Phase 2 Open-Label Extension Study of Patisiran, an RNAi Therapeutic for the Treatment of Familial Amyloidotic Polyneuropathy

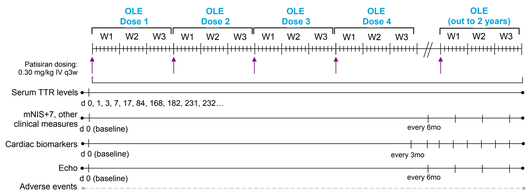
David Adams,[1] Ole Suhr,[2] Teresa Coelho,[3] Isabel Conceicao,[4] Marcia Waddington-Cruz,[5] Hartmut Schmidt,[6] Juan Buades,[7] Josep Campistol,[8] Jean Pouget,[9] John Berk,[10] Rick Falzone,[11] Jamie Harrop,[11] Ricardo De Frutos,[11] Brian Bettencourt,[11] Jeff Cehelsky,[11] Sara Nochur,[11] Akshay Vaishnaw,[11] Jared Gollob[11]

[1]Centre Paris-Sud, APHP, Hopital de Bicetre, INSERM U788, Service de Neurologie, and Centre de Reference des Neuropathies Amyloides Familiales, Le Kremlin-Bicetre, France; [2]Department of Public Health and Clinical Medicine, Umea University, Umea, Sweden; [3]Unidade Clinica de Paramiloidose, Hospital de Santo Antonio, Porto, Portugal; [4]Centro Hospitalar Lisboa Norte-Hospital de Santa Maria, Lisbon, Portugal; [5]Hospital Universitario Clementino Fraga Filho, Rio de Janeiro, Brazil; [6]The University Hospital of Muenster, Muenster, Germany; [7]Hospital Son Llatzer, Palma de Mallorca, Spain; [8]Hospital Clinic, Barcelona, Spain; [9]Centre de Reference des Maladies Naueromusculaires et de la SLA, Hopital de la Timone, Marseille, France; [10]Amyloid Treatment and Research Program, Boston University, Boston, MA, USA; [11]Alnylam Pharmaceuticals, Cambridge, MA, USA

Abstract

Familial amyloidotic polyneuropathy (FAP) is a fatal, autosomal dominant disease caused by deposition of mutant and wild-type transthyretin (TTR). Patisiran is a systemically administered lipid nanoparticle (LNP) formulation of a small interfering RNA (siRNA) targeting wild-type and mutant TTR. This formulation predominantly delivers the siRNA to the liver, thereby inhibiting synthesis of TTR at the primary site of production. A recently completed multi-center, multi-dose Phase 2 trial of patisiran in FAP patients (N=29) showed >80% sustained knockdown of serum TTR when administered at a dose of 0.3 mg/kg every 3 weeks with a favorable safety profile. A Phase 2 open-label extension (OLE) study of patisiran, open to FAP patients who participated in the Phase 2 trial, was initiated in October 2013. The primary objective of the study is to evaluate the safety and tolerability of patisiran 0.3 mg/kg administered intravenously q3 weeks for up to 2 years. Secondary objectives include assessment of patisiran's effect on serum TTR levels, as well as evaluation of its impact on clinical endpoints, including mNIS+7 composite neurologic impairment score and quality of life. Twenty-seven patients were enrolled onto the trial; as of September 8, 2014, the mean duration of treatment was 7 months (range 3-12), with 282 doses administered (median of 11 doses/patient). Chronic dosing with patisiran has been generally well tolerated in FAP patients, including those on concurrent TTR tetramer stabilizers. Sustained TTR lowering of at least 80% has been achieved based on serial TTR measurements for over 9 months, with further nadir of up to 89.6% between doses. Neurologic impairment scores were stable after 6 months of treatment with patisiran; similar results were seen for QOL and additional neurologic and cardiac measures. A mean decrease in mNIS+7 of 0.95 points compares favorably to the rapid increase in mNIS+7 estimated at 6 months from prior FAP studies in a patient population with similar baseline NIS.

Patisiran Phase 2 OLE study design



FAP patients previously dosed on Phase 2 trial eligible to roll over onto Phase 2 OLE study

- Up to 2 years of dosing, with clinical endpoints evaluated every 6 months
  - Clinical endpoints include those in ongoing APOLLO Phase 3 study
  - After 2 years, patients may continue treatment on another extension study
  - Subjects with left ventricular wall thickness of 13 mm or greater on transthoracic echocardiogram eligible to take part in cardiac subgroup
    - Echo performed every 6 months; cardiac biomarkers assessed every 3 months
- Study objectives
  - Primary: Safety and tolerability of long-term dosing with patisiran
  - Secondary: Effects on neurologic impairment (mNIS+7 and NIS), quality of life, mBMI, disability, mobility, grip strength, autonomic symptoms, nerve fiber density in skin biopsies, cardiac involvement (in cardiac subgroup), serum TTR levels

Timelines are not to scale

Patisiran Phase 2 OLE preliminary study results

Demographics

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: 14 • II: 10 • IIIa: 2 • IIIb: 1
Concurrent tetramer stabilizer use at baseline	13 tafamidis, 7 diflunisal, 7 none	
Current tetramer stabilizer use^	12 tafamidis, 6 diflunisal, 9 none	
Total doses administered	282	
Median doses/patient to date	11 (range 4–16 doses)	
Mean treatment duration*	7 months (range 3–12)	

^2 subjects (1 – diflunisal, 1 – tafamidis) reported stabilizer use at the time of first dose but subsequently stopped using stabilizer
**As of September 8, 2014*

Baseline characteristics

Characteristic	N	Mean (range)
Serum TTR (µg/mL)	27	245.6 (154.6–339.9)
NIS (max impairment: 244)	27	34.8 (4.0–93.4)
mNIS+7 (max impairment: 304)	26	52.1 (2.0–122.5)
10-meter walk test (sec)	22	10.1 (4.6–22.0)
Hand grip strength (kg)	27	25.8 (3.2–49.3)
mBMI (kg/m² x albumin [g/L])	27	1031.6 (728.6–1379.6)
EQ-5D-5L QoL (max impairment: 0)	27	0.8 (0.3–1.0)
R-ODS[a] (no limitations: 48)	24	38.2 (15.0–48.0)
COMPASS-31[b] (max impairment: 100)	26	16.2 (0.0–46.1)
Cardiac subgroup: N=11		
NT-proBNP (ng/L)	8	823.3 (105.0–2070.0)
Troponin I[c] (ng/mL)	8	0.14 (0.02–0.7)
LV wall thickness (cm)	7	1.6 (1.3–1.9)
V30M/non-V30M (N)	11	8/3

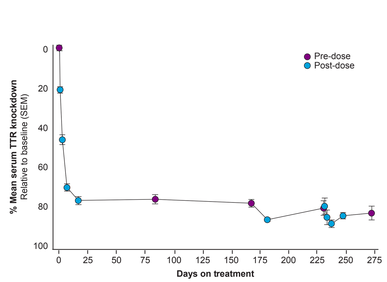
[a]R-ODS: Rasch-built Overall Disability Score, a 24-item questionnaire used to capture activity and social participation (Van Nes SI et al., Neurology *2011); raw scores are presented*
[b]COMPASS-31: 31-item questionnaire used to evaluate 6 autonomic domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor) (Sletten et al., Mayo Clin Proc. *2012)*
[c]Values recorded as '< LLOQ' were imputed to be LLOQ/2

Safety and tolerability – TEAEs related or possibly related

Preferred term	0.30 mg/kg q3w (N=27) N (%)	Severity
Infusion-related reaction (IRR)	4 (14.8%)	Mild
Flushing	4 (14.8%)	Mild
Diarrhea	2 (7.4%)	Mild-moderate
Peripheral edema	2 (7.4%)	Mild
Ectropion	1 (3.7%)	Moderate
Fatigue	1 (3.7%)	Moderate
Infusion site irritation	1 (3.7%)	Moderate
Neuralgia	1 (3.7%)	Mild
Impairment of taste	1 (3.7%)	Mild
Insomnia	1 (3.7%)	Mild

- All TEAEs mild to moderate in severity
- No clinically significant changes in liver function tests, renal function, or hematologic parameters
- 2 subjects with SAEs (unrelated to study drug); both subjects had severe sensory deficit in the legs and feet; one subject with distal femur/proximal tibia fracture and resultant osteonecrosis and one subject with ankle/foot fracture with resultant osteonecrosis which occurred after running a marathon
  - Both patients have continued on study drug

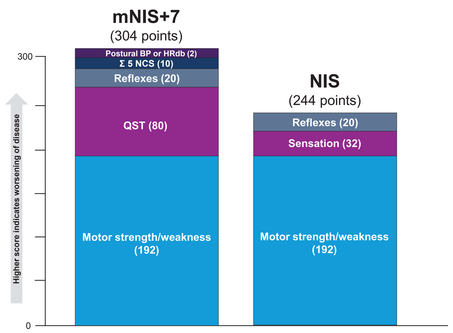
Serum TTR lowering



Day	N	Mean % KD
1	25	21.4
3	25	46.8
7	25	71.1
17	24	77.8
84	23	77.1
168	20	79.1
182	17	87.6
231	3	81.7
232	3	80.7
234	3	86.3
238	3	89.6
248	3	85.5
273	3	84.2

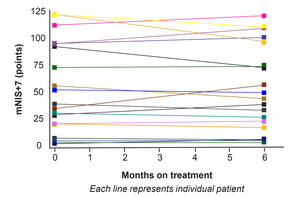
- Similar TTR knockdown in patients on patisiran alone or on patisiran + TTR tetramer stabilizers

Neuropathy impairment scores used in FAP trials



BP: Blood Pressure
HRdb: Heart Rate response to Deep Breathing
NCS: Nerve Conduction Studies
QST: Quantitative Sensory Testing

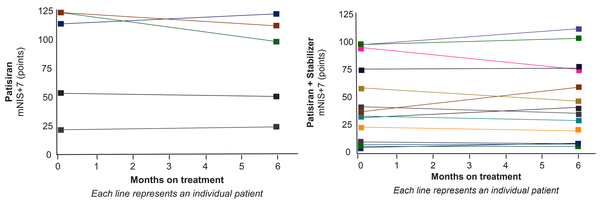
Change in mNIS+7 at 6 months (N=19)



Change from baseline to month 6			
mNIS+7	Mean Δ	Median Δ	SEM
Total	**-0.95**	**0**	**2.59**
NIS-weakness	0.08	0.00	1.53
NIS-reflexes	-0.39	0.00	0.43
QST	-0.68	-2.00	1.82
NCS Σ5	0.11	0.00	0.15
Postural BP	-0.05	0.00	0.10

SEM: Standard Error of the Mean

Change in mNIS+7 at 6 months (N=19) by stabilizer use

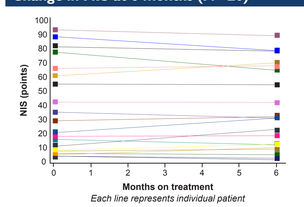


mNIS+7 (N=5)	Mean Δ	Median Δ	SEM
Total	-5.68	-2.75	5.96

mNIS+7 (N=14)	Mean Δ	Median Δ	SEM
Total	0.74	0.25	2.81

SEM: Standard Error of the Mean

Change in NIS at 6 months (N=20)



Change from baseline to Month 6			
NIS	Mean Δ	Median Δ	SEM
Total	0.22	-0.38	1.39
NIS-Weakness	0.24	0.00	1.49
NIS-Sensation	0.78	1.00	0.60
NIS-Reflexes	-0.80	0.00	0.56

SEM: Standard Error of the Mean

Comparison of ΔNIS and ΔmNIS+7 across FAP studies

	Natural History (linear)~	Natural History (nonlinear)#	Tafamidis Fx1A-201*	Diflunisal Phase 3†
Mean (SEM) Δ mNIS+7 at 6 mos.^	8.9 ± 5.7	10.3 ± 5.7	PBO: 8.7 ± 2.0 Drug: 2.5 ± 2.9	PBO: 7.4 ± 6.9 Drug: 2.3 ± 6.0
Mean (SEM) Δ NIS at 6 mos.	7.2 ± 4.6	8.3 ± 4.6	PBO: 7.0 ± 1.6 Drug: 2.0 ± 2.3	PBO: 5.8 ± 5.4 Drug: 1.6 ± 4.8
	Patisiran phase 2 OLE			
Mean (SEM) Δ mNIS+7 at 6 mos.	-0.95 ± 2.59†			
Mean (SEM) Δ NIS at 6 mos.	0.22 ± 1.39			

Adams D et al., XIVth ISA (2014)
Tafamidis EMA assessment report (2011)
Berk JL et al., JAMA. 310:2658-67 (2013)
^Translated algebraically from NIS (Natural History study, Tafamidis study) or NIS+7 (Diflunisal study)
~Linear interpolation between 0 and 12 month progression for median NIS value (from Gompertz curve fit)
#Predicted progression of median NIS value from Gompertz curve fit
**PBO (Placebo) rate estimated from pre-study rate of change; drug rate as reported*
†Estimated from 2-year NIS progression measurement in longitudinal analysis set
†Using mNIS+7 evaluable subset
SEM: Standard Error of the Mean

Changes in other clinical assessments

Assessments	N	Baseline Mean (SEM)	Month 6 Mean (SEM)	Δ Baseline to Month 6† Mean (SEM)
10-Meter Walk^ (sec)	15	10.6 (1.2)	9.6 (0.9)	-1.0 (0.4)
Hand Grip Strength (kg)	22	25.0 (2.7)	24.3 (2.5)	-0.70 (1.0)
EQ-5D (max. impairment: 0)	20	0.77 (0.03)	0.77 (0.03)	-0.002 (0.02)
R-ODS (no limitations: 48)	19	36.8 (2.0)	36.3 (2.4)	-0.53 (0.9)
mBMI (kg/m² x albumin (g/L))	22	1032.9 (35.8)	1032.9 (42.2)	0.01 (15.0)
COMPASS-31 (max. impairment: 100)	17	14.5 (2.9)	16.5 (3.4)	1.93 (2.5)
Orthostatic Intolerance	17	4.5 (1.8)	6.8 (2.1)	2.35 (1.7)
Vasomotor	17	0.5 (0.3)	0.5 (0.3)	0 (0.1)
Secretomotor	17	2.1 (0.8)	2.1 (0.8)	0 (0.7)
Gastrointestinal	17	6.0 (1.1)	5.7 (1.0)	-0.37 (0.4)
Bladder	17	0.7 (0.3)	0.6 (0.2)	-0.13 (0.4)
Pupillomotor	17	0.7 (0.3)	0.8 (0.2)	0.08 (0.2)
IENFD (fibers/mm)				
Location: Leg	15	4.1 (1.9)	3.9 (1.9)	-0.16 (0.6)
Location: Thigh	15	10.2 (2.7)	9.0 (2.8)	-1.19 (0.9)
SGNFD (m/mm³)				
Location: Leg	14	4.1 (1.0)	3.9 (1.0)	-0.19 (0.6)
Location: Thigh	15	7.3 (0.9)	8.4 (1.1)	1.15 (0.6)
Cardiac Biomarkers# (Cardiac Subgroup, N=11)				
NT-proBNP (ng/L)	5	803.8 (391.3)	1005.0 (429.5)	201.2 (51.5)
Troponin I (ng/L)	5	0.2 (0.1)	0.03 (0.01)	-0.15 (0.1)
Echocardiogram (Cardiac Subgroup, N=11)				
LV Mass (g)	7	253.0 (24.1)	253.5 (24.6)	0.5 (8.9)
LV wall thickness (cm)	7	1.6 (0.1)	1.6 (0.1)	0.01 (0.03)
Ejection fraction (%)	7	64.8 (1.9)	62.6 (4.6)	-2.2 (3.1)
Peak longitudinal strain (%)	7	-17.3 (1.5)	-16.9 (1.8)	0.4 (1.5)

†Paired t-tests were performed to determine statistically significant changes at Month 6; none of the assessments were significant after adjustments for multiple testing were performed using a Bonferroni correction.
^One subject with an SAE due to ankle injury prior to Month 6 was removed from the 10-meter walk analysis.
#Values reported as <LLOQ were imputed to be LLOQ/2 for the analysis.
IENFD: Intraepidermal nerve fiber density
SGNFD: Sweat gland nerve fiber density
SEM: Standard Error of the Mean

Summary

- Chronic dosing with q3 weekly patisiran well tolerated in FAP patients, including patients on concurrent tetramer stabilizers
  - 282 doses administered to date, median of 11 doses/patient
  - Mean treatment duration of 7 months, longest treatment duration out to 1 year
  - IRRs infrequent (~15% incidence), mild in severity, did not result in any discontinuations
  - No significant LFT or renal function changes
  - No drug-related SAEs
- Patisiran achieves sustained serum TTR lowering of at least 80%, with further nadir of up to 89.6% between doses
  - Based on serial TTR measurements for over 9 months
  - Pharmacodynamic activity similar in patients on concurrent tetramer stabilizers
- Neuropathy impairment scores stable after 6 months of treatment with patisiran
  - Similar results for QOL and multiple additional neurologic and cardiac measures
  - Similar outcome in patients with or without concurrent tetramer stabilizers
  - Mean *decrease* in mNIS+7 of 0.95 points compares favorably to the rapid *increase* in mNIS+7 estimated at 6 months from prior FAP studies in a patient population with similar baseline NIS.