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

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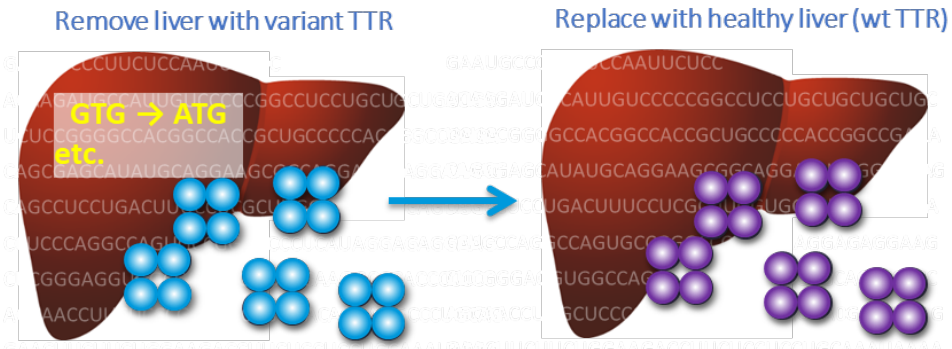
Rationale for Patisiran Use in Patients with hATTR Amyloidosis and Disease Progression Post-OLT

- Hereditary transthyretin-mediated (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**[1–5]; the majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[6–9]
- 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 **wt TTR** in the nerves and heart[5,10,13]
  - Treatment options are currently limited for patients with disease progression post-OLT



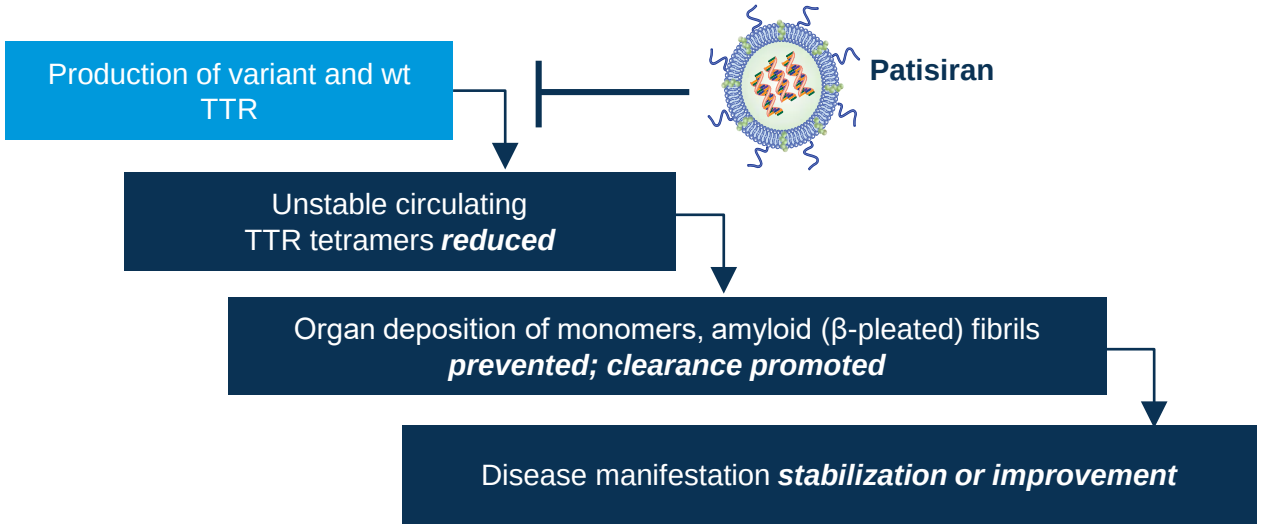
ATTRv, hereditary transthyretin (v for variant); hATTR, hereditary transthyretin-mediated; OLT, orthotopic liver transplantation; TTR, transthyretin; wt, wild-type

1. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 2. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 3. Adams et al. *Neurology* 2015;85:675–82; 4. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 5. Hawkins et al. *Ann Med* 2015;47:625–38; 6. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 7. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 8. Adams et al. *N Engl J Med* 2018;379:11–21; 9. Benson et al. *N Engl J Med* 2018;379:22–3; 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

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**[1,2]
- Patisiran is approved in >30 countries for the treatment of hATTR amyloidosis with polyneuropathy[a,3-8]
  - Approval is based on Phase 3 APOLLO study (NCT01960348), which showed that patisiran was able to **halt or reverse polyneuropathy** and **improve QOL** in the majority of patients[9]

Patisiran Therapeutic Hypothesis



[a]Specific indications vary by country/region

hATTR, hereditary transthyretin-mediated; QOL, quality of life; RNAi, ribonucleic acid interference; TTR, transthyretin; wt, wild-type

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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)

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

[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
AE, adverse event; COMPASS-31, Composite Autonomic Symptom Score 31-item questionnaire; hATTR, hereditarty transthyretin-mediated; IV, intravenous; KPS, Karnofsky Performance Status; LFT, liver function tests; 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; R-ODS, Rasch-Built Overall Disability Scale; TTR, transthyretin

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

Patients received an OLT an average of
3.8 years after diagnosis

On average, patients received their **first dose of patisiran >9 years after the OLT**

BMI, body mass index; hATTR, hereditary transthyretin-mediated; NIS, Neuropathy Impairment Score; OLT, orthotopic liver transplantation; SD, standard deviation; TTR, transthyretin

Baseline Disease Characteristics

Baseline Disease Characteristic	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 **6 months 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

FAP, familial amyloid polyneuropathy; KPS, Karnofsky Performance Status; NYHA, New York Heart Association; PND, polyneuropathy disability

Increase from First Documented PND Score to PND Score at Baseline

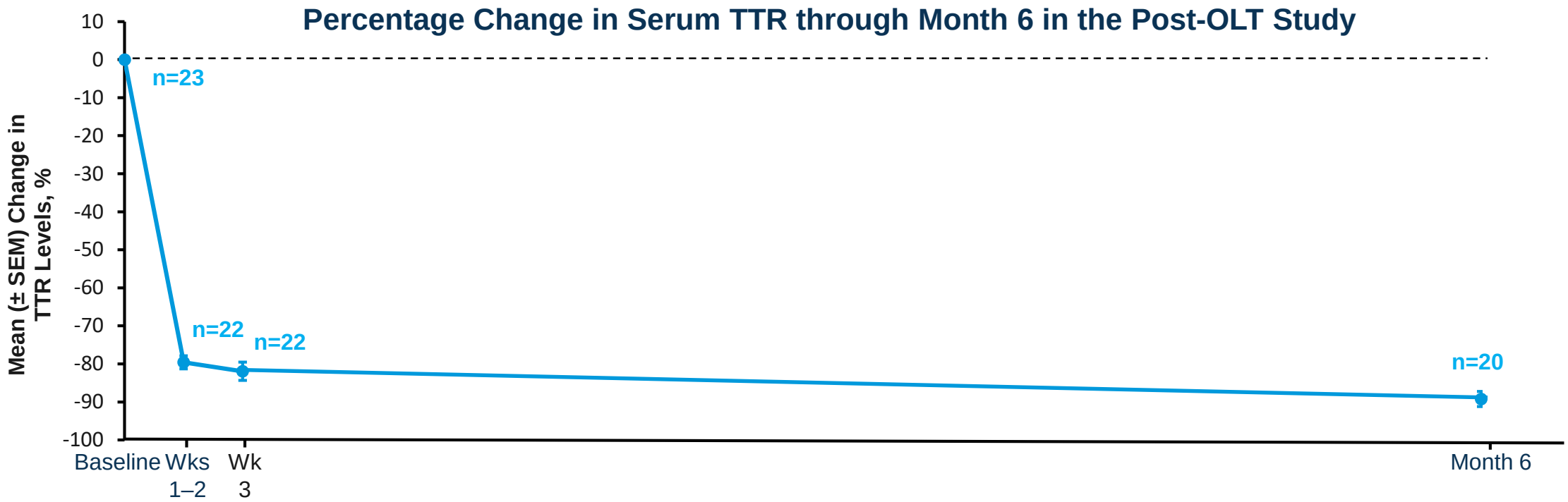
First Documented PND Score[b]	Study Baseline PND Score, n (%)[a]						
	0	I	II	IIIA	IIIB	IV	Total
0	0	1 (4.3)	0	0	0	0	**1 (4.3)**
I	0	0	9 (39.1)	2 (8.7)	3 (13.0)	0	**14 (60.9)**
II	0	0	0	5 (21.7)	2 (8.7)	0	**7 (30.4)**
IIIA	0	0	0	0	1 (4.3)	0	**1 (4.3)**
IIIB	0	0	0	0	0	0	**0**
IV	0	0	0	0	0	0	**0**
Total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

[a]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 first post-OLT PND score if no PND score prior to OLT. OLT, orthotopic liver transplantation; PND, polyneuropathy disability

The majority of patients (n=16, 70%) experienced a 1-unit increase
from the first documented PND score to study baseline, **prior to initiation of patisiran treatment.**
Four (17%) patients experienced a 2-unit increase and 3 (13%) patients experienced a 3-unit increase

Rapid and Durable Reduction in Serum TTR Levels with Patisiran Treatment

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



	Baseline	Wks 1–2	Wk 3	Month 6
Mean (SD) TTR Level, mg/L	202.1 (54.1)	41.1 (19.4)	35.5 (21.2)	21.2 (16.6)

OLT, orthotopic liver transplantation; SD, standard deviation; SEM, standard error of the mean; TTR, transthyretin; Wk, week

Summary of Safety

- At the interim analysis, 23 patients (100%) had experienced an AE
  - **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 IRR**, seen in 4 (17.4%) patients
- **LFTs were stable in the majority of patients**; mild and transient abnormal LFTs (<3× ULN) were observed in 7 (30.4%) patients
  - No AEs of liver disorder were related to study drug
- **Five patients experienced a total of 6 SAEs** (hip break and heart failure, cholangitis, transplant rejection, heart failure, and IRR[a])
  - 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**

Interim Safety in the Post-OLT Study[b]

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)
UTI	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

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

[a]Related to study drug.

AE, adverse event; IRR, infusion-related reaction; LFT, liver function test; OLT, orthotopic liver transplantation; SAE, serious adverse event; ULN, upper limit of normal; UTI, urinary tract infection. 1. Adams et al. *N Engl J Med* 2018;379:11–21; Data as of March 10, 2020

Conclusions

- Patisiran **reduced serum TTR levels by >85%** through 6 months of treatment in patients with hATTR amyloidosis with disease progression post-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 PK of patisiran treatment in patients with disease progression post-OLT will be further investigated in this ongoing study

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the patisiran post-OLT study

hATTR, hereditary transthyretin-mediated; OLT, orthotopic liver transplantation; PK, pharmacokinetics; TTR, transthyretin

1. Adams et al. *N Engl J Med* 2018;379:11–21