Long-Term, Open-Label Clinical Experience with Patisiran, an Investigational RNAi Therapeutic for Patients with Hereditary Transthyretin-Mediated (hATTR) Amyloidosis with Polyneuropathy

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Background and Rationale

Hereditary ATTR (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, life-threatening disease caused by mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and GI tract[1-5]
  - Affecting approximately 50,000 people worldwide[5,6] with mortality within 2 to 15 years of clinical presentation[1-3]
- Multi-systemic disease with heterogeneous clinical presentation; includes sensory, motor, autonomic, cardiac symptoms[2,6,7]
  - Disease continuum includes patients who present with predominantly polyneuropathy symptoms (formerly FAP) or cardiomyopathy symptoms (formerly FAC), yet many experience a variety of symptoms
  - Disease penetrance and rate of progression may be influenced by TTR genotype which can vary by geographical region[8]
- Limited treatment options with continued high unmet medical need for novel therapeutic options
  - Liver transplant: high-risk option for a limited subset of patients
  - Tetramer stabilizers
    - Tafamidis approved in EU for Stage 1 hATTR amyloidosis[9] and certain other countries outside the United States
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study[10]

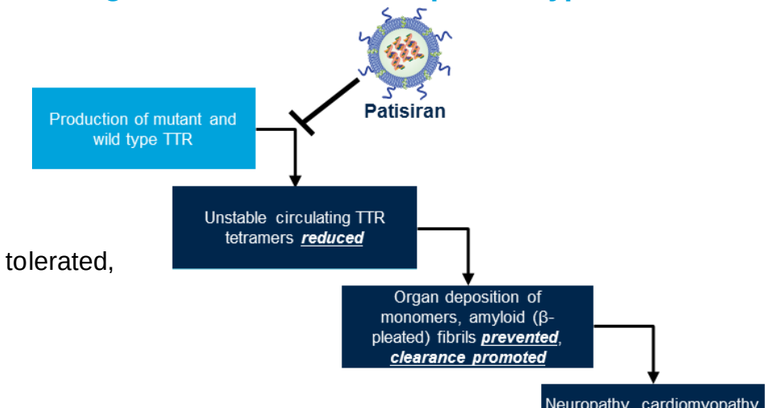
Patisiran

- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR, administered by IV infusion (Figure 1)
- Phase 2: positive multi-dose results in patients with hATTR amyloidosis[11]
- Phase 2 Open-Label Extension (OLE): positive results with sustained mean serum TTR knockdown of 80%, patisiran generally well tolerated, and mean 7.0-point decrease in mNIS+7 at 24 months[12]
- Phase 3, APOLLO: study met primary efficacy endpoint (mNIS+7) and all secondary endpoints with favorable safety profile[13,14]
- APOLLO-OLE: ongoing[15]
- Expanded Access Protocol (EAP) available in the US[16]

Objective

- This abstract describes the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis with polyneuropathy

Figure 1: Patisiran Therapeutic Hypothesis



Methods

Phase 2 OLE Study Design

- Patients with hATTR amyloidosis with polyneuropathy originally dosed on the Phase 2 patisiran study were eligible to roll over onto a Phase 2 OLE study and continue receiving patisiran 0.3mg/kg IV q3W for up to a total of 24 months (NCT01961921) (Figure 2)
- Primary endpoint was safety; secondary objectives included: effects on neurologic impairment (mNIS+7, NIS; Figure 3), QOL, mBMI, mobility, grip strength, autonomic symptoms, and serum TTR levels
- Following completion of the study, patients were eligible to continue treatment on a global OLE study (NCT02510261)

Figure 2: Patisiran Clinical Development Program

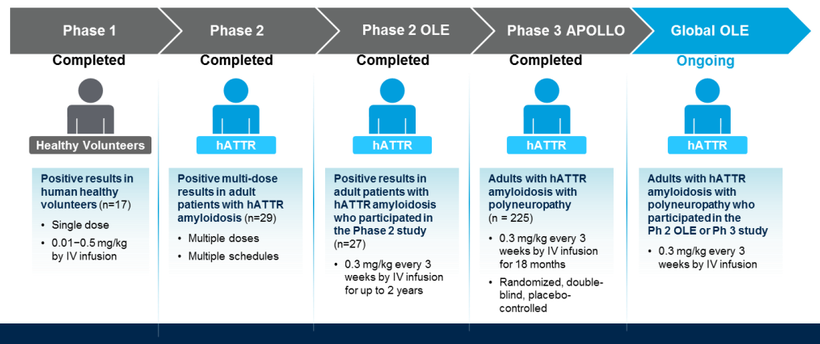
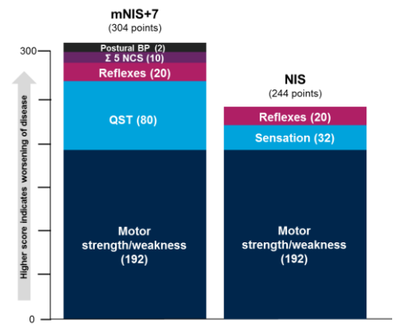


Figure 3: Neuropathy Impairment Scores



Results

Phase 2 OLE Baseline Demographics (Table 1)

Table 1: Phase 2 OLE Baseline Demographics and Characteristics

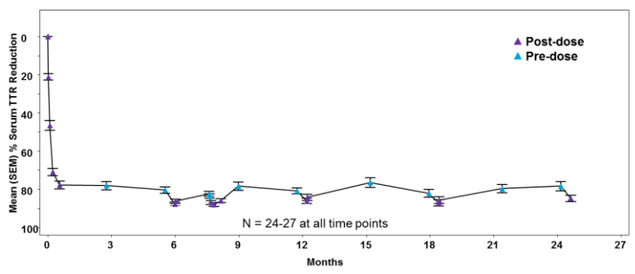
Characteristic	Result
Number of patients	N=27 (includes 11 patients in cardiac subgroup*)
Median age	64.0 years (range 29 - 77)
Gender	18 males, 9 females
TTR genotype	• Val30Met (V30M) = 20 • Ser77Tyr (S77Y) = 2 • Ser77Phe (S77F) = 2 • Tyr116Ser (Y116S) = 1 • Phe64Leu (F64L) = 1 • Arg54Thr (R54T) = 1
FAP stage/PND score	• Stage 1: 24 • Stage 2: 3 • I: 15 • II: 9 • IIIa: 2 • IIIb: 1
Concurrent tetramer stabilizer use at baseline	13 tafamidis, 7 diflunisal, 7 none
Mean mNIS+7[a] (range), max impairment: 304	53.0 (2.0– 122.5)
Mean NIS (range), max impairment: 244	34.8 (4.0– 93.4)
Mean serum TTR (μ g/mL) (range)	245.3 (155.0– 340.0)

*Patients with baseline left ventricular wall thickness of ≥13 mm and no history of uncontrolled hypertension or aortic valve disease
[a]Partial imputation was used to recover mNIS+7 score for one patient missing QST at Baseline

Serum TTR Knockdown (Figure 4)

- Mean serum TTR knockdown: 82%
- Mean maximal serum TTR knockdown: 93%
- Maximal individual patient post-dose knockdown: 97%
- Similar TTR knockdown in patients on patisiran alone or on patisiran + TTR tetramer stabilizers

Figure 4: Serum TTR Knockdown over 24 Months



Summary of Patisiran Safety and Tolerability out to 25 Months (Table 2)

- 7 patients (25.9%) with 10 reports of serious adverse events (SAE); not related to drug
  - One discontinuation for gastroesophageal cancer at ~20 months; patient subsequently died
  - One death due to myocardial infarction after patient completed 24 months of treatment
  - One patient with 3 reports (distal femur fracture/proximal tibia fracture/osteonecrosis/ligament rupture, dehydration/acute prerenal failure/urinary tract infection and thermal burn)
  - One patient with 2 reports (ankle fracture/foot fracture/osteonecrosis and ankle arthrodesis)
  - One patient with venous thrombosis of the lower limb
  - One patient with foot abscess and osteomyelitis
  - One patient with pacemaker implantation due to amyloid cardiomyopathy
- Majority of AEs were mild or moderate
  - 5 patients (18.5%) had severe AEs not related to study drug
  - Related AEs reported in ≥4 patients were infusion related reaction (22.2%) and flushing (22.2%), all of which were mild
- No clinically significant changes in liver function tests, renal function, or hematologic parameters, including platelets

Table 2: Summary of AEs Reported in ≥10% of Patients out to 25 Months

AE by Preferred Term, n (%)	Patisiran (N=27)
Flushing	7 (25.9)
Diarrhea	6 (22.2)
Infusion related reaction	6 (22.2)
Nasopharyngitis	6 (22.2)
Urinary tract infection	6 (22.2)
Vomiting	6 (22.2)
Wound	6 (22.2)
Nausea	5 (18.5)
Insomnia	4 (14.8)
Neuralgia	4 (14.8)
Pyrexia	4 (14.8)
Anemia	3 (11.1)
Bronchitis	3 (11.1)
Cataract	3 (11.1)
Infusion site extravasation	3 (11.1)
Edema peripheral	3 (11.1)
Macular degeneration	3 (11.1)
Musculoskeletal pain	3 (11.1)
Osteoporosis	3 (11.1)

Safety of Patisiran Over 36 Months for Phase 2 OLE Patients (Table 3)

- Following mean 39.6 months of treatment, patisiran remained generally well tolerated among patients from the Phase 2 OLE that continued treatment in the Global OLE Study
- Safety for Phase 2 OLE patients within the Global OLE:
  - 4 patients reported SAEs; all not related to study drug
  - Majority of AEs remained mild or moderate
  - 2 patients with severe AEs, not related
  - No deaths
  - 4 patients with related AEs, all mild
    - Related AEs in ≥2 patients were IRRs (2 patients, 8.0%)

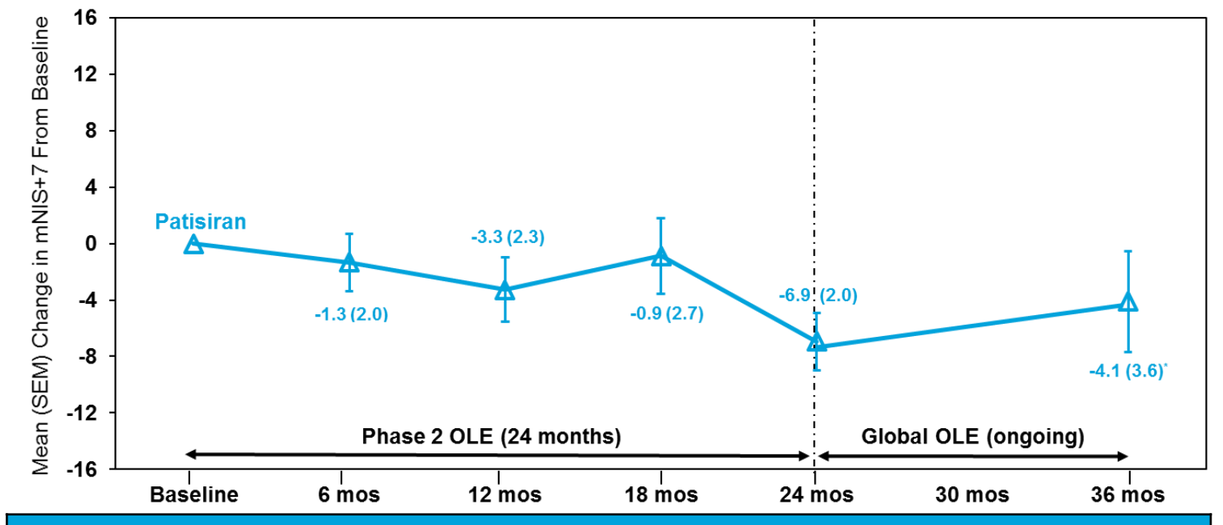
Table 3: Safety of Patisiran in Phase 2 OLE, Global OLE, and Total OLE Trials

Number of Patients with, n (%)	Patisiran		
	Ph 2 OLE (N=27)	Global OLE (N=25)	Total OLE (N=27)
Mean Duration of Exposure, months	24.7	16.2	39.6
Any Adverse Event (AE)	26 (96.3)	25 (100)	27 (100)
Any Severe AE	5 (18.5)	2 (8.0)	6 (22.2)
Any Serious Adverse Event (SAE)	7 (25.9)	4 (16.0)	9 (33.3)
Any AE leading to treatment discontinuation	0	0	0
Any AE leading to study withdrawal	2 (7.4)	0	2 (7.4)
Death	2 (7.4)	0	2 (7.4)

mNIS+7 over 36 Months in Phase 2 OLE Patients (Figure 5)

- Patisiran demonstrated maintenance of effect on mNIS+7 over 36 months in Phase 2 OLE patients

Figure 5: mNIS+7 over 36 Months in Phase 2 OLE Patients



mNIS+7												
	Baseline		6 months		12 months		18 months		24 months			36 months	
Ph 2 OLE/ Global OLE Patients	N	Mean (SEM)	N	Mean (SEM)	N	Mean (SEM)	N	Mean (SEM)	N	Mean (SEM)		N	Mean (SEM)
	27	53.02 (6.86)	27	51.69 (6.59)	27	49.76 (6.58)	27	52.15 (7.18)	26	48.05 (6.54)		24	48.49 (7.75)

*mNIS+7 component scores collected on Day 0 in Global OLE are incorporated into the 24 month mNIS+7 score; therefore, mean (SEM) estimates from the integrated analysis may differ from the parent study estimates

Summary

- Patients with hATTR amyloidosis treated with patisiran had an improvement in neuropathy impairment score at 24 months in the Phase 2 OLE study
- Improvement in mNIS+7 score was maintained with longer term (>36 months) dosing
- Patisiran Phase 3 APOLLO study met the primary and all secondary endpoints, with highly significant reduction in neuropathy progression and improvement in quality of life at 18 months relative to placebo
- Overall, the safety profile of patisiran was favorable

AE, adverse event; IRRs, infusion related reactions; mNIS+7, modified neuropathy impairment score + 7; mBMI, modified body mass index; NSAID, nonsteroidal anti-inflammtory drug; SAE, serious adverse events; RNAi, RNA interfernce; WT, wild type

References: 1. Hanna M. Curr Heart Fail Rep. 2014;11(1):50-57; 2. Mohty D et al. Arch Cardiovasc Dis. 2013;106(10):528-540; 3. Adams D et al. Neurology. 2015;85(8):675-682; 4. Damy T et al. J Cardiovasc Transl Res. 2015;8(2):117-127; 5. Hawkins PN et al. Ann Med. 2015;47(8):625-638; 6. Conceição I et al. J Peripher Nerv Syst. 2016;21(1):5-9; 7. Shin SC et al. Mt Sinai J Med. 2012;79(6):733-748; 8. Mariani LL et al. Ann Neurol. 2015;78(6):901-16; 9. Coelho T et al. Neurology. 2012;79:785-92; 10. Berk J et al. JAMA. 2013;310:2658-67; 11. Suhr OB et al. Orphanet J Rare Dis. 2015;10:109; 12. Adams et al. Neurology. 2017;88:16 Supplement S27.004 (NCT01961921); 13. Clinicaltrials.gov: NCT01960348; 14. Adams D et al. BMC Neurology. 2017;17:181; 15. Clinicaltrials.gov: NCT02510261; 16. Clinicaltrials.gov: NCT02939820; Disclosures: Angela M Partisano and Jared Gollob are employees of Alnylam Pharmaceuticals. Study sponsored by Alnylam.