Leo
Living with hATTR Amyloidosis

Phase 2 Open-Label Extension (OLE) Study of Patisiran, an Investigational RNAi Therapeutic for the Treatment of Polyneuropathy due to Hereditary ATTR (hATTR) Amyloidosis: 24-month safety and efficacy in subgroup of patients with cardiac involvement

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Patisiran

Investigational RNAi Therapeutic for hATTR Amyloidosis

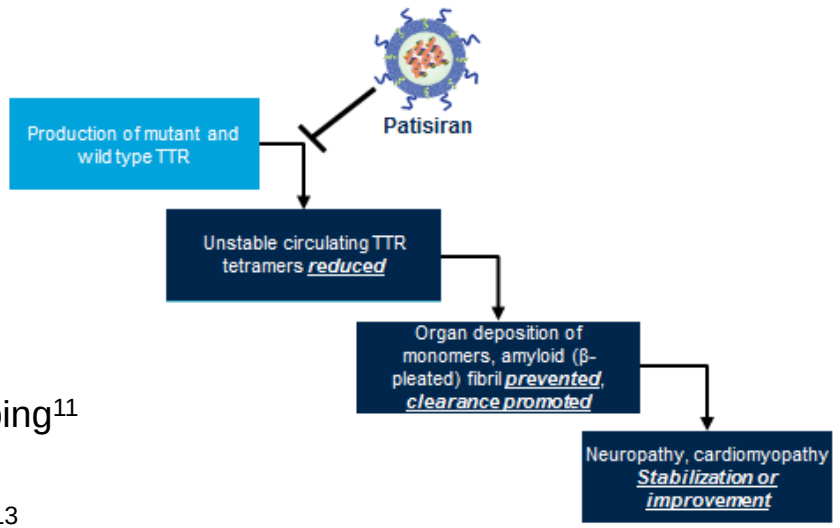
Hereditary ATTR (hATTR) Amyloidosis

- Autosomal dominant hereditary amyloidosis caused by deposition of mutant and wild-type transthyretin (TTR) in nerves, gastrointestinal tract, heart, and eyes[1]
  - Previously known as familial amyloidotic polyneuropathy (FAP) or familial amyloidotic cardiomyopathy (FAC)
  - Median survival 2-15 years[1-3]
- Multi-systemic disease with heterogeneous clinical presentation that includes sensory and motor, autonomic and cardiac symptoms[1,4,5]
- Limited treatment options[6,7]
- Continued high unmet medical need

Patisiran clinical development

- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR
- Administered by IV infusion
- Positive results in human volunteers[8] and in patients with hATTR amyloidosis[9,10]
- APOLLO Phase 3 trial: enrollment complete, trial ongoing[11]
- APOLLO open-label extension (OLE) study ongoing[12]
- Expanded Access Protocol (EAP): available in the US[13]

Patisiran Therapeutic Hypothesis



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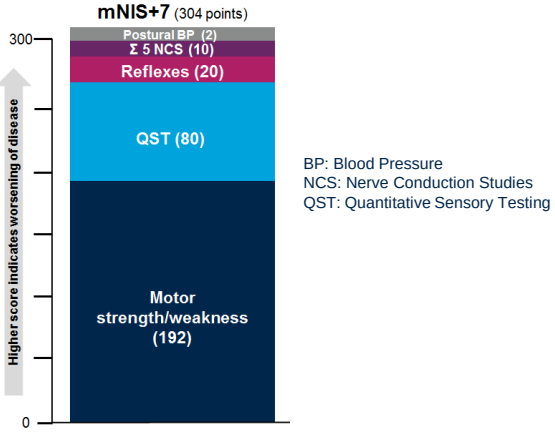
Patisiran Phase 2 OLE Study

Study Design, Baseline Demographics and Characteristics

Study Design and Endpoints

- Patients with hATTR amyloidosis previously dosed on Phase 2 trial eligible to roll over onto this OLE study
- 27 patients with up to 2 years of dosing, 0.30 mg/kg IV every 3 weeks; clinical endpoints evaluated every 6 months
  - Presentation highlights final 24 month data from patients with cardiac involvement (protocol-defined Cardiac Subgroup [N=11])
    - Cardiac Subgroup: patients with baseline left ventricular wall thickness of ≥13 mm and no history of uncontrolled hypertension or aortic valve disease
- Objectives
  - Primary: Safety/tolerability of long-term patisiran dosing
  - Secondary: Effects on neurologic impairment (mNIS+7), quality of life (EQ-5D), mBMI, disability (R-ODS), mobility (10-MWT), grip strength, autonomic symptoms (COMPASS 31), cardiac parameters (echo, biomarkers: Cardiac Subgroup only)



BP: Blood Pressure
NCS: Nerve Conduction Studies
QST: Quantitative Sensory Testing

Baseline Demographics and Characteristics

Demographics	Overall Study Population (N=27)	Cardiac Subgroup (n=11)
Median age (range)	64 years (29, 77)	69 years (58-75)
Gender	18 males, 9 females	8 males, 3 females
TTR genotype, n (%)	V30M: 20 (74) nonV30M: 7 (26)	V30M: 8 (73) nonV30M: 3 (27)
FAP stage, n (%)	Stage 1: 24 (89) Stage 2: 3 (11)	Stage 1: 9 (82) Stage 2: 2 (18)
PND score, n (%)	I: 15 (56) IIIa: 2 (7) II: 9 (33) IIIb: 1 (4)	I: 4 (36) IIIa: 2 (18) II: 5 (46)
NYHA Class, n (%)	Class I: 19 (70) Class II: 7 (26)	Class I: 5 (45) Class II: 6 (55)

Select Characteristics	Overall Study Population (N=27)		Cardiac Subgroup (N=11)	
	N	Mean (range)	N	Mean (range)
mNIS+7	27	53.0 (2.0, 122.5)	11	66.2 (30.0, 122.4)
EQ-5D QOL (max impairment: 0)	27	0.8 (0.3, 1.0)	11	0.8 (0.7,1.0)
mBMI, kg/m^2 × albumin [g/L]	27	1030 (729, 1380)	11	1034.8 (834, 1158)
R-ODS (no limitations: 48)	26*	38.1 (15, 48)	10*	36.8 (26, 48)
10-MWT gait speed, m/sec	22†	1.1 (0.4, 2.2)	7†	1.0 (0.4, 1.5)
Grip strength, kg	27	25.8 (3.2, 49.3)	11	24.5 (9.0, 35.5)
COMPASS 31 (max impairment: 100)	27	15.9 (0, 46.1)	11	12.3 (0, 40.9)

Clinicaltrial.gov Identifier NCT01961921; mNIS+7 = Modified Neuropathy Impairment Score + 7; EQ-5D, Euro Quality of Life-5-Dimension; mBMI, modified body mass index; R-ODS, Rasch-built Overall Disability Scale; 10-MWT, 10 meter walk test; COMPASS 31, composite autonomic symptom scale 31; *All patients had the baseline R-ODS administered, patients listed as missing in this table surpassed the threshold of number of missing individual responses within the questionnaire.; † Missing 10-MWT at Screening/Baseline were reported as minor protocol deviations; in all cases, the reason for the missing test was due to "non-functional stopwatch"

Patisiran Phase 2 OLE Final Study Results

Cardiac Subgroup: Safety and Clinical Activity

Safety and Tolerability

- Overall, 7 patients (26%) with 10 reports of SAEs; none related to study drug*
  - Including 3 patients (27%) in Cardiac Subgroup
    - Death due to MI after patient completed 24 mos treatment (n=1)
    - Venous thrombosis of the lower limb (n=1)
    - Pacemaker implantation due to amyloid cardiomyopathy (n=1)
- Majority of AEs were mild or moderate
- No clinically significant changes in LFTs, renal function, or hematologic parameters, including platelets
- Safety profile of patisiran in patients within the Cardiac Subgroup was comparable to that observed in the overall study population

Clinical Activity

- Patisiran had a similar effect on neuropathy progression, quality of life, nutritional status, functional status, and patient reported autonomic neuropathy symptoms in the Cardiac Subgroup compared to overall population

AEs reported in ≥20% of patients in either group, n (%)

Adverse Event (AE)	Overall Study Population (N=27)	Cardiac Subgroup (N=11)
Flushing	7 (25.9)	4 (36.4)
Diarrhea	6 (22.2)	2 (18.2)
Infusion related reaction	6 (22.2)	1 (9.1)
Nasopharyngitis	6 (22.2)	5 (45.5)
Urinary tract infection	6 (22.2)	3 (27.3)
Vomiting	6 (22.2)	0
Wound	6 (22.2)	3 (27.3)
Insomnia	4 (14.8)	3 (27.3)
Pyrexia	4 (14.8)	3 (27.3)
Cataract	3 (11.1)	3 (27.3)
Infusion site extravasation	3 (11.1)	3 (27.3)

Change in Clinical Assessments from Baseline to Month 24

	Overall Study Population (N=27)		Cardiac Subgroup (N=11)	
	N	Mean (SEM)	N	Mean (SEM)
mNIS+7^	**27**	**-7.0 (2.0)**	**11**	**-10.0 (3.3)**
EQ-5D QOL (max impairment: 0)	26	-0.01 (0.02)	11	-0.07 (0.03)
mBMI, kg/m^2×albumin [g/L]	22	-60.8 (34.9)	7	-57.0 (73.0)
R-ODS (no limitations: 48)	25‡	-1.8 (0.8)	10‡	-4.0 (1.5)
10-MWT gait speed, m/sec	21†	0.03 (0.04)	7†	0.03 (0.05)
Grip strength, kg	26	1.5 (1.2)	11	-1.2 (1.7)
COMPASS 31 (max impairment: 100)	26	1.3 (1.8)	11	0.4 (3.4)

*SAEs in patients without cardiac involvement: Fatal gastroesophageal cancer at ~20 months (n=1); distal femur fracture/proximal tibia fracture/osteonecrosis/ligament rupture, dehydration/ acute prerenal failure/UTI and thermal burn (n=1); ankle fracture/foot fracture/ osteonecrosis and ankle arthrodesis (n=1); foot abscess and osteomyelitis (n=1)
SEM, standard error of the mean; mNIS+7 = Modified Neuropathy Impairment Score + 7; EQ-5D, Euro Quality of Life-5-Dimension; mBMI, modified body mass index; R-ODS, Rasch-built Overall Disability Scale; 10-MWT, 10 meter walk test; COMPASS 31, composite autonomic symptom scale 31
^Partial imputation used to recover mNIS+7 data where components were missing at ≥ 1replicate measurements (per pt/visit)
‡All patients had the baseline R-ODS administered, patients listed as missing in this table surpassed the threshold of number of missing individual responses within the questionnaire;
†Missing 10-MWT at Screening/Baseline were reported as minor protocol deviations; in all cases, the reason for the missing test was due to "non-functional stopwatch"

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Patisiran Phase 2 OLE Final Study Results

Cardiac Subgroup: Cardiac Measures and Summary

Cardiac Measures

- Troponin I, NT-proBNP and echocardiogram results stable throughout the 2-year treatment period

Changes in Cardiac Measures from Baseline to Month 24 in Cardiac Subgroup (N=11)

	Baseline		Change from Baseline to Month 24	
	N	Mean (range)	N	Mean (SEM)
Cardiac Biomarkers				
NT-proBNP, ng/L	9	809.8 (105, 2070)	8	-49.6 (170.83)
Troponin I[d], ng/mL	8	0.14 (0.03, 0.69)	8	-0.09 (0.08)
Echocardiogram Results				
LV wall thickness, mm	11	1.6 (1.3, 1.9)	10	-0.08 (0.05)
Ejection Fraction	11	62.5 (40.7, 75.7)	10	0.63 (1.45)
Average Peak Longitudinal Strain	11	-16.6 (-23, -9.2)	10	0.85 (0.89)

SEM=standard error of the mean; LV=left ventricular

Summary

- Patisiran generally well tolerated in patients with hATTR amyloidosis; safety profile in patients with cardiac involvement comparable to that observed in the overall study population
- Among patients with evidence of cardiac involvement patisiran exhibited a mean 10.0-point decrease (improvement) in mNIS+7 at 24 months that was comparable to the overall study population
- Echocardiographic measures or cardiac biomarkers remained stable throughout the study in the Cardiac Subgroup
- All eligible patients from Cardiac Subgroup have rolled into APOLLO-OLE study; 8 of whom have received ≥ 36 months of patisiran dosing

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Thank you

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