

## 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 trial period were excluded.<sup>1,2</sup>
- An open-label study in patients with hATTR post-OLT was conducted to evaluate the safety, efficacy, and pharmacokinetics of patisiran in this patient population.<sup>3</sup>
  - 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).<sup>3</sup>
  - At Week 54 following repeat q3w dosing, the PK values were similar to those observed after first dose.<sup>4</sup>
  - 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.<sup>3</sup>

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### 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 pharmacokinetics 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 below in **Table 1**.<sup>3</sup>

**Table 1. Key Inclusion and Exclusion Criteria.<sup>3</sup>**

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> <li>• Age <math>\geq</math>18 years</li> <li>• Received OLT for hATTR <math>\geq</math>12 months prior to study entry</li> <li>• Worsening PND score after OLT (either compared with pre-OLT assessment or between 2 assessments post-OLT)</li> <li>• KPS <math>\geq</math>70%</li> </ul>	<ul style="list-style-type: none"> <li>• NYHA class <math>&gt;</math>II</li> <li>• PND score IV</li> <li>• Serum levels of AST, ALT, or total bilirubin greater than the ULN</li> <li>• Previous liver allograft rejection episodes or abnormal LFTs suggestive of possible allograft rejection <math>\leq</math>6 months prior to the study</li> <li>• eGFR <math>\leq</math>30 ml/min/1.73 m<sup>2</sup> at screening</li> <li>• Any other organ transplant</li> <li>• Unable to comply with required premedications</li> <li>• Previous use of patisiran and current or past use of inotersen</li> <li>• Use of TTR stabilizers, tauroursodeoxycholic acid, doxycycline, or other investigational agents during study</li> </ul>

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.<sup>3</sup>

#### Patient Demographics and Baseline Characteristics

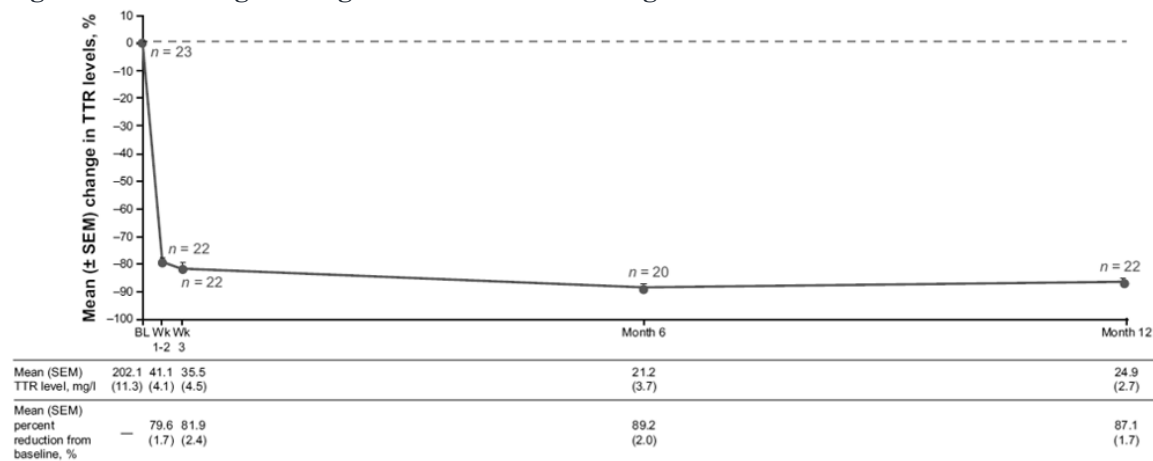
A total of 23 patients across 7 European countries were enrolled and received patisiran. Baseline demographics of the patients enrolled are summarized in **Table 2**.<sup>3</sup>

**Table 2. Baseline Demographics and Characteristics.<sup>3</sup>**

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 <sup>a</sup> , n (%)	15 (65.2)
Previous TTR stabilizer use <sup>b</sup> , 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 <sup>c</sup>	6 (26.1)
BMI, kg/m <sup>2</sup> , mean (SD)	23.5 (3.6)
Serum TTR level, mg/L, mean (range)	202.1 (123.7 – 315.1)
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)



**Figure 1. Percentage Change in Serum TTR Through Month 12.<sup>3,a</sup>**



Abbreviations: BL = baseline; CI = confidence interval; SEM = standard error of the mean; TTR = transthyretin; Wk = week.

<sup>a</sup>Data for safety analysis set shown.

### 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  $\leq 2$  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  $[\pm \text{SEM}]$  from baseline  $-3.7 \pm 2.7$ ). 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 ( $-6.5 \pm 4.9$ ) and LS mean total COMPASS-31 score ( $-5.0 \pm 2.6$ ), respectively, from baseline.<sup>3</sup>

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.<sup>3</sup>

### PK Endpoints

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



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.<sup>3,5</sup>

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<sup>3</sup>.<sup>3</sup>

## 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.000000000000368<sup>6</sup>*

- 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 has 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<sup>7</sup>*

- 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 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<sup>8</sup>*

- 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 minimi 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 suffered a stroke resulting in impaired mobility and patisiran treatment was discontinued. The peripheral neuropathy had 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<sup>9</sup>*

- 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 to be 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<sub>τ</sub> = area under the concentration-time curve over a dosing interval; BL = baseline; BMI = body mass index; CI = confidence interval; CL<sub>ss</sub> = systemic clearance at steady state; C<sub>max</sub> = maximum observed concentration; COMPASS-31 = Composite Autonomic System Score-31; DLT = domino liver transplantation; eGFR = estimated glomerular filtration rate; 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; t<sub>1/2</sub> = half life; t<sub>max</sub> = time to reach maximum concentration; TTR = transthyretin; ULN = upper limit of normal; Vd<sub>ss</sub> = apparent volume of distribution at steady state; Wk = week.

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