Patisiran: Post-Orthotopic Liver Transplant

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SUMMARY

- In the APOLLO and APOLLO-B studies, patients with prior liver transplant or those who were planning to undergo liver transplantation during the study period were excluded.[1,2]
- An open-label study in patients with hATTR post-OLT was conducted to evaluate the safety, efficacy, and PK of patisiran in this patient population.[3]
  - After 12 months of patisiran treatment, the median serum TTR percent reduction from baseline (average of Month 6 and Month 12) was 91.0% (95% CI: 86.1, 92.3; p<0.001).[3]
  - At week 54 following repeat q3w dosing, the PK values were similar to those observed after first dose.[4]
  - All 23 patients completed the study (1 patient discontinued treatment but completed the study). There were no discontinuations due to AEs, and no deaths occurred during the study.[3]

INDEX

CLINICAL DATA

Open-Label Study of Patisiran in Patients with hATTR Post-OLT

Overview and Design

A phase 3b, open-label study was conducted to evaluate the safety, efficacy, and PK of patisiran in patients with hATTR who had polyneuropathy progression post-OLT. Patients in the study (N=23) received IV patisiran 0.3 mg/kg every 3 weeks for 12 months.

Key inclusion and exclusion criteria for the study are presented in **Table 1**.[3]

Table 1. Key Inclusion and Exclusion Criteria.[3]

Inclusion Criteria	Exclusion Criteria
• Age ≥18 years • Received OLT for hATTR ≥12 months prior to study entry • Worsening PND score after OLT (either compared with pre-OLT assessment or between 2 assessments post-OLT) • KPS ≥70%	• NYHA class >II • PND score IV • Serum levels of AST, ALT, or total bilirubin greater than the ULN • Previous liver allograft rejection episodes or abnormal LFTs suggestive of possible allograft rejection ≤6 months prior to the study • eGFR ≤30 ml/min/1.73 m^2 at screening • Any other organ transplant • Unable to comply with required premedications • Previous use of patisiran and current or past use of inotersen • Use of TTR stabilizers, tauroursodeoxycholic acid, doxycycline, or other investigational agents during study

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; KPS = Karnofsky Performance Status; LFT = liver function test; NYHA = New York Heart Association; OLT = orthotopic liver transplantation; PND = polyneuropathy disability; TTR = transthyretin; ULN = upper limit of normal.

The primary endpoint assessed was the average of Month 6 and Month 12 serum TTR percent reduction from baseline. Secondary endpoints were change from baseline to Month 12 in NIS, Norfolk QOL-DN, COMPASS-31, R-ODS, and mBMI.[3]

Patient Demographics and Baseline Characteristics

A total of 23 patients across 7 European countries were enrolled and received patisiran. Baseline demographics of the patients enrolled are summarized in **Table 2**.[3]

Table 2. Baseline Demographics and Characteristics.[3]

Baseline Demographics and Characteristics	Safety Analysis Set (N=23)
Age, years, mean (SD)	58.1 (9.9)
Male, n (%)	13 (56.5)
Race, n (%)	
White	22 (95.7)
Asian	1 (4.3)
Age at hATTR diagnosis, years, mean (SD)	46.7 (11.7)
V30M genotype[a], n (%)	15 (65.2)
Previous TTR stabilizer use[b], n(%)	13 (56.5)
Age at liver transplant, years, mean (SD)	50.1 (10.8)
Time from hATTR diagnosis to OLT, years, mean (SD)	3.7 (3.0)
Time from OLT to first patisiran dose, years, mean (SD)	9.4 (5.1)
Immunosuppression regimen at baseline, n (%)	
Tacrolimus	10 (43.5)
Tacrolimus + mycophenolate	7 (30.4)
Other[c]	6 (26.1)
BMI, kg/m^2, mean (SD)	23.5 (3.6)
Serum TTR level, mg/L, mean (range)	202.1 (123.7 – 315.1)

Baseline Demographics and Characteristics	Safety Analysis Set (N=23)
NIS Total Score, mean (range)	60.3 (7.0 – 136.5)
Norfolk QOL-DN score, mean (range)	66.7 (16.0 – 98.0)
PND score, n (%)	
I: preserved walking, sensory disturbances	1 (4.3)
II: impaired walking but can walk without stick/crutch	9 (39.1)
IIIA: walk with 1 stick/crutch	7 (30.4)
IIIB: walk with 2 sticks/crutches	6 (26.1)
NYHA class, n (%)	
0: no heart failure	13 (56.5)
I	5 (21.7)
II	5 (21.7)

Abbreviations: BMI = body mass index; hATTR = hereditary transthyretin amyloidosis; NIS = Neuropathy Impairment Score; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NYHA = New York Heart Association; OLT = orthotopic liver transplantation; PND = polyneuropathy disability; SD = standard deviation; TTR = transthyretin.

[a]Other genotypes include: S77Y (3), G47A (1), G47V (1), L12V (1), F64L (1), and Y116S (1).

[b]Tafamidis in 11 (47.8%) patients; diflunisal in 2 (8.7%) patients.

[c]Other immunosuppression regimens at baseline include: everolimus (1), ciclosporin (1), tacrolimus + everolimus (1), tacrolimus + azathioprine (1), ciclosporin + everolimus (1), ciclosporin + mycophenolate (1).

Prior to initiation of patisiran treatment, the majority of patients (56.5%) had a PND score of IIIA/B. The first documented PND score was either the most recent PND score prior to OLT, or the first post-OLT PND score if no PND score was recorded prior to the OLT. Sixteen patients (69.6%) had experienced a 1-unit increase from first documented PND score to study baseline, prior to patisiran treatment. Four patients (17.4%) experienced a 2-unit increase and three patients (13.0%) experienced a 3-unit increase in PND score (**Table 3**).[3]

Table 3. Increase from First Documented PND Score to PND Score at Baseline.[3]

First Documented PND Score[b]	Study Baseline PND Score, n (%)[a]						
	0[c]	I[c]	II[c]	IIIA[c]	IIIB[c]	IV[c]	Total
0	0	1 (4.3)	0	0	0	0	**1 (4.3)**
I	0	0	9 (39.1)	2 (8.7)	3 (13.0)	0	**14 (60.9)**
II	0	0	0	5 (21.7)	2 (8.7)	0	**7 (30.4)**
IIIA	0	0	0	0	1 (4.3)	0	**1 (4.3)**
IIIB	0	0	0	0	0	0	**0**
IV	0	0	0	0	0	0	**0**
Total	**0**	**1 (4.3)**	**9 (39.1)**	**7 (30.4)**	**6 (26.1)**	**0**	**23 (100.0)**

Abbreviations: OLT = orthotopic liver transplantation; PND = polyneuropathy disability.

[a]Percentages are based on total number of patients in the safety analysis set

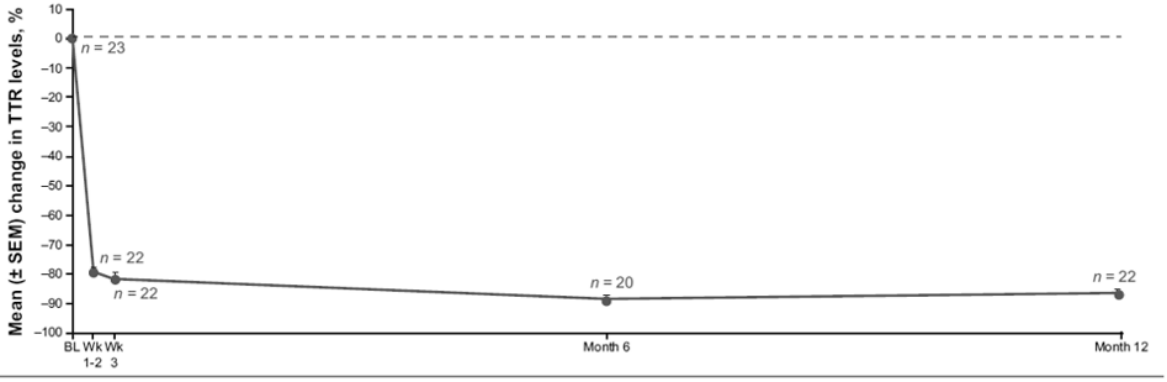
[b]First documented PND score was either the most recent PND score prior to OLT, or the first post-OLT PND score if no PND score prior to the OLT

[c]PND is scored from 0 to IV; 0: No symptoms; I: Sensory disturbances but preserved walking capability; II: Impaired walking capacity but ability to walk without a stick or crutch; IIIA: Walking with the help of one stick or crutch; IIIB: Walking with the help of two sticks or crutches; IV: Confined to a wheelchair or bedridden.

Efficacy Results: Primary Endpoint

After 12 months of patisiran treatment, the median serum TTR percent reduction from baseline (average of Month 6 and Month 12) was 91.0% (95% CI: 86.1, 92.3; p<0.001) (**Figure 1**).[3]

Figure 1. Percentage Change in Serum TTR Through Month 12.[3,a]



Mean (SEM) TTR level, mg/l	202.1 (11.3)	41.1 (4.1)	35.5 (4.5)	21.2 (3.7)	24.9 (2.7)
Mean (SEM) percent reduction from baseline, %	—	79.6 (1.7)	81.9 (2.4)	89.2 (2.0)	87.1 (1.7)

Abbreviations: BL = baseline; CI = confidence interval; SEM = standard error of the mean; TTR = transthyretin; Wk = week.
[a]Data for safety analysis set shown.
From Schmidt et al.[3]

Efficacy Results: Secondary Endpoints

For the secondary endpoint measures, data from the per protocol analysis set was analyzed (N=21), which included patients who met the criteria of ≤2 missing doses of patisiran due to COVID-19. At 12 months, there was a decrease in observed mean total NIS score from baseline, indicating an improvement in neuropathy (mean [± SEM] from baseline -3.7 ± 2.7). Improvements were also seen at 12 months in quality of life and autonomic symptoms as indicated by a decrease in observed mean total Norfolk QOL-DN score (-6.5 ± 4.9) and LS mean total COMPASS-31 score (-5.0 ± 2.6), respectively, from baseline.[3]

Through 12 months, the measures of disability (total R-ODS) and nutritional status (mBMI) were stable relative to baseline. Mean change [SEM] from baseline was -0.1 [1.1] for R-ODS and +4.4 [21.8] for mBMI.[3]

PK Endpoints

The PK profile of patisiran, including siRNA (ALN-18328) and lipid excipients DLin-MC3-DMA and PEG_{2000}-C-DMG, was assessed. PK samples were collected pre-dose, at end of infusion, at 4-hours, 24-hours, and 72-hours post-end of infusion on day 1 and week 54. Following the first dose administration of patisiran, the median t_{max} of ALN-18328, DLin-MC3-DMA, and PEG_{2000}-C-DMG were about 1.4 hours. At week 54 following q3w dosing, the PK of ALN-18328 and PEG_{2000}-C-DMG were similar to those observed after first dose. For DLin-MC3-DMA, a higher AUC but a lower C_{max} was observed at week 54 compared to day 1. **Table 4** presents a summary of select PK data obtained from the analysis.[4]

Table 4. Plasma PK Parameters of ALN-18328, DLin-MC3-DMA, and PEG_{2000}-C-DMG after Administration of Patisiran-LNP 0.3 mg/kg q3w on Day 1 and Week 54.[4]

PK Parameter, mean (%CV)	ALN-18328 (n = 22)		DLin-MC3-DMA (n = 22)		PEG2000-C-DMG (n = 22)	
	Day 1 (n = 22)	Week 54 (n = 21)	Day 1 (n = 22)	Week 54 (n = 21)	Day 1 (n = 22)	Week 54 (n = 21)
C_{max} (µg/mL)	6.42 (26.9)	6.11 (45.5)	62.9 (31.7)	33.9 (45.6)	3.69 (21.4)	4.34 (43.0)
t_{max} (h)[a]	1.43 (1.25, 2.00)	1.45 (1.33, 25.3)	1.43 (1.25, 2.00)	1.45 (1.33, 5.33)	1.43 (1.25, 2.0)	1.45 (1.33, 6.08)
AUC_{τ} (µg*h/mL)	117 (75.1)	140 (59.5)	901 (27.0)	1429 (34.3)	128 (31.1)	150 (27.8)
$t_{1/2}$ (h)	65.5 (33.5)[c]	66.2 (45.0)	135 (25.4)[b]	162 (24.3)[d]	103 (32.3)	97.9 (25.7)[e]
CL_{ss} (L/h)	n/a	0.211 (73.4)	n/a	0.016 (47.1)	n/a	0.145 (35.0)
Vd_{ss} (L)	n/a	19.1 (70.7)	n/a	3.77 (32.1)[d]	n/a	13.6 (28.6)[e]

Abbreviations: %CV = coefficient of variation; AUC_{τ} = area under the concentration-time curve over a dosing interval; CL_{ss} = systemic clearance at steady state; C_{max} = maximum observed concentration; PK = pharmacokinetics; t_{max} = time to reach maximum concentration; $t_{½}$ = half life; Vd_{ss} = apparent volume of distribution at steady state.
[a]Median (minimum, maximum), [b]n = 21, [c]n = 20, [d]n =10, [e]n =19.

Safety Outcomes

At 12 months, 23 patients (100%) experienced an AE, a majority of which were mild or moderate (**Table 5**). Common AEs were consistent with the Phase 3 APOLLO study. The most common AEs were diarrhea (34.8%) and IRRs (26.1%). Thirteen SAEs were reported in 5 patients (21.7%), 1 of which, an IRR, was considered related to patisiran. All 23 patients completed the study (1 patient discontinued treatment but completed the study). There were no discontinuations due to AEs, or deaths during the study.[3]

Table 5. Summary of Safety Results.[3]

Patients with ≥ 1 Event, n (%)	Patients Receiving Patisiran (N=23)
Any AE	23 (100.0)
AEs reported in ≥10% of patients	
Diarrhea	8 (34.8)
IRR	6 (26.1)
Peripheral Edema	5 (21.7)
Back Pain	5 (21.7)
Cardiac Failure	3 (13.0)
Fall	3 (13.0)
Fatigue	3 (13.0)
Headache	3 (13.0)
Pyrexia	3 (13.0)
Urinary Tract Infection	3 (13.0)
AE related to study drug	8 (34.8)
Any SAE[a]	5 (21.7)
SAE related to study drug[b]	1 (4.3)
AE leading to study drug discontinuations	0
AE leading to study drug interruption	5 (21.7)
AE leading to death	0

Abbreviations: AE = adverse event; IRR = infusion-related reaction; SAE = serious adverse event.
[a]Only term reported in >1 patient was cardiac failure, occurring in 3 patients with history of cardiomyopathy.
[b]Occurred after patient's first infusion, with symptoms of dizziness associated with an IRR. The event resolved the following day without intervention and without a change in patisiran treatment

Liver transplant rejection occurred in 1 patient, which was deemed unrelated to patisiran by the investigator.[3] This patient had a medical history of liver re-transplantation, and a liver biopsy 15 years after liver re-transplantation was consistent with mild acute cellular rejection likely due to inadequate immunosuppression. During the study, the patient's immunosuppression regimen was modified, and LFTs remained stable, ranging from 1-2x the ULN. The patient remained on study drug and completed the study.[3,5]

LFTs were normal in the majority of patients. Transient ALT elevation of >3x ULN associated with cholangitis in 1 patient was observed and deemed unrelated to patisiran by the investigator. There were no cases of platelet count < 50,000/mm^3.[3]

CASE REPORTS

The following information provides an overview of published case reports regarding patients receiving patisiran after having a liver transplant. It is not intended to be an all-inclusive list or summary of relevant publications, abstracts, and manuscripts.

Orthotopic Liver Transplant Case Reports

Seibert K, et al. *J Clin Neuromusc Dis*. 2022;23:143–147. doi: 10.1097/CND.0000000000000368[6]

- A case report detailed a 61-year-old African American male, who presented with advanced biventricular heart failure and progressive numbness from the hands to the feet. After an evaluation including but not limited to nerve conduction studies, cardiac MRI, cardiac biopsy, and genetic testing, the patient was diagnosed with hATTR, homozygous for the V122I variant. The patient underwent heart and liver transplantation for the management of hATTR.
- Over the 5 years following transplantation, the patient developed progressive weakness of the upper limbs, with increasing muscle atrophy in the hands. The patient was started on patisiran about 5.5 years post transplantation and had maintained treatment for over 2 years, with reported stabilization of his neuropathy symptoms on serial clinical examination.

Bulinski C, et al. *J Neurol*. 2022;269(7):3912-3914. doi:10.1007/s00415-022-10978-3[7]

- A case report detailed a male patient diagnosed with hATTR with a Glu54Gly variant in 2012 at age 36. Tafamidis was initiated in 2013. The patient underwent living split-liver transplantation in 2013, at which time tafamidis was discontinued.
- Following transplant, the patient experienced polyneuropathy progression and in 2018, tafamidis was re-started. In 2019, the patient required permanent assistance while walking and was unable to walk stairs. Treatment with patisiran was started in 2019.
- After 18 months of patisiran treatment, the patient could walk independently with two dynamic peroneal splints and could climb 7-8 stairs with assistance.

Domino Liver Transplant Case Reports

Ball HA, et al. Peripheral neuropathy secondary to a 'domino' liver transplant: a case report. *J Med Case Rep*. 2023;17(1):291. doi:10.1186/s13256-023-04001-0[8]

- A case report detailed a 74-year-old male patient with acquired ATTR after DLT for non-alcoholic steatohepatitis. The patient underwent a liver transplant in 2009 from a compatible donor, who underwent a transplant due to hATTR, with a V30M variant.

- About 8 years after transplant, the patient began to develop neuropathic symptoms, with some weight loss, which began with numbness and paraesthesia in his feet. His symptoms progressed over 2 years to include sensory involvement of his knees then hands, and motor involvement in his ankles. His mobility was significantly impaired, requiring a wheelchair at some times. The patient's clinical course was complicated by chronic infection of the right knee and calf, and development of a Charcot knee joint. In addition, the patient reported some dizziness on standing without loss of consciousness.
- On examination, he had moderate to severe peripheral neuropathy, including bilateral reduced ankle dorsiflexion and plantar flexion (power MRC grade 1/5), as well as reduced inversion and eversion. The power was intact in the upper limbs, aside from the first dorsal interosseous and adductor digiti mimini bilaterally with an MRC grade 4/5. Pinprick and light touch were impaired in a length-dependent manner as far as his knees and over his fingers. Vibration was impaired as far as the anterior superior iliac spines.
- In consideration of the presence of ATTR amyloid deposits and clinical symptoms, the patient began patisiran treatment at the standard dose of 0.3 mg/kg every 3 weeks. However, he then experienced a stroke resulting in impaired mobility and patisiran treatment was discontinued. The peripheral neuropathy remained stable on examination for the duration of patisiran treatment, and the authors concluded that the treatment period was too short to expect any clinical improvement. Four years after the onset of neuropathic symptoms, the patient passed away due to complications of his comorbidities, including the stroke.

Tsamis KI, et al. *Clin Transplant*. 2022; e14822. doi:10.1111/ctr.14822[9]

- A case report detailed an 80-year-old male patient with acquired ATTR after DLT for hepatocellular carcinoma. The patient underwent a liver transplant in 2007 from a compatible donor, who, in turn, underwent a transplant due to hATTR, with a V30M variant.
- About ten years after transplant, the patient began to develop symptoms from the peripheral nervous system, including distal limb paresthesia, tingling, and mild weakness. A nerve biopsy was conducted and confirmed the diagnosis of amyloid polyneuropathy. In addition, the patient's course was also impacted by the comorbidities of coronary heart disease, an abdominal aortic aneurysm, and chronic lymphocytic leukemia.
- At the time of diagnosis in 2018, the patient was classified as FAP stage 1 and PND score 2, and was started on tafamidis. In 2020, the patient was classified as FAP stage 2 and PND score 3B. In 2020, patisiran treatment was started. Over the following months, the patient experienced a slow improvement of symptoms and was then classified as FAP stage 1 and PND score 2. The patient's neurologic status was considered stable at 2 years after initiating patisiran.

ABBREVIATIONS

%CV = coefficient of variation; AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; ATTR = transthyretin amyloidosis; AUC_{τ} = area under the concentration-time curve over a dosing interval; BL = baseline; BMI = body mass index; CI = confidence interval; CL_{ss} = systemic clearance at steady state; C_{max} = maximum observed concentration; COMPASS-31 = Composite Autonomic System Score-31; COVID-19 = coronavirus disease 2019; DLT = domino liver transplantation; eGFR = estimated glomerular filtration rate; FAP = Familial Amyloid Polyneuropathy; hATTR = hereditary transthyretin amyloidosis; IRR = infusion-related reaction; IV = intravenous; KPS = Karnofsky Performance Status; LFT = liver function test; LS = least squares; mBMI = modified body mass index; MRC = Medical Research Council; MRI = magnetic

resonance imaging; NIS = Neuropathy Impairment Score; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NYHA = New York Heart Association; OLT = orthotopic liver transplantation; PK = pharmacokinetic; PND = polyneuropathy disability; R-ODS = Rasch-built Overall Disability Scale; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; siRNA = small interfering ribonucleic acid; $t_{½}$ = half life; t_{max} = time to reach maximum concentration; TTR = transthyretin; ULN = upper limit of normal; Vd_{ss} = apparent volume of distribution at steady state; Wk = week.

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