

Results

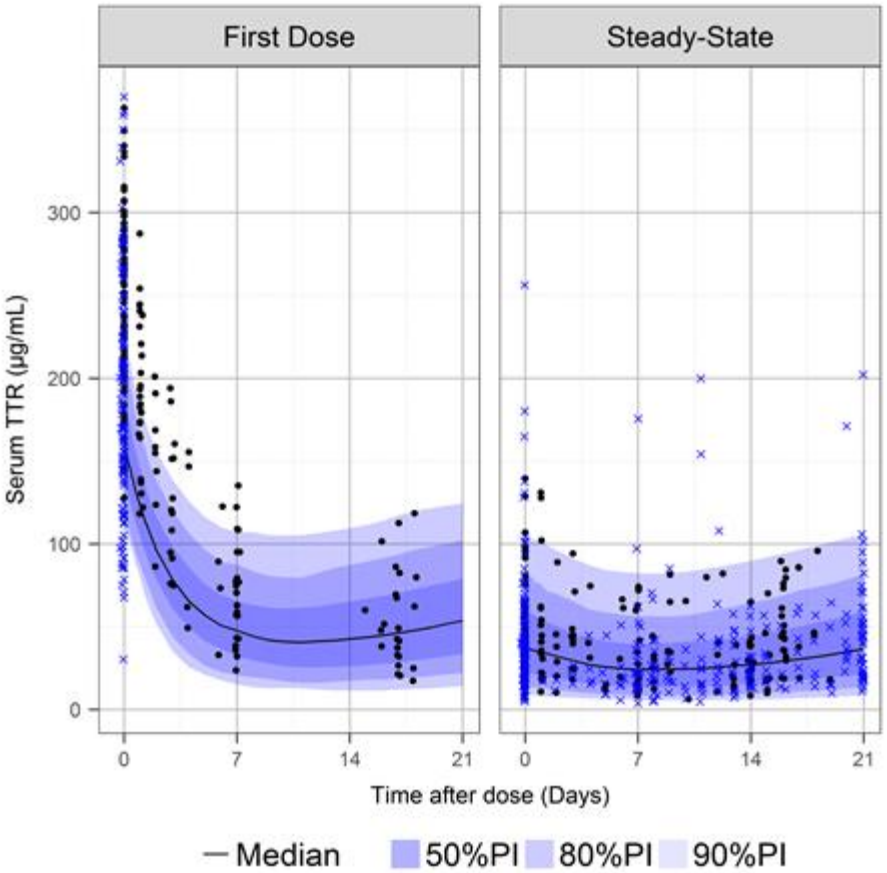
Schematic Representation of Indirect Response Model Linking Plasma ALN-18328 Concentrations and Serum TTR



CL20= elimination clearance from compartment 2; CL12= clearance from compartment 1 to compartment 2; CL23= clearance from compartment 2 to compartment 3; CL32= clearance from compartment 3 to compartment 2; K_{syn} = rate of TTR formation; K_{deg} = rate of TTR degradation; IV= intravenous; LNP= lipid nanoparticles; TTR = transthyretin; V1= distribution volume of compartment 1; V2= distribution volume of compartment 2; V3= distribution volume of compartment 3

Note: ALN-18328 concentrations in plasma are observed in compartment V1 and V3 and serum TTR is reflective of TTR levels in the liver.

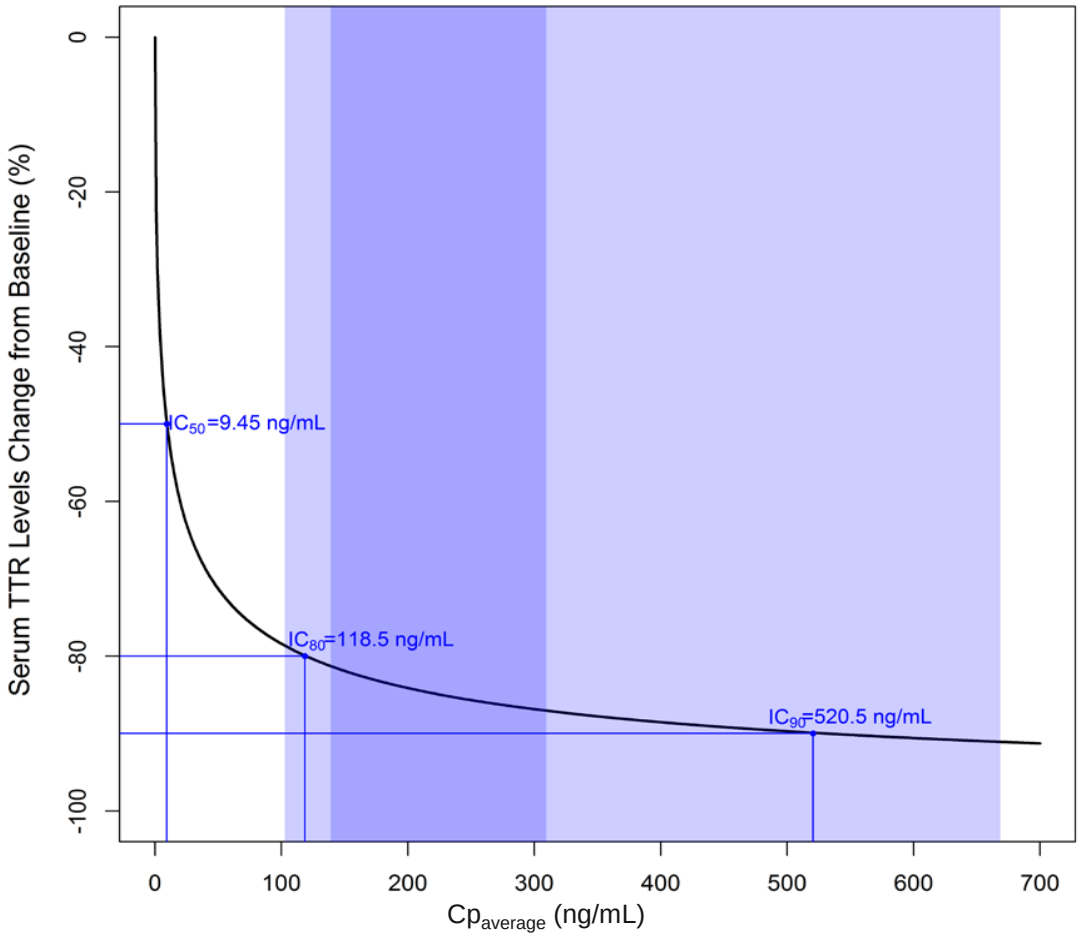
PK/PD Model Adequately Described Observed Serum TTR Levels in hATTR Patients Long Term Studies: Phase 2 OLE and APOLLO



Note: Blue crosses represent observed concentrations in Study 004 (Day 546) and black circles represent observed concentrations in Study 003 (Week 106).

- Average baseline TTR level in APOLLO is estimated to be ~185 ug/mL
- Model describes rapid decline in serum TTR following first dose of 0.3 mg/kg patisiran, with nadir ~ 10 -20 days post first dose
- 0.3 mg/kg q3w regimen effectively lowered TTR levels in majority of patients at steady state
  - Model predicted median steady-state TTR reduction from baseline was 80% to 88% during the dosing interval

Model Estimated Relationship Between Plasma ALN-18328 Levels and Serum TTR Levels (%Change from Baseline)



- A sigmoidal relationship best described the PK/PD Relationship
- Average ALN-18328 plasma levels over dosing interval for 50% TTR lowering (IC50) is estimated to be 9.45 ng/mL
- Patisiran dosing with 0.3 mg/kg q3w results in average ALN-18328 plasma concentrations that result in 80% to 90% TTR reduction from baseline
- Plasma concentrations from 0.3 mg/kg q3w dosing regimen is at the plateau portion of the concentration-response relationship i.e. between IC_{80} – IC_{90}

$Cp_{average}$: average plasma ALN-18328 levels over the 21 day dosing interval; IC_{50} = ALN-18328 concentration producing 50% of maximal inhibition; IC_{80}= ALN-18328 concentration producing 80% of maximal inhibition; IC_{90} = ALN-18328 concentration producing 90% of maximal inhibition; V30M= valine to methionine mutation at position 30 in human TTR gene

Note: The shaded area represent the 25th-75th percentiles and 5th- 95th percentiles of average concentration of ALN-18328 (i.e., 144.8-313.5 ng/mL and 105.2 – 676.6 ng/mL, respectively)

Impact of Demographics and Disease State Covariates on TTR Reduction Following Patisiran 0.3 mg/kg q3w Administration

- Similar TTR reduction was predicted following patisiran 0.3 mg/kg q3w administration across all covariates investigated in the model and includes, baseline TTR levels, baseline age, sex, renal function (mild and moderate renal impairment), mild hepatic impairment, V30M genotype, race (Caucasians versus non-Caucasians) and body weight

Summary

- PK/PD model adequately described the time-course and inter-individual variability in TTR reduction in healthy subjects and in patients with hATTR amyloidosis
- A sigmoidal relationship best described the ALN-18328 plasma level to serum TTR lowering relationship
- Average plasma ALN-18328 levels associated with 80% (IC_{80}) and 90% (IC_{90}) TTR lowering, were estimated to be 119 ng/mL and 521 ng/mL, respectively
- Almost all patients receiving 0.3 mg/kg patisiran q3w have average ALN-18328 plasma concentrations that yield 80% to 90% TTR reduction from baseline
- Similar and consistent TTR reduction is predicted across various covariates following patisiran 0.3 mg/kg q3w regimen
- No dose adjustment is required for any of the covariates tested