Patisiran: Half-Life and Duration of Effect

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SUMMARY

- The terminal elimination half-life (mean ± SD) of patisiran is 3.2 ± 1.8 days. Patisiran is mainly cleared through metabolism, and the total body clearance (mean ± SD) at steady state (CL_{ss}) is 3.0 ± 2.5 mL/h/kg.[1]
- Patisiran is an siRNA therapeutic formulated with an active ingredient (ALN-18328) and 4 lipid excipients.[2]
- In the Phase 2 MAD and OLE studies, the plasma PK profiles of ALN-18328 demonstrated 2 phases. The first phase is the short distribution half-life ($t_{1/2}$); the second phase is a minor peak and relatively long terminal elimination half-life ($t_{1/2\beta}$).[2]

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ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

The DOSAGE AND ADMINISTRATION section provides the following information[1]:

Dosing Information

ONPATTRO should be administered by a healthcare professional.

ONPATTRO is administered via intravenous (IV) infusion. Dosing is based on actual body weight.

For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg once every 3 weeks.

For patients weighing 100 kg or more, the recommended dosage is 30 mg once every 3 weeks.

The CLINICAL PHARMACOLOGY section provides the following information[1]:

Pharmacokinetics

Following a single intravenous administration, systemic exposure to patisiran increases in a linear and dose-proportional manner over the range of 0.01 to 0.5 mg/kg. Greater than 95% of patisiran in the circulation is associated with the lipid complex. At the recommended dosing regimen of 0.3 mg/kg every 3 weeks, steady state is reached by 24 weeks of treatment. The estimated mean ± SD steady-state peak concentrations (C_{max}), trough concentrations (C_{trough}), and area under the curve (AUC_t) were 7.15 ± 2.14 µg/mL, 0.021 ± 0.044 µg/mL, and 184 ± 159 µg·h/mL, respectively. The accumulation of AUC_t was 3.2-fold at steady state, compared to the first dose. In the placebo-controlled study, inter-patient variability in patisiran exposure did not result in differences in clinical efficacy (mNIS+7 change from baseline) or safety (adverse events, serious adverse events).

Distribution

Plasma protein binding of ONPATTRO is low, with ≤2.1% binding observed in vitro with human serum albumin and human α1-acid glycoprotein. ONPATTRO distributes primarily to the liver. At the recommended dosing regimen of 0.3 mg/kg every 3 weeks, the mean ± SD steady-state volume of distribution of patisiran (V_{ss}) was 0.26 ± 0.20 L/kg.

Elimination

The terminal elimination half-life (mean ± SD) of patisiran is 3.2 ± 1.8 days. Patisiran is mainly cleared through metabolism, and the total body clearance (mean ± SD) at steady state (CL_{ss}) is 3.0 ± 2.5 mL/h/kg.

Metabolism

Patisiran is metabolized by nucleases to nucleotides of various lengths.

Excretion

Less than 1% of the administered dose of patisiran is excreted unchanged into urine.

MECHANISM OF ACTION

Patisiran is an RNA interference therapeutic composed of an siRNA, ALN-18328, formulated with 4 lipid excipients, of which 2 are 1,2-distearoyl-sn-glycero-3-phosphocholine and cholesterol, and 2 were novel excipients, DLin-MC3-DMA and PEG_{2000}-C-DMG. The excipients are part of the LNP components that support stabilizing and targeting ALN-18328 towards the liver, the primary site of TTR synthesis. The ratio of LNP components is optimized for delivery to the liver.[2]

Following IV administration, the LNPs are opsonized by ApoE and then enter the liver, where they bind to ApoE receptors on the surface of hepatocytes. Once patisiran enters the cytoplasm of hepatocytes, it suppresses TTR gene expression by binding to the RISC, which, in turn, specifically cleaves wild-type and mutant TTR messenger RNA, thereby reducing TTR synthesis.[2]

ANIMAL DATA

Plasma PK

In cynomolgus monkeys exposed to a single IV bolus (0.03, 0.30 or 1.0 mg/kg) of patisiran, the clearance was reduced while the $t_{1/2}$ increased with increasing dose. This dose-dependent increase in $t_{1/2}$ was also observed in monkeys during the toxicological repeated dose (3 mg/kg/q2w for 6 weeks and ≥1 mg/kg/q3w for 39 weeks) studies.[3]

Hepatic PK

Targeted delivery of patisiran to the liver via the ApoE-dependent LDL receptor pathway was confirmed by the male adult rat QWBA with a 0.3 mg/kg single dose of IV patisiran with radiolabeling, where most of the radioactivity (>90%) was rapidly distributed to the liver, between 1 to 3.5 hours in Sprague Dawley rats and 1 to 6 hours in Long Evans rats. While much of the patisiran radioactivity was rapidly distributed to the liver within an hour, there was a delay in the initial uptake of patisiran into hepatocytes as most of the radioactivity signal was found in the liver sinusoid lumens. After 24 to 72 hours, the signal started to increase in the cytoplasm of hepatocytes, becoming approximately equal to the signal in the vascular lumen.[3]

The levels of DLin-MC3-DMA excipient reached maximum concentration between 4 and 24 hours in rat liver and between 5 and 15 hours in cynomolgus monkey liver. The level of PEG_{2000}-C-DMG excipient reached maximum concentration by 1 hour in rat liver and by 2 hours in cynomolgus monkey liver. Animal

studies and modelled clinical PK data suggested that there is no further liver accumulation of the DLin-MC3-DMA and PEG_{2000}-C-DMG excipients after reaching steady state following 24 weeks of multiple dosing of patisiran.[3]

CLINICAL DATA

Patisiran Phase 2 Multiple Ascending Dose Study

The Phase 2 study was a multicenter, international, open-label, MAD study in patients with hATTR-PN. Cohorts of 3 patients received 2 doses of patisiran, with each dose administered as an IV infusion.[4]

Phase 2 Open-Label Extension Study

The Phase 2 OLE study (N=27) was a multicenter, international study in patients with hATTR-PN. Patients who previously received and tolerated patisiran in the Phase 2 study were eligible to enroll in the Phase 2 OLE study. Patients received IV patisiran 0.3 mg/kg every 3 weeks for approximately 2 years.[5]

Overview of PK Analyses

In both the Phase 2 MAD and OLE studies, the PK profile of ALN-18328 and DLin-MC3-DMA demonstrated 2 distinct phases, the first phase characterized by a short distribution $t_{1/2}$ and the second phase by minor peak with relatively long $t_{1/2\beta}$. The first phase represents the rapid uptake of ALN-18328 encapsulated within LNP by the hepatocytes; the second phase represents the exocytosis of the ALN-18328 lipid complex from the hepatocytes back into plasma.[2]

Following patisiran 0.3 mg/kg every-3-week dosing in patients, the plasma concentration of ALN-18328 accumulated over time and reached steady state by 24 weeks of dosing, stabilizing thereafter. At steady state, ALN-18328 achieved the following PK parameters[2]:

- Maximum concentration ($C_{max,ss}$ [mean ± SD]) of 7.2 ± 2.1 µg/mL,
- Minimum concentration ($C_{min,ss}$ [mean ± SD]) of 0.0210 ± 0.0442 µg/mL,
- Time to maximum concentration (t_{max} [median [range]]) of 1.30 (1.17 – 2.10) hours,
- Total body clearance ($CL_{,ss}$ [mean ± SD]) of 3.0 ± 2.5 mL/kg/h and
- $t_{1/2\beta,\ ss}$ (mean ± SD) of 3.2 ± 1.8 days.

Based on the estimated $t_{1/2\beta}$ of ALN-18328 of 2-4 days, 97% of the ALN-18328 administered would be expected to be eliminated by approximately 12-20 days, leading to no accumulation with every-3-week dosing. However, following repeated doses, the plasma concentration of patisiran reached steady state at 24 weeks in the clinical trials. The disparity between the half-life and the observed accumulation can be explained by the high (>95%) association of ALN-18328 with DLin-MC3-DMA, an LNP constituent, such that the PK of ALN-18328 is dependent on the PK of DLin-MC3-DMA, which has a relatively longer $t_{1/2\beta,ss}$ (mean ± SD) of 10.9 ± 7.9 days.[2]

ABBREVIATIONS

ApoE = apolipoprotein E; AUC_t = area under the curve; C_{max} = peak concentration; $C_{min,ss}$ = trough concentration; CL_{ss} = steady-state clearance; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; LDL = low-density lipoprotein; LNP = lipid nanoparticle; MAD = multiple ascending dose; mNIS+7 = modified neuropathy impairment score +7; OLE = open-label extension; PK = pharmacokinetic; q2w = every 2 weeks; q3w = every 3 weeks; QWBA = quantitative whole body autoradiography; RISC = RNA-induced silencing complex; RNA = ribonucleic acid; SD = standard deviation; siRNA = small interfering ribonucleic acid; $t_{1/2}$ = half-life; $t_{1/2\beta}$ = terminal half-life; t_{max} = time to maximum concentration; TTR = transthyretin; V_{ss} = steady-state volume of distribution.

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