Clinical Update on Patisiran Phase 2 Trials in Familial Amyloidotic Polyneuropathy

April 30, 2014

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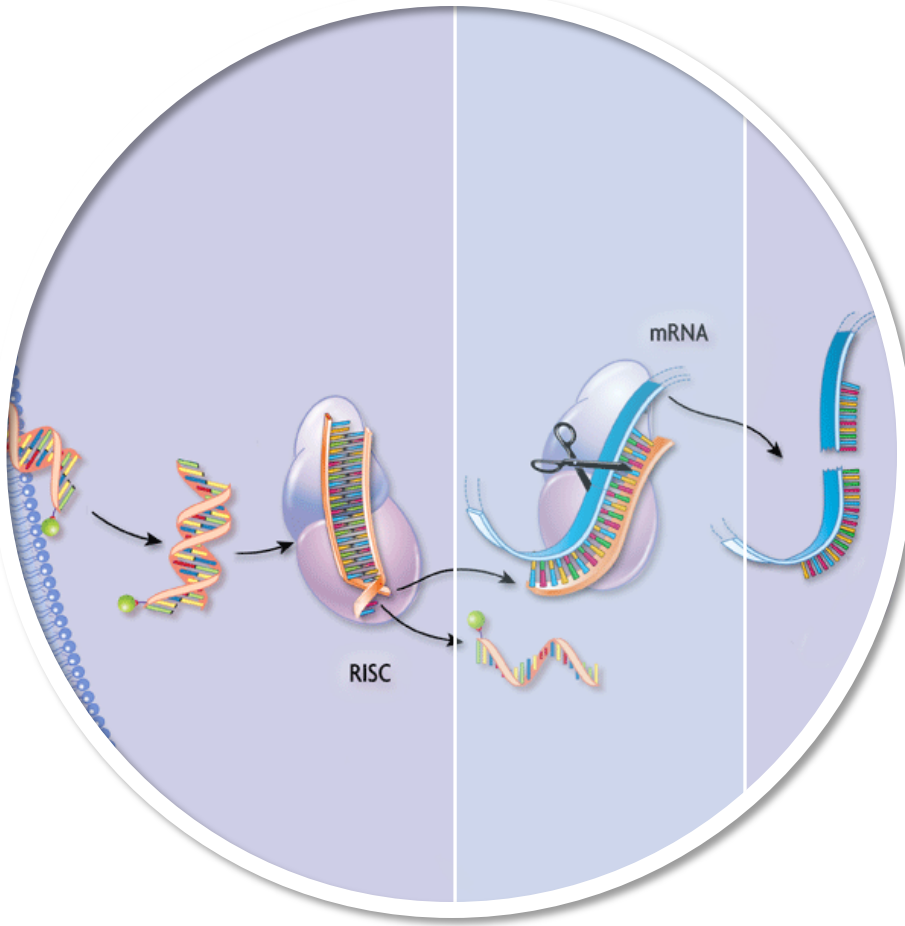
RNA Interference (RNAi)
A New Class of Innovative Medicines

RNAi Therapeutics

- Harness natural pathway
  - » Catalytic mechanism
  - » Mediated by small interfering RNA or “siRNA”
- Therapeutic gene silencing
  - » Any gene in genome
  - » Distinct mechanism of action vs. other drug classes
  - » Unique opportunities for innovative medicines
- Clinically validated platform



Patisiran (ALN-TTR02)
Familial Amyloidotic Polyneuropathy (FAP)

Patisiran in clinical development

- International Nonproprietary Name designation for ALN-TTR02 = Patisiran (Pa-TEE-sa-ran)
- Orphan drug status in US/EU
- Fast track designation by FDA
- Positive Phase 1 results in human volunteers
  - » Data published in *New England Journal of Medicine*[1]
- Positive multi-dose Phase 2 results in FAP patients[2]
- Phase 2 Open-Label Extension (OLE) study ongoing
  - » Includes clinical endpoints measured every 6 months
- APOLLO Phase 3 trial ongoing

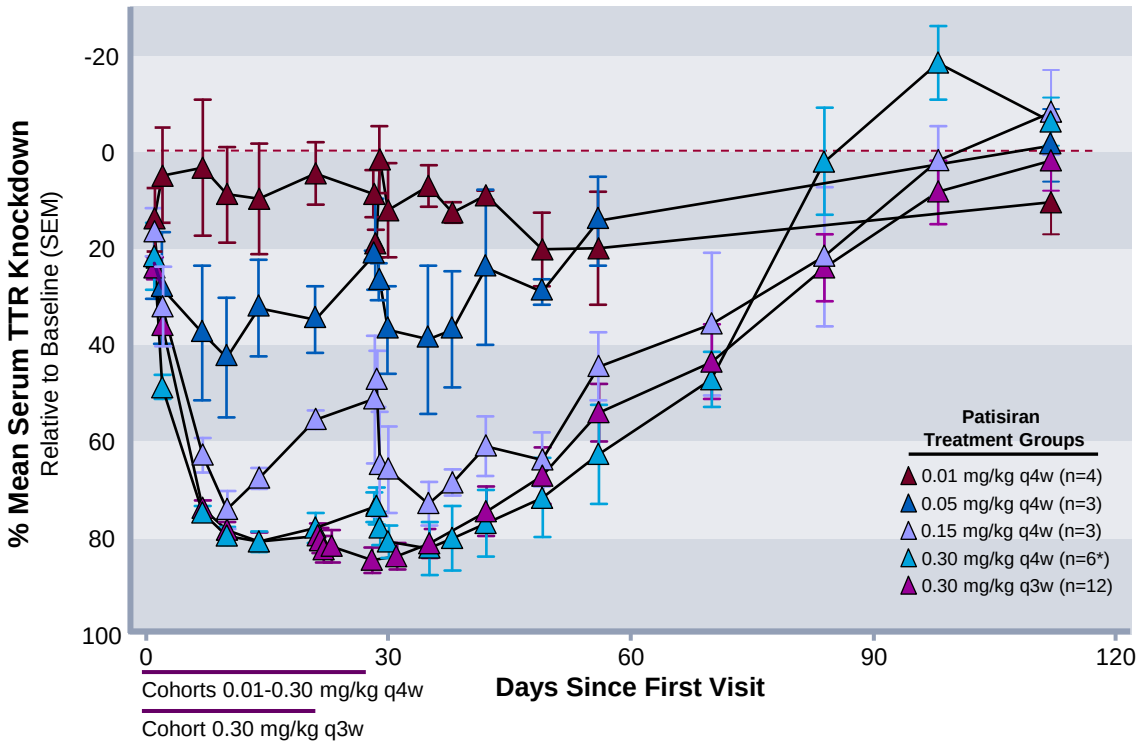
[1]Coelho *et al., N Engl J Med*;369:819-29(2013)
[2]*Int'l Symp. FAP, Nov. 2013*

Updated Patisiran Phase 2 Study Results

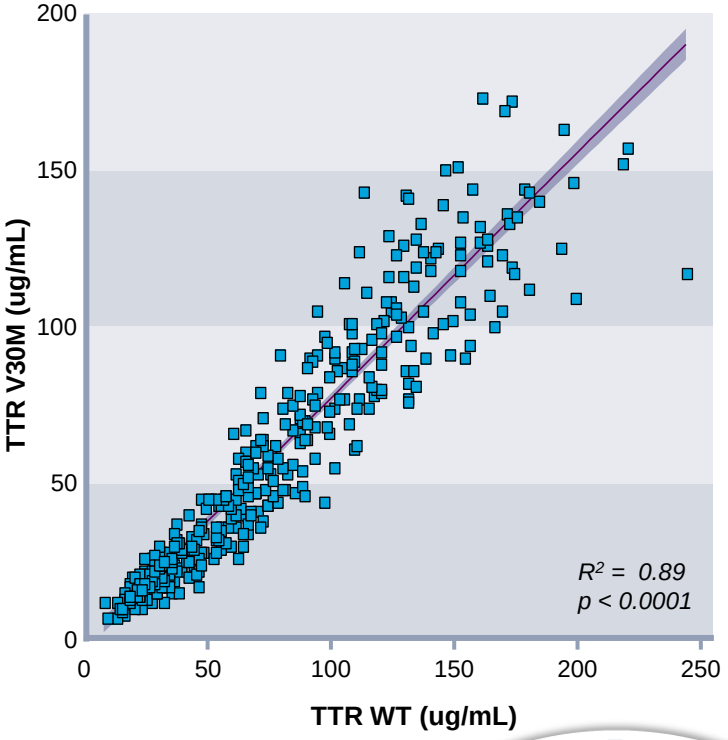
Robust knockdown of both wild-type and mutant TTR in ATTR patients

- Open label, multi-center, multi-dose, dose escalation study
- Results (n=29) show up to 96% TTR knockdown; 84% and 87% mean TTR knockdown after 1st and 2nd doses in 0.30 mg/kg q3w cohort ($p<0.001$ *vs.* 0.01 mg/kg)
- 1:1 Knockdown of wild-type and mutant TTR; Similar efficacy in patients with TTR stabilizers

Dose Response and Duration of TTR Knockdown



Wild Type vs. Mutant



**Excludes post-day 28 data from one patient that experienced drug extravasation during second infusion*

Patisiran Open-Label Extension (OLE) Study

FAP patients 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 APOLLO Phase 3 study
  - » Dosing at 0.30 mg/kg every 3 weeks
  - » 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 and cardiac biomarkers taken every 6 months
- Study objectives
  - » Primary: Safety and tolerability of long-term dosing with patisiran
  - » Secondary: Effects on neurologic impairment (mNIS+7), quality of life, mBMI, disability, mobility, nerve fiber density in skin biopsies, and serum TTR levels
- Status
  - » 23 Patients in current analysis based on April 3, 2014 data cut-off
  - » 25 Patients enrolled to date
  - » Expect enrollment to be completed in May with final N=27

Patisiran Phase 2 OLE Preliminary Study Results*

Demographics

Characteristic	Result	
Number of patients	N=23	
Median age	65.5 years (range 30-77)	
Gender	16 males, 7 females	
TTR genotype	• Val30Met (V30M) = 16 • Ser77Tyr (S77Y) = 2 • Ser77Phe (S77F) = 2	• Tyr116Ser (Y116S) = 1 • Phe64Leu (F64L) = 1 • Arg54Thr (R54T) = 1
FAP stage/PND score	• Stage 1: 20 • Stage 2: 3	• I: 12 • II: 8 • IIIa: 2 • IIIb: 1
Concurrent tetramer stabilizer	10 tafamidis, 7 diflunisal, 6 none	
Total doses administered to date	81	
Median doses/patient to date	4 (range 1-8 doses)	

**Preliminary results as of April 3, 2014*

Patisiran Phase 2 OLE Preliminary Study Results*

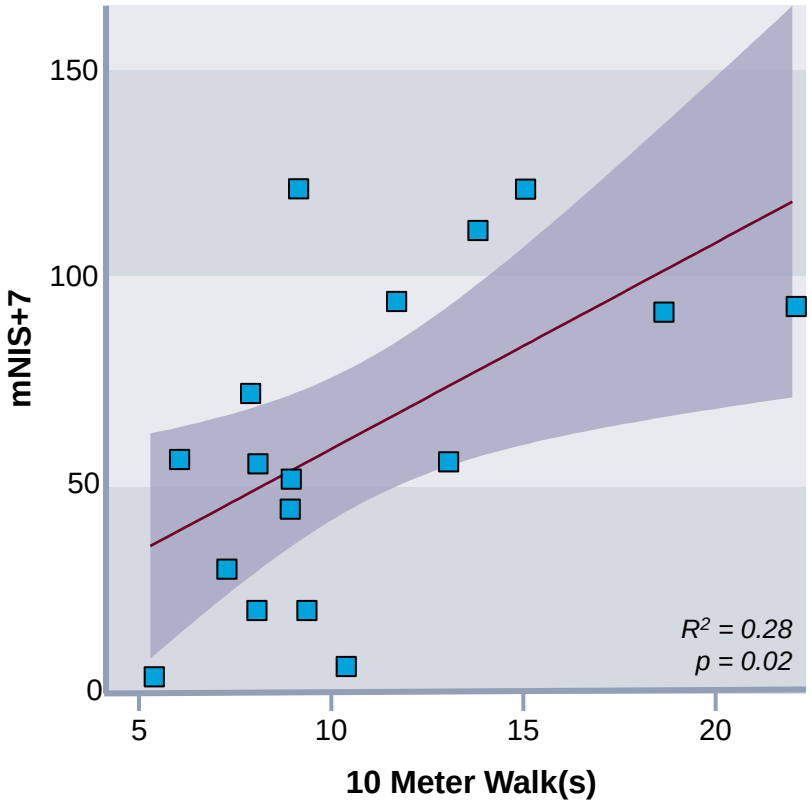
Baseline Characteristics

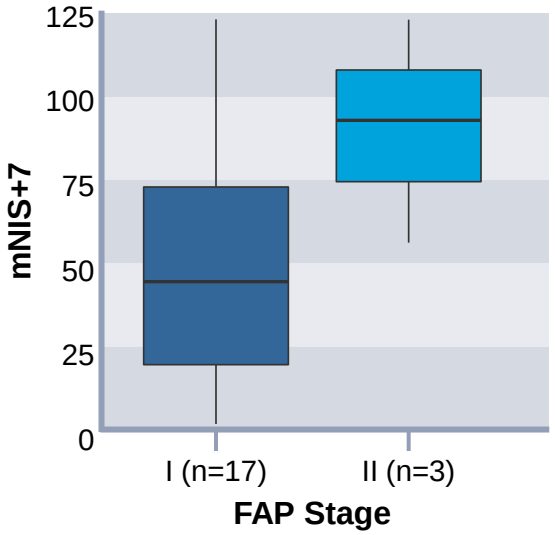
Characteristic	Result (mean, range)
Serum TTR (µg/mL)	241.4 (179.2 – 313.7)
NIS (max impairment: 244 points)	35.4 (4.0 - 93.4)
mNIS+7 (max impairment: 304 points)	55.0 (3.0 – 122.5)
mBMI	1030.3 (747.8 – 1410.9)
EQ-5D-5L (max impairment: 0)	0.8 (0.3-1.0)
10-Meter walk test (sec)	10.7 (5.3-22.0)
Cardiac subgroup: n = 9	
NT-proBNP (ng/L)	911.6 (105.0-2070.0)
Troponin I (ng/mL)	0.16 (0.0–0.7)
LV wall thickness (cm)	1.5 (1.3-1.7)
V30M/non-V30M (N)	6/3

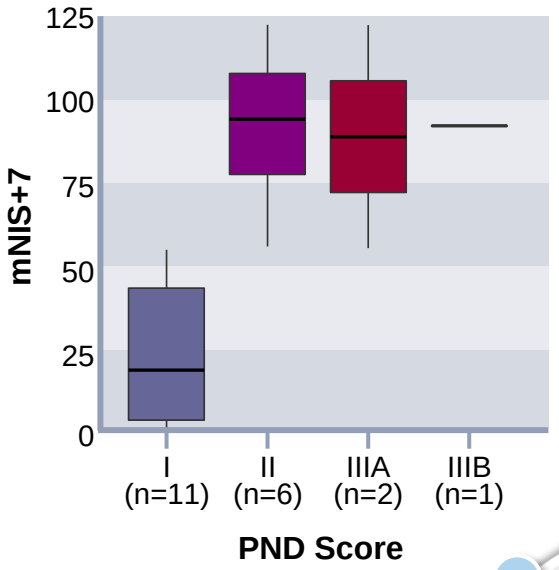
**Preliminary results as of April 3, 2014*

Patisiran Phase 2 OLE Preliminary Study Results*

Correlation of mNIS+7 with 10m walk, FAP stage, PND score







*Preliminary results as of April 3, 2014

Patisiran Phase 2 OLE Preliminary Study Results*

Safety and Tolerability - TEAEs Related or Possibly Related

Preferred Term	0.30 mg/kg q3w (n=23) n (%)	Severity
Infusion-related reaction**	1 (4.3%)	Mild
Increase of diarrhea	1 (4.3%)	Moderate
Impairment of taste	1 (4.3%)	Mild

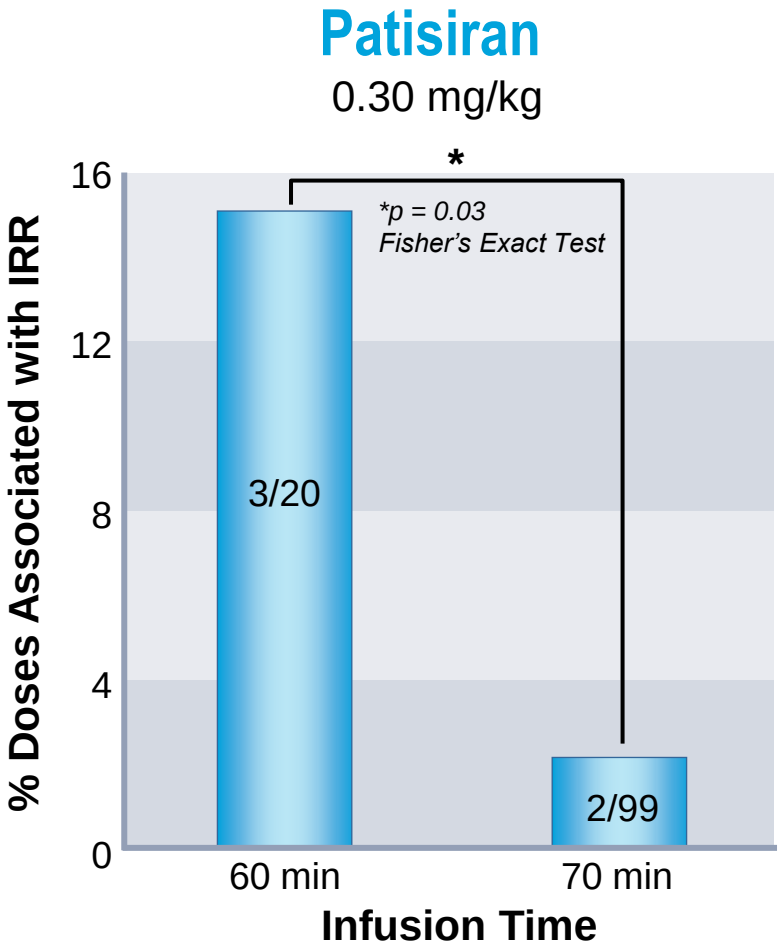
**Single patient had mild, transient reactions after 2nd and 3rd doses not requiring dose interruption

- All TEAEs mild to moderate in severity
- No SAEs
- No changes in liver function tests, renal function, or hematologic parameters

Preliminary results as of April 3, 2014

Patisiran Phase 2 OLE Preliminary Study Results*

Reduction in IRR Rate with 70-minute Microdosing Regimen

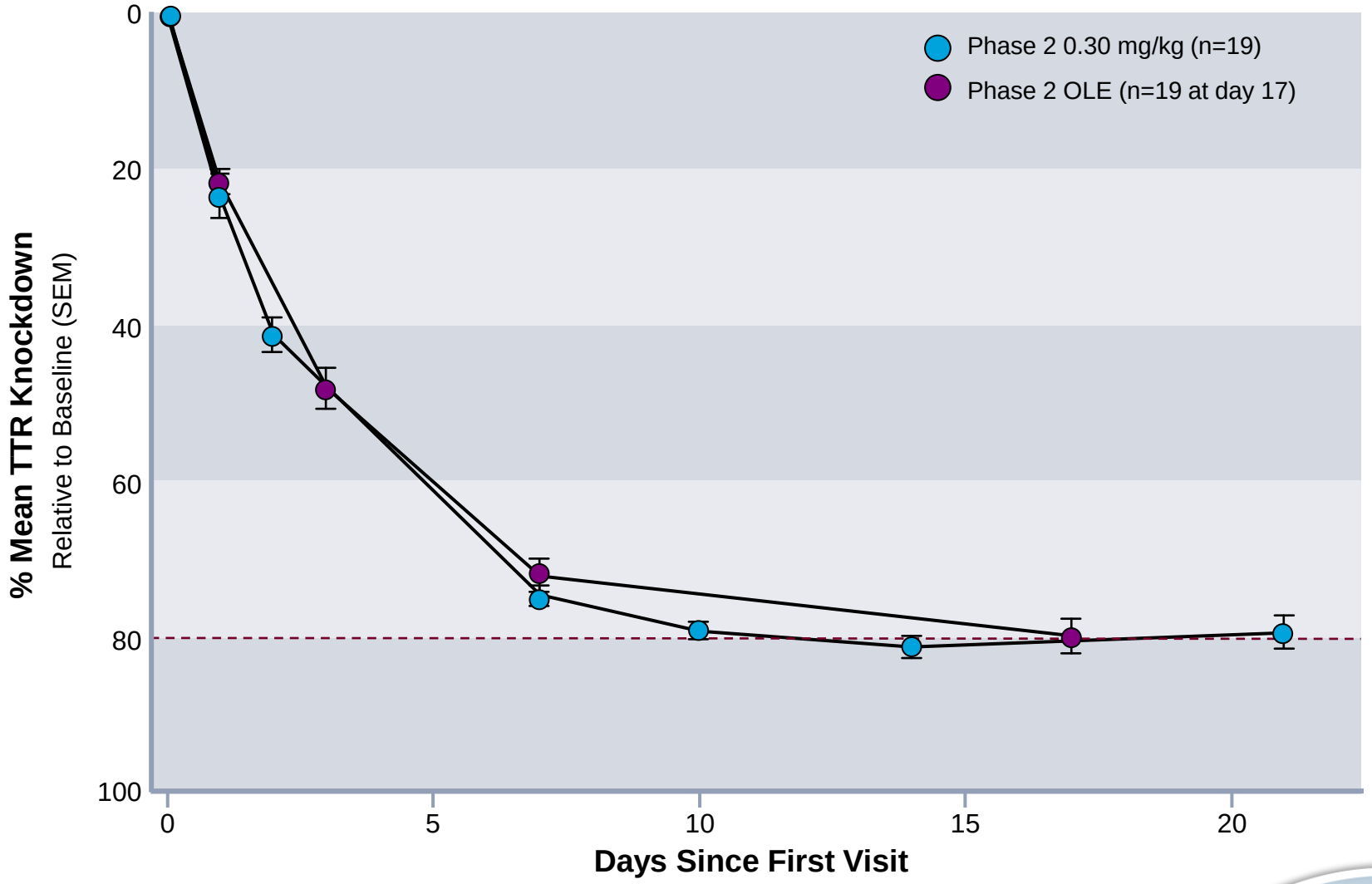


Clinical Study	Patisiran Infusion Time (0.30 mg/kg)	
	60 min (# of patients)	**70 min** (# of patients)
Phase 2	10	9
Phase 2 OLE	--	23

*Preliminary results as of April 3, 2014

Patisiran Phase 2 OLE Preliminary Study Results*

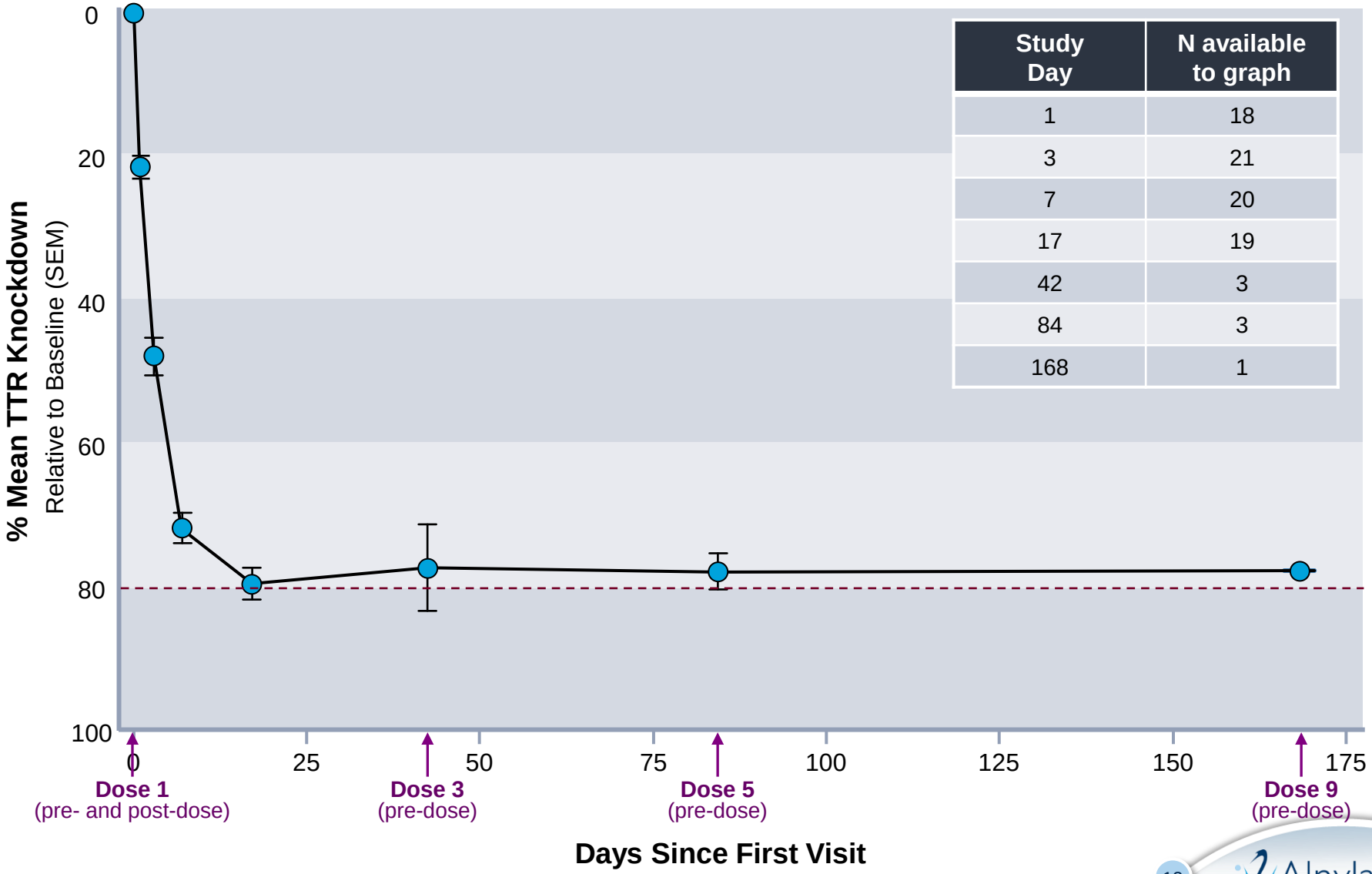
Phase 2 and Phase 2 OLE Study: TTR Knockdown After First Dose



*Preliminary results as of April 3, 2014

Patisiran Phase 2 OLE Preliminary Study Results*

Sustained TTR Knockdown of ~80% at Pre-Dose Measurement



Study Day	N available to graph
1	18
3	21
7	20
17	19
42	3
84	3
168	1

Preliminary results as of April 3, 2014

APOLLO Phase 3 Trial of Patisiran in FAP
Study Ongoing

Randomized, double-blind, placebo-controlled, global study

- Sample size and randomization
  - N=200
  - 2:1, Patisiran vs. placebo
- Key eligibility criteria
  - V30M and non-V30M FAP
  - Baseline NIS 10-100 (FAP stages 1 and 2)
- Treatment regimen
  - Patisiran 0.30 mg/kg vs. placebo IV q3w for 18 months
  - All completers eligible for patisiran treatment on Phase 3 OLE study

Primary Endpoint

- mNIS+7 at 18 months

Secondary Endpoints

- Norfolk QOL-DN, NIS-weakness, mBMI, timed 10-meter walk, COMPASS-31 autonomic symptom score

Statistical Considerations

- Placebo mNIS+7 progression rate of 17.8 points/yr derived from natural history study of 283 FAP patients
- Study with 90% power to detect as little as 37.5% difference in ΔmNIS+7 between treatment groups with 2-sided alpha = 0.05
- Blinded interim analysis of variability planned for potential sample size re-estimation

Patisiran Program for FAP
Summary and Next Steps

Robust and durable TTR knockdown demonstrated in patients with multi-dose regimen in Phase 2

- Similar activity against mutant and wild-type TTR as well as both V30M and non-V30M
- Favorable safety profile to date

Phase 2 OLE study ongoing with enrollment expected to be completed in May

- Safety profile encouraging to date with significant reduction in IRR rate using 70-minute microdosing infusion regimen
- Mean baseline NIS of 35.4, in line with inclusion criteria for APOLLO Phase 3
- Preliminary assessment of TTR knockdown with 0.30 mg/kg dosed every 3 weeks shows results consistent with Phase 2 data
  - » Superimposable 1st dose TTR knockdown in Phase 2 OLE (n=19) as compared to patients treated at 0.30 mg/kg dose in Phase 2 (n=19)
  - » Sustained TTR knockdown of approximately 80% based on pre-dose samples with data available out to 168 days
- Interim 6-month data on approximately 20 patients, including mNIS+7 and other clinical activity endpoints, expected to be presented in late 2014

APOLLO Phase 3 study ongoing

Acknowledgments

Patisiran (ALN-TTR02) Phase 2 Investigators

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  - Boston University, Boston, MA USA

TTR Program - Scientific Collaborators

- Maria Saraiva
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- Yukio Ando and Hiro Jono
  - Kumamoto University, Japan

Alnylam has licenses to Tekmira LNP intellectual property for use in RNAi therapeutic products using LNP technology