Open-Label Study of Patisiran in Patients with hATTR Amyloidosis Post-Orthotopic Liver Transplant

Teresa Coelho[1], Julian D Gillmore[2], David Adams[3], Francisco Muñoz Beamud[4], Anna Mazzeo[5], Jonas Wixner[6], Violaine Planté-Bordeneuve[7], Laura Llado[8], **Seth Arum[9]**, Jing Jing Wang[9], Xingyu Li[9], Hartmut H Schmidt[10]

[1]Hospital de Santo António, Porto, Portugal; [2]National Amyloidosis Centre, University College London, London, UK; [3]Neurology Department, APHP, CHU Bicêtre, Université Paris-Saclay, INSERM 1195, France; [4]Juan Ramón Jiménez Hospital, Huelva, Spain; [5]Unit of Neurology and Neuromuscular Diseases, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [6]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [7]University Hospital Henri Mondor, Créteil, France; [8]Hospital Universitari de Bellvitge, Barcelona, Spain; [9]Alnylam Pharmaceuticals, Cambridge, MA, USA; [10]University Hospital Münster, Münster, Germany

Conclusions

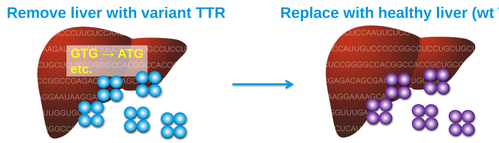
- **Patisiran reduced serum transthyretin (TTR) levels by >85% through 6 months of treatment in patients with hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, with disease progression post-orthotopic liver transplantation (OLT), consistent with the results observed in the Phase 3 APOLLO study[1]**
- **To date, the safety profile remains consistent with the Phase 3 APOLLO study[1]**
- **The efficacy, safety, and pharmacokinetics of patisiran treatment in patients with disease progression post-OLT will be further investigated in this ongoing study**

Background

Rationale for Patisiran Use in Patients with hATTR Amyloidosis and Disease Progression Post-OLT

- hATTR amyloidosis, also known as ATTRv amyloidosis, is a rare, rapidly progressive, debilitating, and potentially fatal disease caused by a variant in the *TTR* gene[2–6]; the majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[1,7–9]
- OLT eliminates circulating variant TTR, and has therefore been a treatment option used to slow disease progression in early-stage hATTR amyloidosis[10,11]
- Disease progression (neurologic and cardiologic impairment) post-OLT has been reported[12–15] from continued deposition of amyloid fibrils containing wild-type (wt) TTR in the nerves and heart[6,10,13]
  - Treatment options are currently limited for patients with disease progression post-OLT

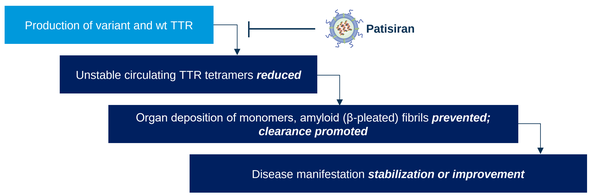
Figure 1. Orthotopic Liver Transplantation in hATTR Amyloidosis



Patisiran: An RNAi Therapeutic

- Patisiran is a lipid nanoparticle-delivered RNAi therapeutic that reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing variant and wt TTR[16,17]
- Patisiran is approved in >30 countries for the treatment of hATTR amyloidosis with polyneuropathy[a,18–23]
  - Approval is based on the Phase 3 APOLLO study (NCT01960348), which showed that patisiran was able to halt or reverse polyneuropathy and improve quality of life in the majority of patients[1]

Figure 2. Patisiran Therapeutic Hypothesis



Objective

- To describe the 6-month interim efficacy and safety results in enrolled patients with hATTR amyloidosis with polyneuropathy with disease progression post-OLT

Methods

Figure 3. Patisiran Post-OLT Study (NCT03862807)

Phase 3b, Open-Label Study Conducted across Several European Countries[a]

Patient population (n=23)
- Age ≥18 years
- Received OLT for hATTR amyloidosis ≥12 months before study start
- Worsening PND score after OLT[b]
- KPS ≥70%
- NYHA class ≤II
- No previous or current use of patisiran or inotersen, and will not be using a TTR stabilizer during the study
- No liver allograft rejection episodes[c] ≤6 months prior to study

Patisiran IV q3w, 0.3 mg/kg for 12 months

Primary endpoint:
- Average of Month 6 and Month 12 TTR percent reduction

Secondary endpoints:
- Change at Month 12 in:
  - NIS
  - Norfolk QOL-DN
  - R-ODS
  - COMPASS-31
  - mBMI

Safety (frequency of AEs)

[a]Countries: UK, Sweden, France, Germany, Italy, Portugal, Spain. [b]Either compared with pre-OLT assessment or between 2 assessments post-OLT. [c]Including abnormal LFTs suggestive of possible allograft rejection

Results

- Patients received an OLT an average of 3.8 years after diagnosis **(Table 1)**
- On average, patients received their first dose of patisiran >9 years after the OLT

Table 1. Baseline Demographics

Baseline Characteristics	Patients Receiving Patisiran (n=23)
Median age, years (range)	58.0 (43.0–76.0)
Male, n (%)	13.0 (56.5)
Country, n (%)	
Spain	7 (30.4)
France	5 (21.7)
Germany	3 (13.0)
Portugal	3 (13.0)
Italy	2 (8.7)
Sweden	2 (8.7)
UK	1 (4.3)
Mean age at hATTR amyloidosis diagnosis, years (SD)	46.7 (11.7)
V30M genotype[a], n (%)	15.0 (65.2)
Mean age at liver transplant[b], years (SD)	49.7 (10.9)
Mean time from hATTR amyloidosis diagnosis to OLT[b], years (SD)	3.8 (3.1)
Mean time from OLT to first patisiran dose[b], years (SD)	9.4 (5.2)
Mean BMI[c], kg/m^2 (SD)	23.5 (3.6)
Mean serum TTR level at baseline, mg/L (range)	202.1 (123.7–315.1)
Mean NIS (range)	60.2 (7.0–136.5)

[a]Other genotypes include: G47A, G47V, L12V, F64L, S77Y, and Y116S
[b]n=22. [c]n=21; data missing for 2 patients as height data missing at screening visit

Results continued

Table 2. Baseline Disease Characteristics

Baseline Disease Characteristics	Patients Receiving Patisiran (n=23)
KPS, n (%)	
70–80	17 (73.9)
90–100	6 (26.1)
NYHA class, n (%)	
No heart failure	13 (56.5)
I	5 (21.7)
II	5 (21.7)
PND score, n (%)	
0: no symptoms	0
I: preserved walking, sensory disturbances	1 (4.3)
II: impaired walking but can walk without stick/crutch	9 (39.1)
IIIA/B: walk with 1 or 2 sticks/crutches	13 (56.5)
FAP stage, n (%)	
0	0
1	10 (43.5)
2	13 (56.5)
3	0

- At the 6-month interim analysis (data as of March 10, 2020), patients had received patisiran for a mean (range) of 7.9 (0.7–10.5) months, with a total of 265 doses administered
- The majority of patients (n=16, 70%) experienced a 1-unit increase from the first documented polyneuropathy disability (PND) score to study baseline, prior to initiation of patisiran treatment **(Table 3)**
- Four (17%) patients experienced a 2-unit increase and 3 (13%) patients experienced a 3-unit increase

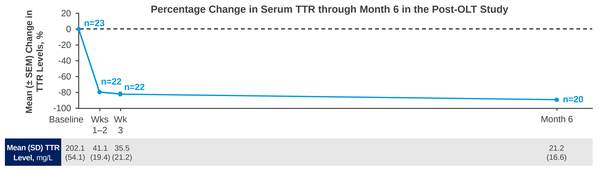
Table 3. Increase from First Documented PND Score to PND Score at Baseline

First Documented PND Score[a]	Study Baseline PND Score, n (%)[b]						
	0	I	II	IIIA	IIIB	IV	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)**

[a]First documented PND score was either the most recent PND score prior to OLT, or first post-OLT PND score if no PND score prior to OLT. [b]Percentages are based on total number of patients in the safety analysis set

- After 6 months of patisiran treatment, the mean reduction from baseline in serum TTR levels was 89.2% **(Figure 3)**

Figure 3. Rapid and Durable Reduction in Serum TTR Levels with Patisiran Treatment



Summary of Safety

- At the interim analysis, 23 patients (100%) had experienced an adverse event (AE) **(Table 4)**
  - The majority of AEs were mild or moderate
  - Common AEs were consistent with the Phase 3 APOLLO study[1]
- The most common treatment-related AE was infusion-related reaction (IRR), seen in 4 (17.4%) patients
- Liver function tests (LFTs) were stable in the majority of patients; mild and transient abnormal LFTs (<3× upper limit of normal) were observed in 7 (30.4%) patients
  - No AEs of liver disorder were related to study drug
- Five patients experienced a total of 6 serious AEs (SAEs) (hip break and heart failure, cholangitis, transplant rejection, heart failure, and IRR[b])
  - Transplant rejection in one patient was likely due to insufficient immunosuppression
    - Liver biopsy 15 years after liver re-transplantation: slight lesions of acute cellular rejection, likely showing slightly low immunosuppression; patient remains in the study and is continuing study drug treatment
  - Of the 6 SAEs, only one (the IRR) was considered related to study drug

Table 4. Interim Safety in the Post-OLT Study[a]

Patients with Event, n (%)	Patients Receiving Patisiran (n=23)
Any AE	23 (100.0)
AEs observed in ≥10% of patients	
Diarrhea	8 (34.8)
Peripheral edema	5 (21.7)
Back pain	5 (21.7)
IRR	4 (17.4)
Urinary tract infection	3 (13.0)
Fatigue	3 (13.0)
AE related to study drug	5 (21.7)
Any SAE	5 (21.7)
SAE related to study drug	1 (4.3)
AE leading to study drug interruption	8 (34.8)
AE leading to study withdrawal	0
Death	0

[a]Data cleaning impacted by COVID-19; future iterations of data may be slightly different once data cleaning complete

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[a]Specific indications vary by country/region; [b]Related to study drug. **Disclosures:** TC has nothing to disclose. JDG has received personal compensation for serving as a Consultant for Alnylam Pharmaceuticals. DA has received personal compensation for serving as a Consultant for Alnylam Pharmaceuticals and for serving on a Scientific Advisory or Data Safety Monitoring board for Pfizer. FMB has no disclosure on file. AM has nothing to disclose. JW has received personal compensation for serving as a Consultant for Alnylam Pharmaceuticals and Akcea Therapeutics. JW has also received personal compensation for serving on a Speakers Bureau for Alnylam Pharmaceuticals. VP-B has received personal compensation for serving as a Consultant for Alnylam Pharmaceuticals and Ionis/Akcea. LL has no disclosure on file. SA, JJW, and XL have received personal compensation for serving as an employee of Alnylam Pharmaceuticals. SA has also received personal compensation for serving as an Editor, Associate Editor, or Editorial Advisory Board Member for Wolters Kluwer. HHS has nothing to disclose. **Abbreviations:** AE, adverse event; ATTRv, hereditary transthyretin (v for variant); BMI, body mass index; COMPASS-31, Composite Autonomic Symptom Score 31-item questionnaire; hATTR, hereditary transthyretin-mediated; IRR, infusion-related reaction; IV, intravenous; KPS, Karnofsky Performance Status; LFT, liver function test; mBMI, modified body mass index; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; NYHA, New York Heart Association; OLT, orthotopic liver transplantation; PND, polyneuropathy disability; q3w, every 3 weeks; RNAi, ribonucleic acid interference; R-ODS, Rasch-Built Overall Disability Scale; SAE, serious adverse event; SD, standard deviation; SEM, standard error of the mean; TTR, transthyretin; ULN, upper limit of normal; Wk, week; wt, wild-type. **References:** 1. Adams et al. *N Engl J Med* 2018;379:11–21; 2. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 3. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 4. Adams et al. *Neurology* 2015;85:675–82; 5. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 6. Hawkins et al. *Ann Med* 2015;47:625–38; 7. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 8. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 9. Benson et al. *N Engl J Med* 2018;379:22–31; 10. Ando et al. *Orphanet J Rare Dis* 2013;8:31; 11. Ericzon et al. *Transplantation* 2015;99:1847–54; 12. Adams et al. 1st *European Congress on Hereditary ATTR Amyloidosis* 2015. Poster P19; 13. Liepnieks et al. *Neurology* 2010;75:324–7; 14. Liepnieks et al. *Amyloid* 2007;14:277–82; 15. Olofsson et al. *Transplantation* 2002;73:745–51; 16. Coelho et al. *N Engl J Med* 2013;369:819–29, 17. Suhr et al. *Orphanet J Rare Dis* 2015;10:109; 18. Alnylam Pharmaceuticals Inc. US prescribing information: ONPATTRO (patisiran) lipid complex injection, for intravenous use. 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf (accessed March 9, 2021); 19. European Medicines Agency. Summary of product characteristics: Onpattro 2 mg/mL concentrate for solution for infusion. 2018; 20. Alnylam Pharmaceuticals Inc. Alnylam announces approval in Japan of ONPATTRO® for the treatment of hereditary ATTR amyloidosis with polyneuropathy. Alnylam 2019. Available from: https://investors.alnylam.com/press-release?id=23886 (accessed March 9, 2021); 21. Canadian Agency for Drugs and Technologies in Health. Available from: https://www.cadth.ca/patisiran (accessed March 9, 2021); 22. Swiss prescribing information. Abbreviated information for health care professionals for ONPATTRO 10mg/5ml, concentrate for solution for infusion (Version September 2019). Available from: https://www.swissmedic.ch/dam/swissmedic/de/dokumente/zulassung/swisspar/67304-Onpattro-01-SwissPAR-20191113.pdf (accessed March 9, 2021); 23. Alnylam announces approval in Brazil of ONPATTRO® for the treatment of hereditary ATTR amyloidosis with polyneuropathy. Available from: https://investors.alnylam.com/press-release?id=24606 (accessed March 9, 2021).

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