Pharmacokinetics of Patisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis

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Introduction

Hereditary Transthyretin-Mediated (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. [1-5]
- Multi-systemic disease with heterogeneous clinical presentation (sensory and motor, autonomic and cardiac symptoms).[2,6,7]

Patisiran

- Small interfering RNA (siRNA) formulated in lipid nanoparticle (LNP) targeting hepatic production of wild type (wt) and mutant TTR.
- LNP is composed of siRNA (ALN-18328), 2 novel lipid excipients (DLin-MC3-DMA and PEG_{2000}-C-DMG) and 2 approved lipid excipients (DSPC and cholesterol).[8,9]
- LNP system exhibits an electron-dense core where siRNA is associated with cationic lipid and protected from external RNase.[10]
- Phase 2 Open-Label Extension (OLE) study of patisiran was a study evaluating long term clinical efficacy, safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and anti-drug antibody (ADA) of patisiran over 24 months of treatment.

Objectives of Analyses

- To characterize the PK of ALN-18328 and 2 novel lipids (DLin-MC3-DMA and PEG_{2000}-C-DMG) following intravenous (IV) infusion of patisiran 0.3 mg/kg every 3 weeks (Q3W) dosing over 24 months in Phase 2 OLE study.
- To evaluate the incidence of ADA and its impact on PK, PD and safety.

Methods

Patisiran Phase 2 OLE Study Design

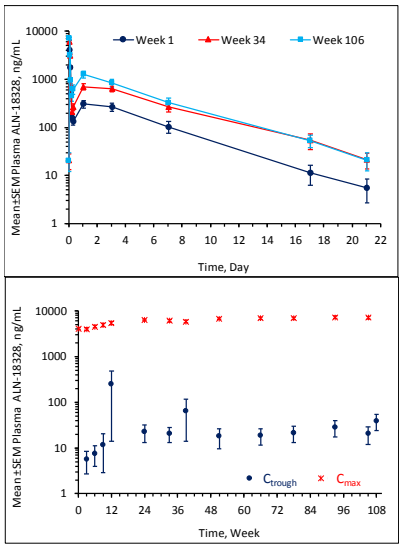
- hATTR amyloidosis patients who completed phase 2 multiple ascending dose study [11] were eligible to roll over onto Phase 2 OLE study.[12] (Figure 1)
- Of 29 patients enrolled in Phase 2, 27 patients completed study; all 27 completers enrolled in Phase 2 OLE Study.
- Intensive plasma PK sampling was performed at weeks 1, 34 and 106.
- Sparse peak (C_{max}) ad trough (C_{trough}) samples were collected over 24-months of treatment.
- Pre- and post- dose samples were taken for evaluation of ADA
- Standard non-compartmental analysis method was used for PK parameter computation.

Figure 1: Phase 2 OLE Study Design

Results

siRNA (ALN-18328) PK

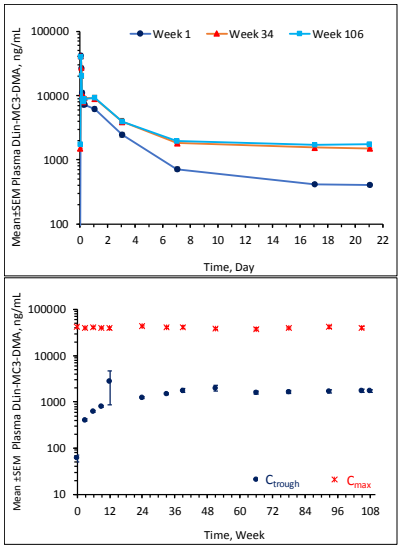
Figure 2: Mean Plasma Concentration-time Profiles at Weeks 1, 34 and 106 (Top Panel) and Mean C_{trough} and C_{max} Over 24 Months of Treatment (Bottom Panel)



- ALN–18328 concentrations declined rapidly following IV infusion due to uptake of LNP by the liver with an half-life less than 1 hour.
- A minor 2nd peak was observed within 24 hours after end of infusion due to re-distribution from the liver.
- Terminal elimination half-life is ~ 3 days .
- Peak and trough concentration accumulated by 2-3 fold and approached steady state by week 24.

Lipid (DLin-MC3-DMA) PK

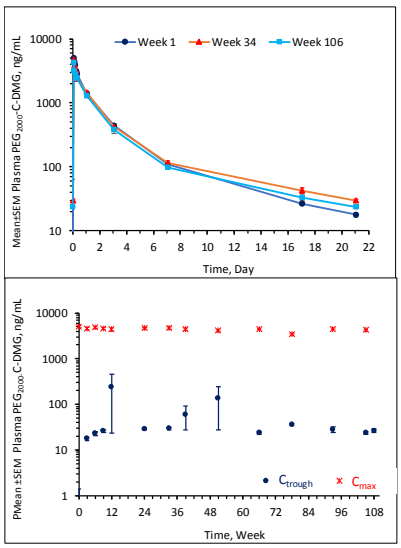
Figure 3: Mean Plasma Concentration-time Profiles at Weeks 1, 34 and 106 (Top Panel) and Mean C_{trough} and C_{max} Over 24 Months of Treatment (Bottom Panel)



- DLin-MC3-DMA concentrations declined rapidly after IV infusion due to uptake of LNP by the liver with an half-life less than 1 hour.
- A minor 2nd peak was also observed within 24 hours after end of infusion due to re-distribution from the liver.
- Peak concentration did not accumulate.
- Trough concentration accumulated by 2-3 fold and approached steady state by week 24.
- Based on accumulation ratio, the estimated effective half-life is ~ 17 days.

Lipid (PEG_{2000}-C-DMG) PK

Figure 4. Plasma Concentration-time Profiles at Weeks 1, 34 and 106 (Top Panel) and Mean C_{trough} and C_{max} Over 24 Months of Treatment (Bottom Panel)



- Plasma concentrations of PEG_{2000}-C-DMG declined in a multiphasic manner:
  - PEG_{2000}-C-DMG is dissociated from LNP in plasma within 6 hours after end of infusion.
  - No 2nd peak was observed.
- Peak concentration did not accumulate.
- Trough accumulation is negligible.

Anti-Drug Antibody

- Of 27 patients in the study, one patients (3.2%) had positive ADA test result at 3 time points: Screening, Day 21 and Day 84; the titer for all 3 samples was low (80).
- This patients developed ADA in the prior Phase 2 study after first dose of patisiran and remained ADA positive after enrolling in the Phase 2 OLE study.
- There was no impact of ADA on PK of ALN-18328, TTR reduction from baseline or safety profile in this patient.

Summary

- Plasma PK for ALN-18328, DLin-MC3-DMA, and PEG_{2000}-C-DMG PK were linear with time.
- PK profiles of ALN-18328 and DLin_MC3-DMA were similar, implying close association of siRNA and lipid in LNP.
- Plasma concentrations were predictable and stable after chronic dosing; approaching steady state by week 24.
- Incidence of ADA was low (3.2%), transient, and had no impact on PK, PD or safety profile.

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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