Heredity 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.9

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 PEG2000-C-DMG) and 2 approved lipid excipients (DSPC and cholesterol).10

• 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 PEG2000-C-DMG) to describe pharmacokinetics of LNP in plasma.

• Evaluate covariates that impact ALN-18328 pharmacokinetics.

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

• Age (Caucasian versus non-Caucasian).

• Sex.

• Baseline age.

• Baseline body weight.

• Presence of anti-drug antibody (ADA).

• Concomitant administration of moderate or strong CYP3A4 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.

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 Q2W regimen.

• Model predicts PEG2000-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.

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.

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 Geographic Mean (See CV)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>ALN-18328 (siRNA)</th>
<th>DLin-MC3-DMA (Excipient)</th>
<th>PEG2000-C-DMG (Excipient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>0.180 (53.6%)</td>
<td>0.122 (28%)</td>
<td>0.134 (24.1%)</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>17.2 (45.1%)</td>
<td>250 (27.5%)</td>
<td>48.9 (24.8%)</td>
</tr>
<tr>
<td>$T_{1/2}$ (days)</td>
<td>2.77 (10.9%)</td>
<td>59.5 (15.8%)</td>
<td>10.6 (12.7%)</td>
</tr>
<tr>
<td>Accumulation</td>
<td>2.39 (11.9%)</td>
<td>2.06 (16.1%)</td>
<td>1.02 (11.9%)</td>
</tr>
</tbody>
</table>

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.

Figure 1: Delivery of siRNA into hepatocytes with LNP

Figure 2: Proposed Characteristics of LNP PK Following IV administration

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

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

Figure 5: Model Predictions (Shown as Shaded Areas) Describe Observed (Shown as Dots) PK of ALN-18328 (siRNA) and Lipid Excipients (DLin-MC3-DMA & PEG2000-C-DMG) Following Administration of 0.3 mg/kg Patisiran Every Three Week Regimen Over 2 Years.

Note: Week 1, Week 3, and Week 16 are three occasions where intensive PK samples were collected in the Phase 2 open label extension study.