Open-Label Study of Patisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy Post-Orthotopic Liver Transplant

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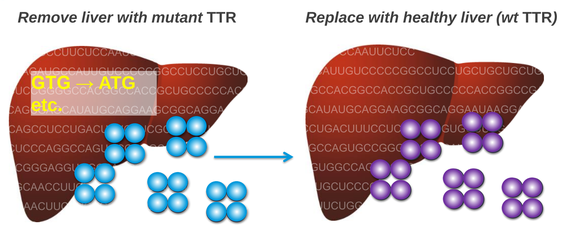
Introduction

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

- Hereditary ATTR amyloidosis is a progressive, life-threatening disease caused by a mutation in the *TTR* gene[1–5]; majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[6–9]
- OLT eliminates circulating mutant TTR, and has therefore been a treatment option used to slow disease progression in early-stage hereditary ATTR amyloidosis (**Figure 1**)[10,11]
- In selected patients, OLT can improve survival[10–13] but it is much less utilized with the introduction of other therapeutic options[11]
- Disease progression (neurologic and cardiologic impairment) post-OLT has been reported[14–17] from continued deposition of amyloid fibrils containing wt TTR in the nerves and heart[5,10,15]
  - Treatment options are currently limited for patients with disease progression post-OLT

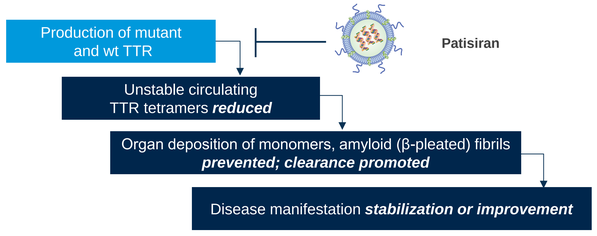
Figure 1. Rationale for OLT



Patisiran: An RNAi Therapeutic

- Patisiran is approved in certain countries globally for the treatment of hereditary ATTR amyloidosis with polyneuropathy[18–23]
  - 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[8]
- Patisiran is a lipid nanoparticle-delivered RNAi therapeutic that reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing mutant and wt TTR (**Figure 2**)[24,25]

Figure 2. Patisiran Therapeutic Hypothesis



Objectives

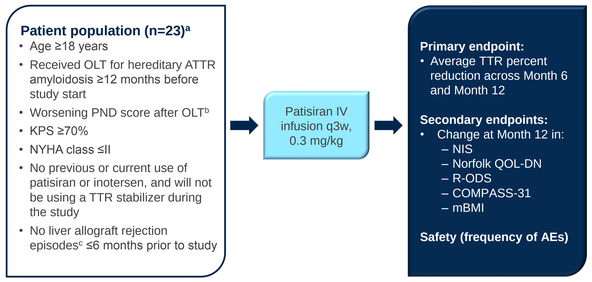
- To describe the baseline demographics, 3-week reduction in serum TTR levels, and the interim safety results in enrolled patients with hereditary ATTR amyloidosis with polyneuropathy with disease progression post-OLT

Methods

Patisiran Post-OLT Study (NCT03862807) Design

- Phase 3b, open-label study conducted across several European countries (**Figure 3**)

Figure 3. Patisiran Post-OLT Study Design



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

Results

Patisiran Post-OLT Baseline: Patient Baseline Demographics and Disease Characteristics (Tables 1 and 2)

- 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

Table 1. Baseline Demographics at Post-OLT Baseline

Baseline characteristics	Patients receiving patisiran (n=23)
Median age, years (range)	58.0 (43.0–76.0)
Male, n (%)	13 (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 hereditary ATTR amyloidosis diagnosis, years (SD)	46.7 (11.7)
V30M genotype[a], n (%)	15 (65.2)
Mean age at liver transplant[b], years (SD)	49.7 (10.9)
Mean time from hereditary ATTR 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)	23.4 (3.7)
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

Table 2. Disease Characteristics at Post-OLT 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 3 months interim analysis (data as of December 5, 2019), patients had received patisiran for a mean (range) of 23.1 (3–32.7) weeks, with a total of 174 doses given

Patisiran Post-OLT Baseline: Shift from First Documented PND Score to Baseline PND Score (Table 3)

- The majority of patients (n=16, 70%) experienced a 1-unit increase in PND score (**Table 3**)
- Four (17%) patients experienced a 2-unit increase and 3 (13%) patients experienced a 3-unit increase from earliest historic PND score to study baseline

Table 3. Patisiran Post-OLT Baseline: Shift from First Documented PND Score to Baseline PND Score

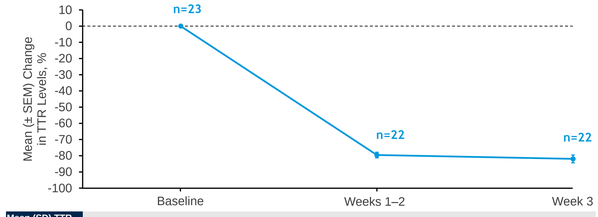
First documented PND score[b]	Study baseline PND score, n (%)[a]						
	0	I	II	IIIA	IIIB	IV	Total
0	0	1 (4.3)	0	0	0	0	**1 (4.3)**
I	0	0	9 (39.1)	2 (8.7)	3 (13.0)	0	**14 (60.9)**
II	0	0	0	5 (21.7)	2 (8.7)	0	**7 (30.4)**
IIIA	0	0	0	0	1 (4.3)	0	**1 (4.3)**
IIIB	0	0	0	0	0	0	**0**
IV	0	0	0	0	0	0	**0**
Total	**0**	**1 (4.3)**	**9 (39.1)**	**7 (30.4)**	**6 (26.1)**	**0**	**23 (100)**

[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

Patisiran Post-OLT: Serum TTR Levels

- After 3 weeks of patisiran treatment, there was a rapid reduction in serum TTR levels (**Figure 4**); the mean reduction from baseline in serum TTR levels was 81.9%

Figure 4. Percentage Change in Serum TTR through Week 3 in the Post-OLT Study



Mean (SD) TTR Level, mg/L	Baseline	Weeks 1–2	Week 3
	202.1 (54.1)	41.1 (19.4)	35.5 (21.1)

Patisiran Post-OLT: Safety Summary (Table 4)

- At the interim analysis, 21 (91.3%) patients had experienced an AE
  - Majority of AEs were mild or moderate
  - The most common AEs were consistent with the Phase 3 APOLLO study[8]
- The most common treatment-related AE was IRR, seen in 4 (17.4%) patients
- LFTs were stable in majority of patients; mild abnormal LFTs (<2x ULN) observed in 5 (21.7%) patients and were likely due to normal fluctuation; no AEs of liver disorder were related to study drug
- Three patients experienced one SAE each (cholangitis, abnormal LFT, and IRR [IRR related to study drug])

Table 4. Interim Safety in the Post-OLT Study

Patients with event, n (%)	Patients receiving patisiran post-OLT (n=23)
Any AE	21 (91.3)
AEs observed in ≥5% of patients	
Diarrhea	8 (34.8)
IRR	4 (17.4)
Peripheral edema	4 (17.4)
Back pain	4 (17.4)
UTI	3 (13.0)
Fatigue	3 (13.0)
Headache	2 (8.7)
Nausea	2 (8.7)
Oliguria	2 (8.7)
Vomiting	2 (8.7)
AE related to study drug	5 (21.7)
Any SAE	3 (13.0)
SAE related to study drug	1 (4.3)
AE leading to study drug interruption	8 (34.8)

Conclusions

- Patisiran reduced serum TTR levels >80% at 3 weeks following the first dose of patisiran in patients with hereditary ATTR amyloidosis with disease progression post-OLT, indicating the potential benefit of patisiran treatment in this patient population
- To date, the safety profile remained consistent with the Phase 3 APOLLO study and patisiran continues to show a positive benefit:risk profile[8]
- The efficacy, safety, and PK of patisiran treatment in patients with disease progression post-OLT will be further investigated in this ongoing study

Disclosure: Professor Gillmore reports participating in expert advisory boards for Alnylam, Akcea and Eidos; and is Co-Chair of the Steering Committee for the ATTRibute-CM (Eidos) trial.

Abbreviations: AE, adverse event; ATTR, transthyretin-mediated; BMI, body mass index; COMPASS-31, Composite Autonomic Symptom Score 31-item questionnaire; FAP, familial amyloid polyneuropathy; 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; PK, pharmacokinetic; PND, polyneuropathy disability; q3w, every 3 weeks; QOL, quality of life; RNAi, RNA interference; R-ODS, Rasch-Built Overall Disability Scale; SAE, serious adverse event; SD, standard deviation; SEM, standard error of the mean; TTR, transthyretin; UTI, urinary tract infection; wt, wild-type.

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