Population Pharmacokinetic (PK) of Patisiran in Healthy Volunteers and hATTR Patients

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Background and Rationale

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rapidly progressive, debilitating, and often fatal disease caused by mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract[1-5]

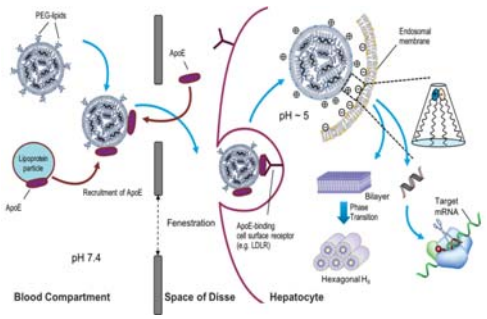
Patisiran

- Lipid nanoparticle (LNP) formulation of siRNA (ALN-18328), targeting reduction of hepatic production of wild type 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)[6,7].
- LNP is an effective way to protect and target siRNA in liver, Figure 1.
- The proposed LNP PK is a multi-step process as described in Figure 2.

Analysis Objectives

- Develop population PK models of ALN-18328 and the two novel lipid excipients (DLin-MC3-DMA and PEG_{2000}-C-DMG) to describe pharmacokinetics of LNP in plasma.
- Evaluate covariates that impact ALN-18328 pharmacokinetics.

Figure 1: Delivery of siRNA into hepatocytes with LNP



Abbreviations: ApoE=apolipoprotein E; LDLR= low density lipoprotein receptor; LNP-lipid nanoparticle; mRNA=messenger RNA; PEG lipids=PEG_{2000}-C-DMG. RISC=RNAi induced silencing complex; siRNA=small interfering ribonucleic acid (adapted from [8 Coelho] Figure 1 and [6 Cullis]).

Figure 2: Proposed Characteristics of LNP PK Following IV administration

PEG_{2000}-C-DMG dissociates from LNP in plasma

↓

LNP enters hepatocytes through ApoE mediated uptake

↓

LNP structure perturbed: ALN-18328 is released into cytoplasm

↓

Majority of internalized siRNA is recycled back into the circulation as lipid complex via exocytosis

↓

A minor second peak is observed in plasma due to exocytosis

Methods

Features of Pooled Analysis Datasets

- PK data pooled from five clinical studies from healthy volunteers and hATTR amyloidosis patients.
- Dose levels: 0.01 mg/kg – 0.5 mg/kg.
- Dosing frequency: single and multiple dosing up to 24 months.
- Dosing duration: 0.3 mg/kg administered every three weeks over 2 years.
- PK sampling: intensive in Phase 1 and Phase 2 and sparse in Phase 3 studies.

Analysis Methods

- Non-linear mixed effects modeling was used to develop population PK models.
- Impact of covariates on PK were evaluated.
- Simulations were done to evaluate model fit to the data and obtain PK parameters in patient population.

Covariates Evaluated

- Mild and moderate renal impairment
- Mild hepatic impairment
- Race (Caucasian versus non-Caucasian)
- Sex
- Baseline age
- Baseline body weight
- Presence of anti-drug antibody (ADA)
- Concomitant administration of moderate or strong CYP3A inhibitors or inducers
- Healthy volunteers versus hATTR amyloidosis patients

Results

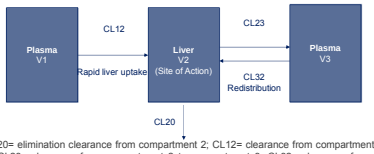
Pooled Data Covariate Summary

- Pooled data consisted of 177 patients and 22 healthy subjects.
- Among patients, median age was 62 years, majority were male (73%), Caucasian (80.2%), with normal hepatic (91%) and normal renal function (68%).
- 22% of patient had mild renal impairment, and 10% had moderate renal impairment.
- 9% of patient had mild hepatic impairment.

PK Model of siRNA (ALN-18328)

- A semi mechanistic model best described the PK of ALN-18328, Figure 3.
- Model predicts terminal $T_{1/2}$ of 3 days and 2-3 fold accumulation of ALN-18328 in plasma following Q3W regimen due to association with DLin-MC3-DMA lipid.

Figure 3: PK Model of ALN-18328 (siRNA)



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; 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 1 and 3.

PK of Lipid Excipients

- Three compartment pharmacokinetic models best described the PK of novel LNP excipients.
- Model predicts DLin-MC3-DMA terminal $T_{1/2}$ of 60 days and 2 fold accumulation in plasma following Q3W regimen.
- Model predicts PEG_{2000}-C-DMG terminal $T_{1/2}$ of 10.6 days and no accumulation in plasma with Q3W regimen.

Covariate Effect on PK

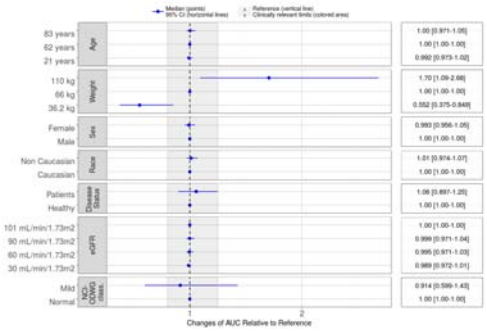
- There was slight trend of increasing PK exposure with increasing body weight; however that did not result in differences in TTR lowering.
- None of the other covariates impacted PK exposure of patisiran.
- Based on these results, no dosing adjustment is required for evaluated subgroups.

Table 1: Summary of Model Derived PK Parameters for Patients Enrolled in Phase 3 Trial Following Patisiran 0.3 mg/kg Every Three Week Regimen; Values Are Geometric Mean (Geo CV)

Parameters	ALN-18328 (siRNA)	DLin-MC3-DMA (Excipient)	PEG_{2000}-C-DMG (Excipient)
CL (L/h)	0.180 (53.6%)	0.122 (28%)	0.134 (24.1%)
Vd (L)	17.2 (45.1%)	250 (27.5%)	48.9 (24.8%)
$T_{1/2}$ (days)	2.77 (10.9%)	59.5 (15.8%)	10.6 (12.7%)
Accumulation	2.39 (11.9%)	2.06 (16.1%)	1.02 (11.9%)

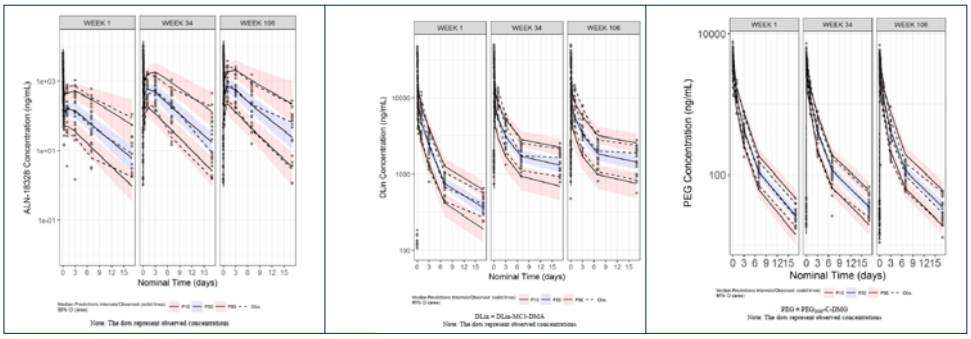
CL = plasma clearance; Geo CV = geometric coefficient of variation; $T_{1/2}$ = terminal half-life; Vd = volume of distribution based on terminal phase
Note: The accumulation ratio is calculated by taking the ratio of AUCtau at steady state to AUCtau after first dose. The CL is derived as Dose / AUC0-inf , where AUC0-inf is the area under the curve from time 0 to infinity, and lambda_z is the terminal rate of elimination. The Vd is derived as Dose / AUC0-inf x lambda_z, where lambda_z is the terminal rate of elimination. Tau is dosing interval.

Figure 4: Impact of Covariates on ALN-18328 (siRNA) PK



The dots and the horizontal segments: mean and 95% CI of covariate effect relative to the reference patient.
The shaded area represents effect size of 80% -125%.
eGFR: estimated glomerular filtration rate; Renal function category was based on FDA guidance [9].
Hepatic function category was based on NCI-ODWG classification[10].

Figure 5: Model Predictions (Shown as Shaded Areas) Describe Observed (Shown as Dots) PK of ALN-18328 (siRNA) and Lipid Excipients (DLin-MC3-DMA & PEG_{2000}-C-DMG) Following Administration of 0.3 mg/kg Patisiran Every Three Week Regimen Over 2-Years



Note: Week 1, Week 34, and Week 106 are three occasions where intensive PK samples were collected in the Phase 2 open label extension study.

Summary

- Population PK modeling adequately described the plasma PK profile of patisiran components in hATTR amyloidosis patients following single and multiple dosing over 2-years.
- Model indicates patisiran PK is linear, dose-proportional, time-invariant and predictable with repeated dosing of 0.3 mg/kg every three week regimen.
- Steady state was reached by week 24 following repeat administration.
- Covariate analysis indicated slight trend of increasing PK exposure with increasing body weight.
- None of the other covariates had meaningful impact on PK.
- Based on these results, no dose modifications are required for any of the evaluated subgroups.
- Patisiran 0.3 mg/kg every three week regimen is appropriate for hATTR amyloidosis patients.

Acknowledgement

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Abbreviations: DLin-MC3-DMA: (6Z, 9Z, 28Z, 31Z)-heptatriaconta-6, 9, 28, 31-tetraen-19-yl-4-(dimethylamino) butanoate; PEG_{2000}-C-DMG: (α (3' {[1,2 di(myristyloxy)proponoxyy]carbonylamino}propyl)-ω-methoxy, polyoxyethylene); (R)-methoxy-PEG2000-carbamoyl-di-O-myristyl-sn-glyceride; DSPC: 1,2-distearoyl-sn-glycero-3-phosphocholine; Q3W: once every three weeks

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