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VIIIth International Symposium on FAP

Phase I Safety, Pharmacokinetic and Pharmacodynamic Results for ALN-TTR01

Preliminary Study Results

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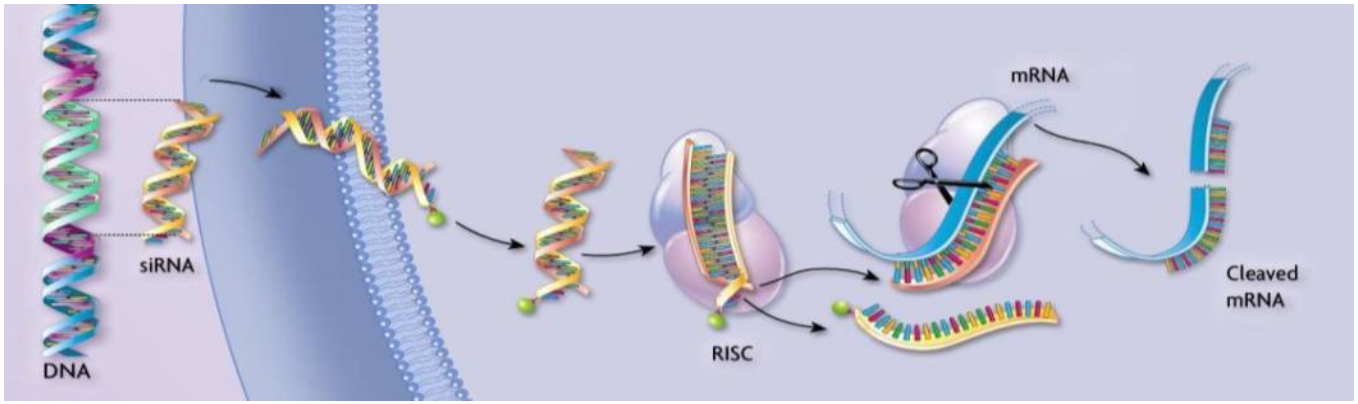
November 21, 2011

ALN-TTR Program Agenda

- Background and Preclinical Data
- ALN-TTR01 Phase 1 Trial Study Design
- Safety and Pharmacokinetic Data
- Pharmacodynamic and Clinical Activity Data
- Summary

RNA Interference (RNAi)
A New Class of Innovative Medicines



RNAi Therapeutics

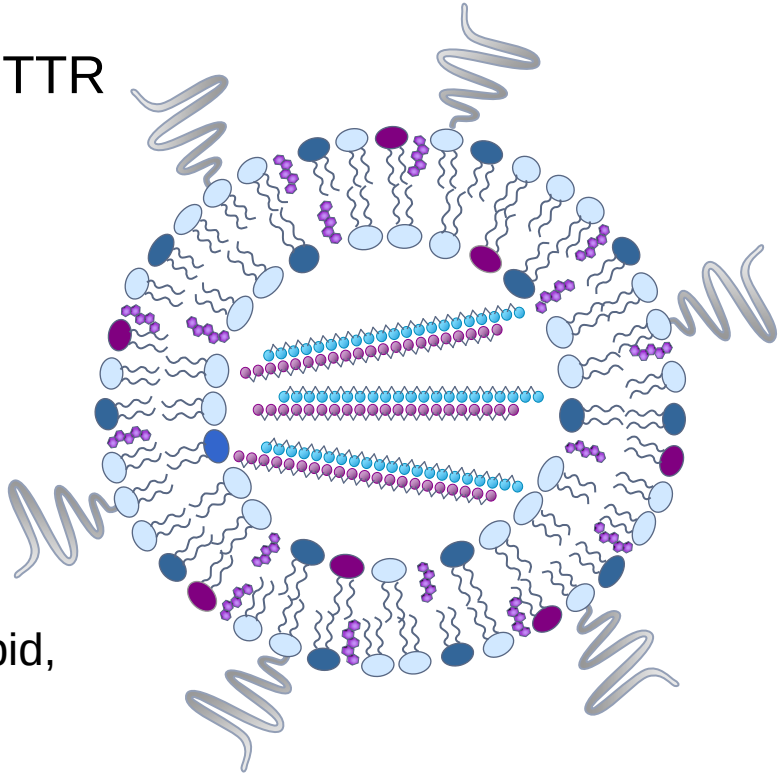
- Harness natural pathway
  - » Catalytic mechanism
  - » Mediated by small interfering RNAs or “siRNAs”
- Treat disease with therapeutic gene silencing
  - » Any gene in genome

TTR Amyloidosis Program
ALN-TTR01

First RNAi drug for ATTR
- Targets wild-type and all mutant forms of TTR

Lead siRNA candidate selected
- Potent, *in vitro* IC_{50} = 3 pM
- Highly specific for TTR
  - » Both wild-type and mutant TTR
- Non-immunostimulatory

Formulated with 1st generation LNP
- LNP is multi-component formulation
  - » Includes cationic lipid, fusogenic lipid, PEG lipid, and cholesterol
- Highly efficient for liver delivery
  - » Achieves robust, reproducible hepatocyte-specific gene silencing



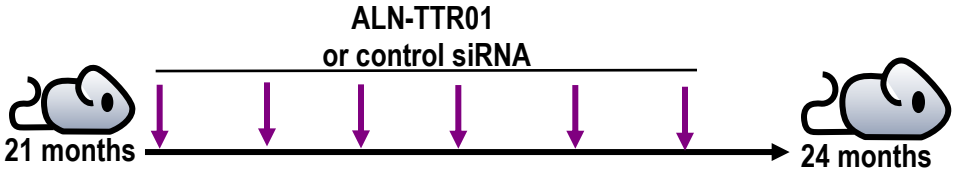
ALN-TTR01

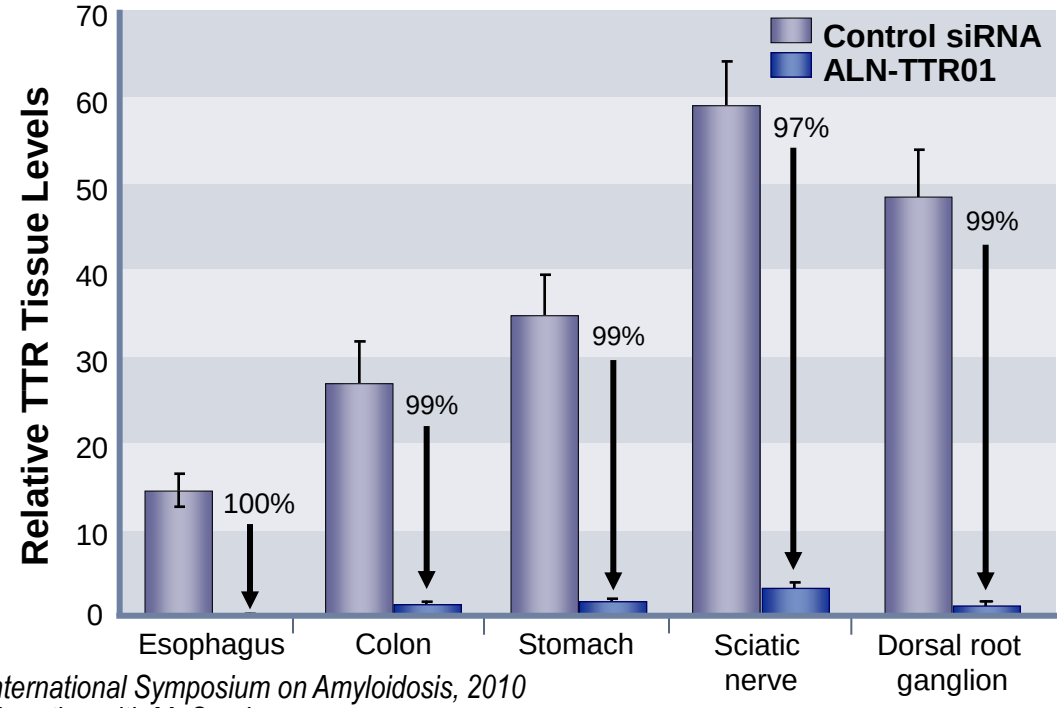
ALN-TTR01 Therapeutic Efficacy

V30M TTR Transgenic Mouse Model

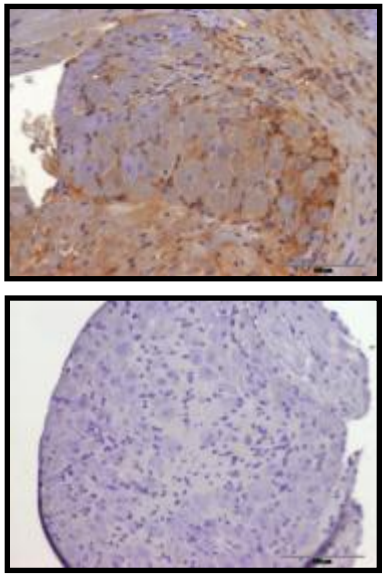
ALN-TTR01 promotes regression of pathogenic mutant human TTR deposits in peripheral tissues

- >90% Regression of existing V30M hTTR tissue deposits
- Multi-dose i.v. bolus of ALN-TTR01 or control siRNA, 3 mg/kg (d0, 14, 28, 42, 56, and 70)
- Quantitation of TTR deposition by immunohistochemistry (day 77)





Dorsal Root Ganglion



Control siRNA

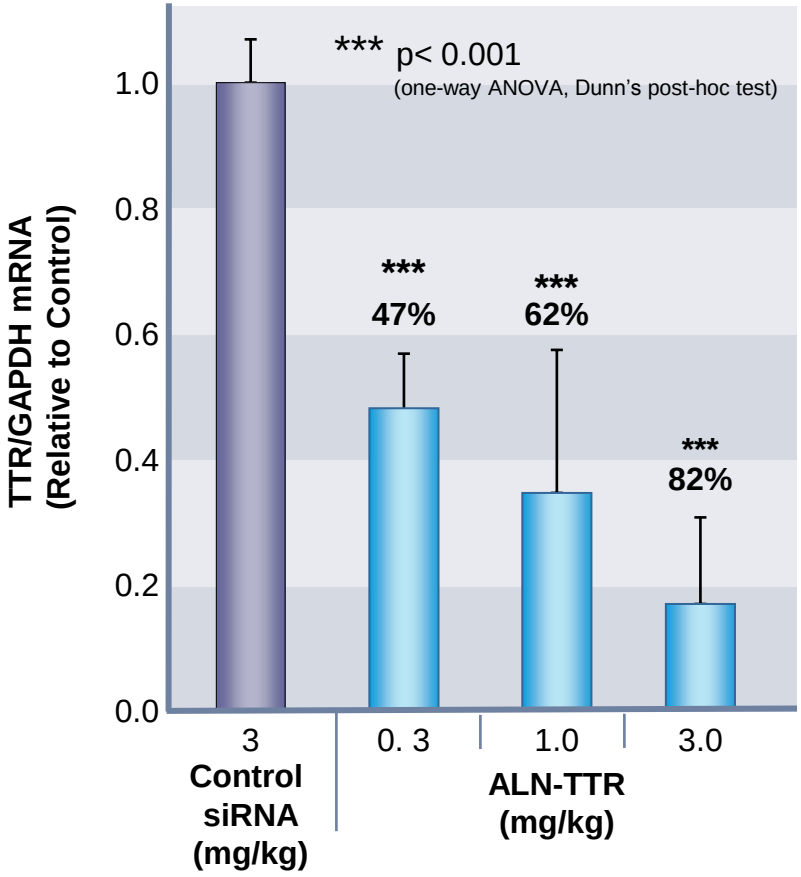
ALN-TTR01

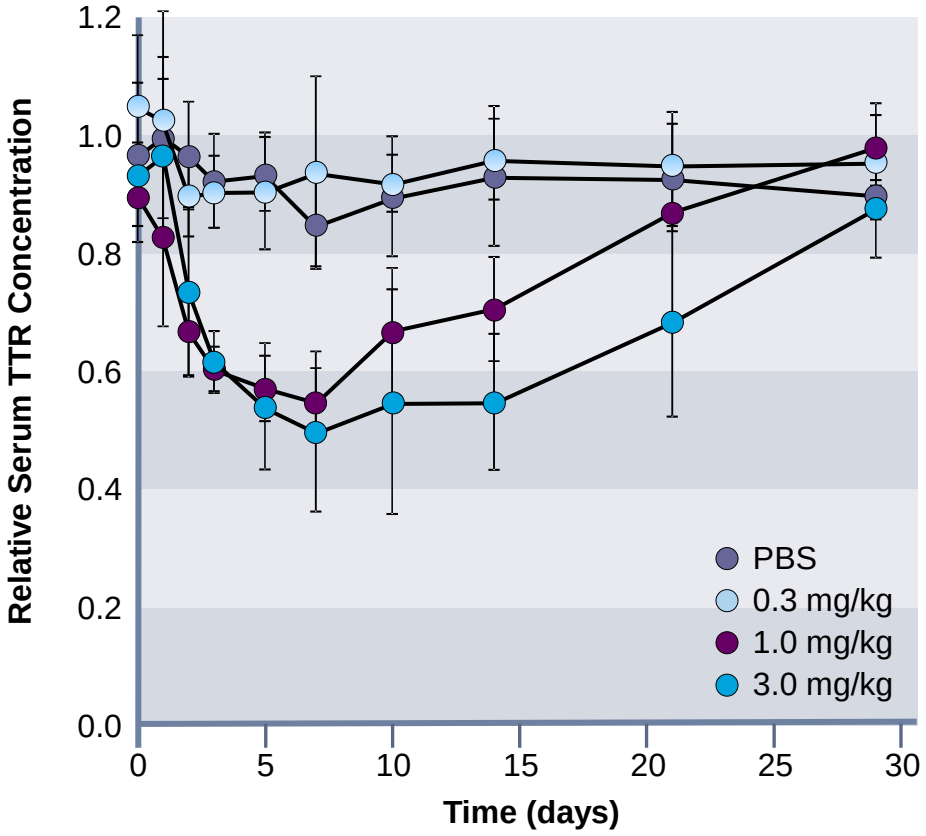
XII International Symposium on Amyloidosis, 2010
Collaboration with M. Saraiva

ALN-TTR01 Activity
Non-Human Primates

ALN-TTR01 shows dose-dependent silencing of TTR mRNA and protein

- Single i.v. infusion of ALN-TTR01 or control siRNA
- Liver mRNA levels measured 48hr post-dose, serum protein levels measured over 28d post-dose





Keystone RNAi, Feb 2009

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ALN-TTR01 Phase I Study

Study Design

- Randomized, placebo-controlled, single-blind, single-dose escalation study
  - » 3:1 randomization
  - » 4 patients/cohort
- Up to 36 patients with ATTR
  - » Conducted in Portugal (T. Coelho, A. Silva), Sweden (O. Suhr), France (D. Adams, P. Lozeron) and UK (T. Mant, P. Hawkins)

Primary Objective

- Evaluate safety and tolerability of ALN-TTR01

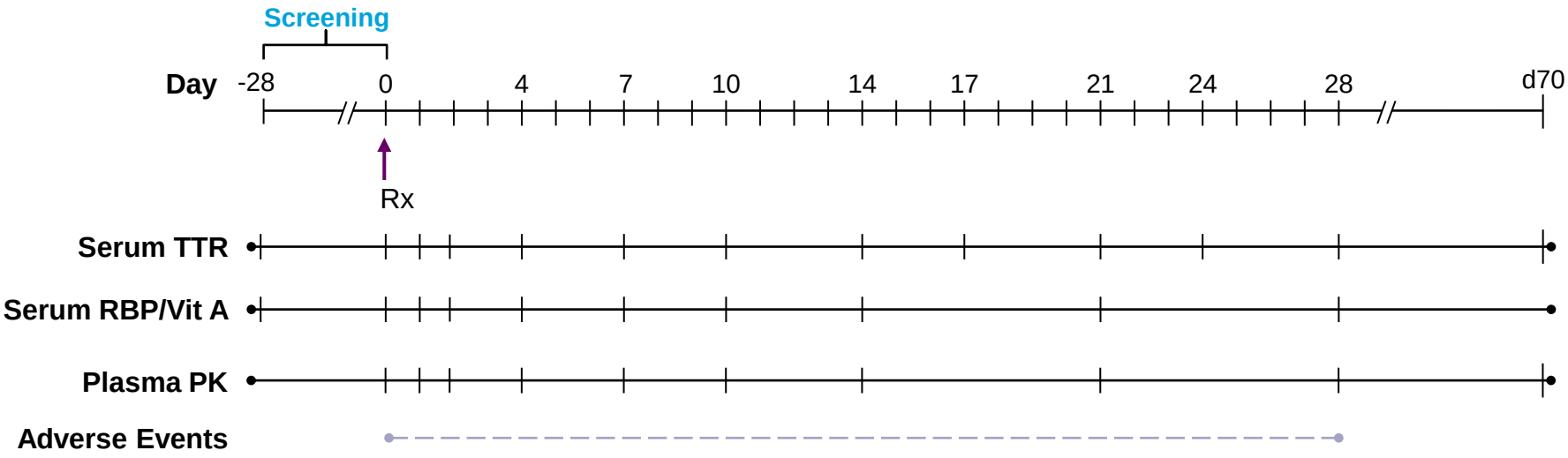
Secondary Objective

- Characterize plasma PK
- Assess preliminary pharmacodynamics and clinical activity
  - » Serum TTR, RBP, Vitamin A levels

Study Status

- Dose escalation completed; accruing additional patients at top dose

ALN-TTR01 Phase I Study Design



Dose levels and dosing schedule

- 0.01, 0.03, 0.1, 0.2, 0.4, 0.7 and 1.0 mg/kg
  - » Option of enrolling up to 2 additional cohorts at top planned dose to further assess safety, PK and PD/clinical activity
- Single 15-min i.v. infusion; premedication including corticosteroid

ALN-TTR01 Phase I Study Results

Baseline Characteristics

- Total Patients N=31
  - ALN-TTR01: Placebo = 23:8
- Median Age = 38 years (range 21-76)
- Male:Female = 17:14
- Enrollment by Country
  - Portugal = 22
  - Sweden = 5
  - France = 3
  - UK = 1
- TTR Genotype
  - Val30Met = 28
  - Ser77Tyr = 2
  - Ser77Phe =1
- Stage of Disease
  - 1 (Early) = 31
  - $\geq$ 2 = 0
- Mean BMI = 23.9 kg/m^2 (range 18.5-31.7)
- Mean Serum TTR at Study Entry = 266.6 μg/mL (range 117.2-393.5)

Preliminary, Study Ongoing

ALN-TTR01 Phase I Study Results

Treatment Emergent Adverse Events

	ALN-TTR01 Dose Level (mg/kg)							All ALN-TTR01 (n=23)	Placebo** (n=8)
	0.01 (n=3)	0.03 (n=3)	0.10 (n=3)	0.20 (n=3)	0.40 (n=3)	0.70 (n=3)	1.00 (n=5)		
TEAE*	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infusion-Related Reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(33.3)	1(33.3)	1 (20.0)	3 (13.0)	0 (0.0)
Fatigue	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	1 (12.5)
Constipation	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)
1st Degree A-V Block	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)

No SAEs related to study drug administration

**Includes TEAEs probably or possibly related to study drug: all mild-moderate in severity. No significant increases in liver function tests (LFTs).*

*** One placebo patient underwent elective hospitalization for liver transplant, scored as SAE unrelated to study drug.*

Preliminary, Study Ongoing

ALN-TTR01 Phase I Study Results

Plasma PK Data Summary

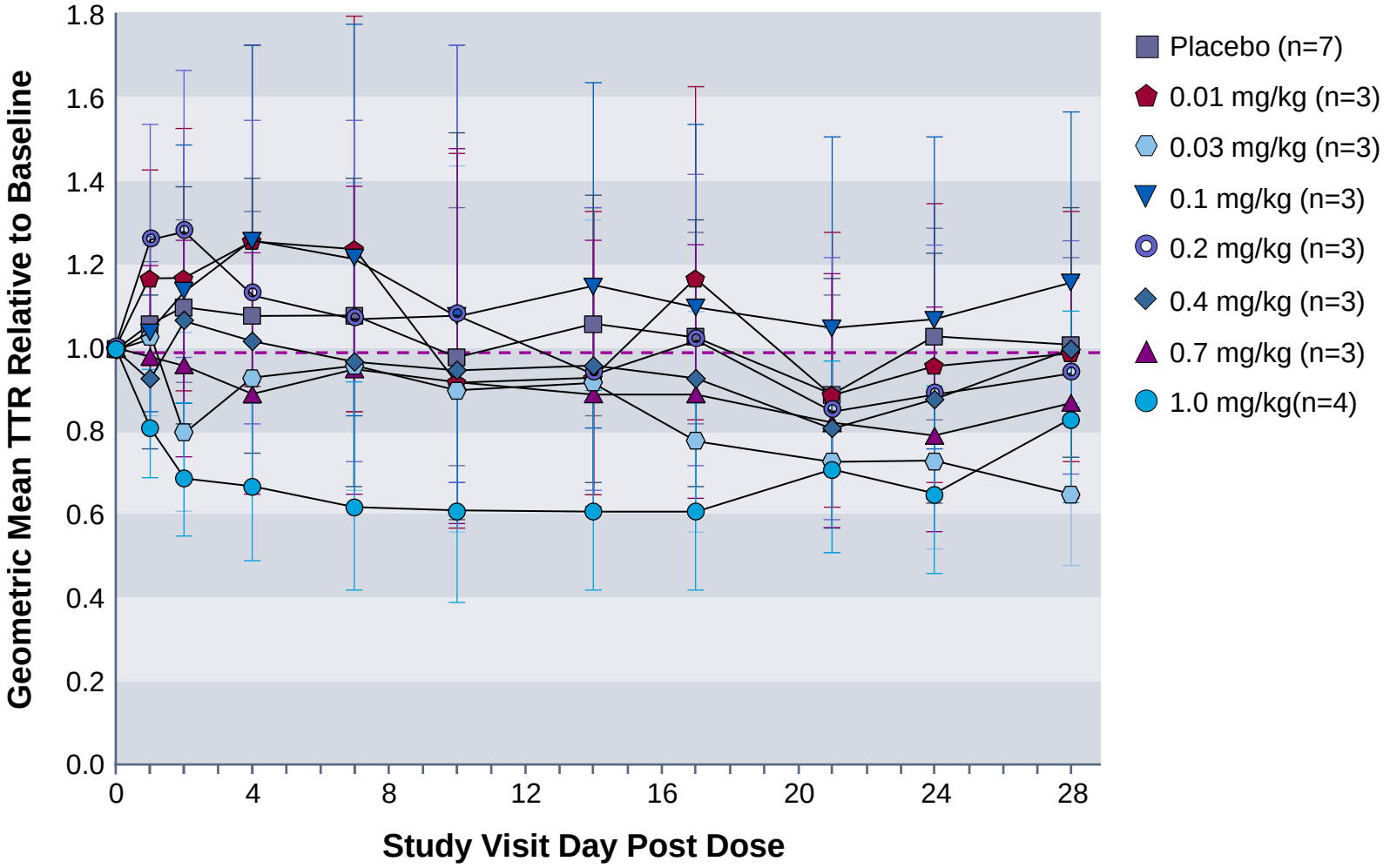
ALN-TTR01 (mg/kg)	0.01 (n=3)	0.03 (n=3)	0.1 (n=3)	0.2 (n=3)	0.4 (n=3)	0.7 (n=3)	1.0 (n=4)
C_{max} (µg/mL)	0.03	0.44	1.14	2.83	7.49	15.45	22.11
$AUC_{0\text{-last}}$ (min*µg/mL)	0.55	102	275	967	2,722	9,035	7,385

- Cmax and $AUC_{0\text{-last}}$ increase linearly in approximately dose-proportional manner

Preliminary, Study Ongoing

ALN-TTR01 Phase I Study Results

TTR Protein Time Courses, All Dose Groups



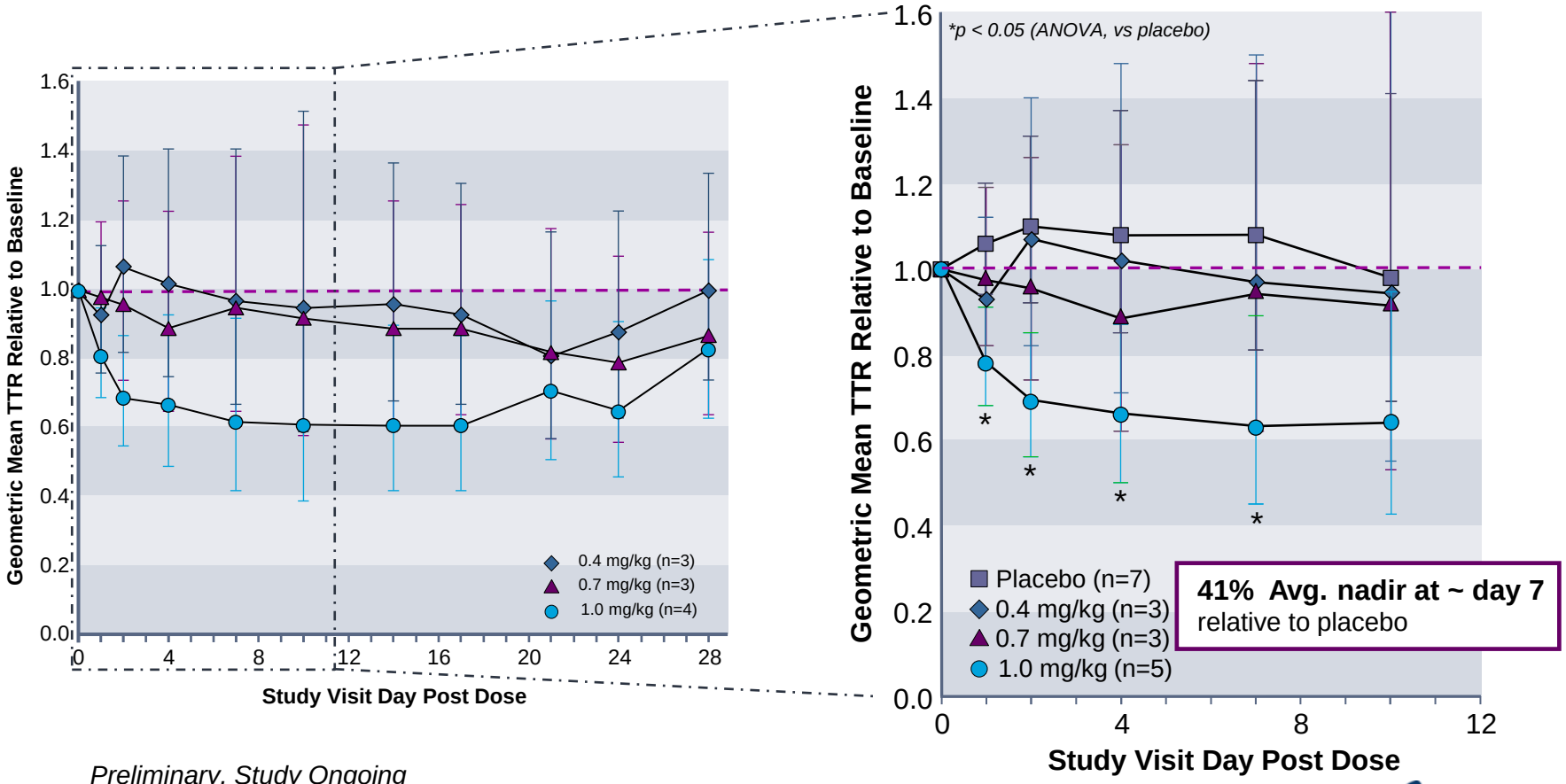
Preliminary, Study Ongoing

ALN-TTR01 Phase I Study Results

Dose-Dependent TTR Lowering at 0.4 to 1.0 mg/kg

ALN-TTR01 single dose results in rapid, dose-dependent, and durable lowering of serum TTR protein levels

- All patients show TTR lowering at 1.0 mg/kg, ranging 25-81%
- Average nadir at approximately Day 7 of 41% relative to placebo (geometric mean vs. placebo, p=0.02)



Preliminary, Study Ongoing

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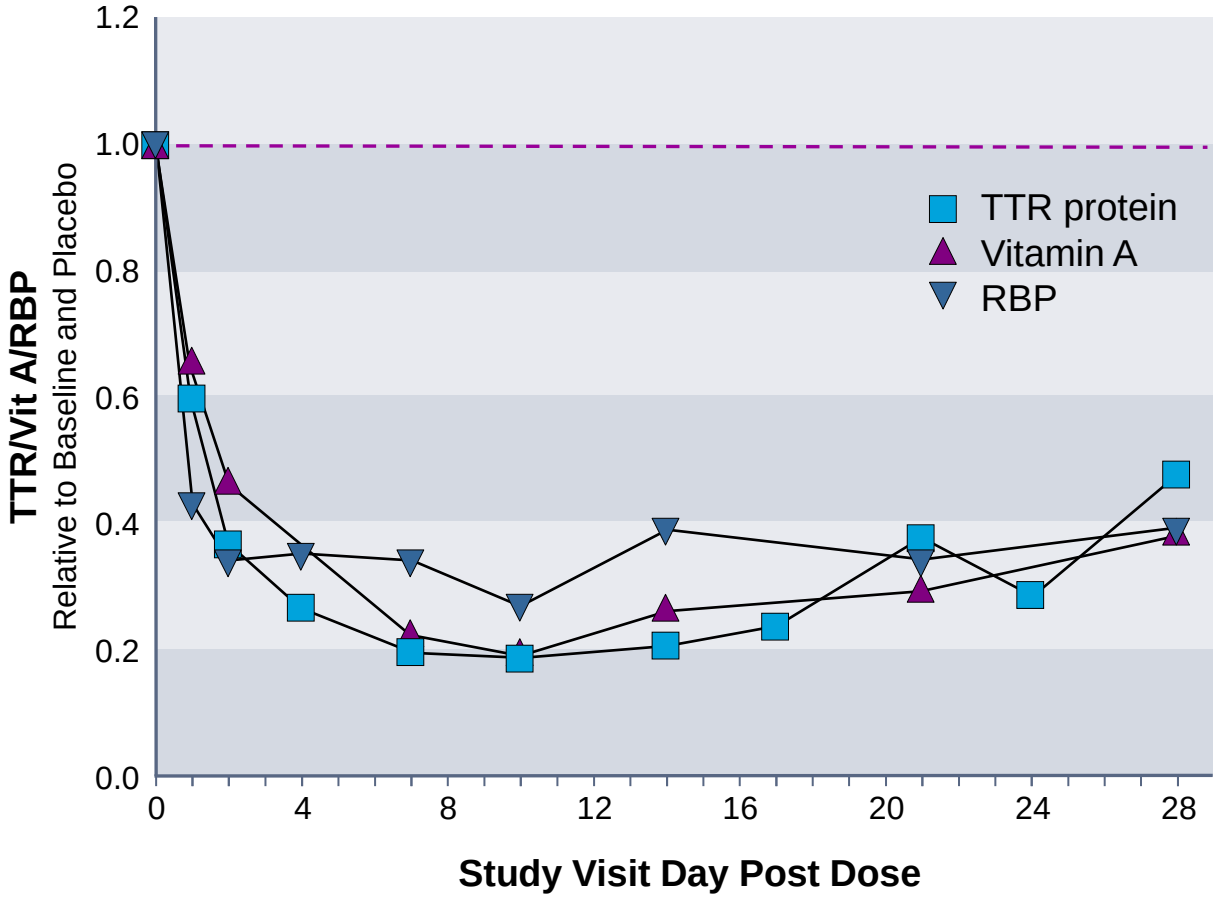
ALN-TTR01 Phase I Study Results

Robust RNAi in Patient at 1 mg/kg ALN-TTR01



- Single 1 mg/kg dose lowers serum TTR protein, RBP and vitamin A levels
- TTR protein reduced by 81% at nadir
- Rapid onset of effect with >50% lowering at day 2
- Nadir at ~day 7
- Durable effect with ~50% lowering at day 28

Preliminary, Study Ongoing

ALN-TTR01 Phase I Summary

Human Proof of Concept for RNAi Therapeutics in ATTR Patients

- ALN-TTR01 is safe and well-tolerated
- Single dose results in rapid onset, dose-dependent, and durable lowering of serum TTR protein levels
  - » At 1.0 mg/kg, all patients show evidence of TTR lowering, with average nadir of 41% relative to placebo at ~day 7 (p=0.02)
- Demonstration of human proof of concept with ALN-TTR01
  - » 1st Demonstration of RNAi silencing of disease-causing protein in humans
  - » Continued clinical development, including ALN-TTR02 which uses 2nd generation LNP

TTR Program
Next Steps

ALN-TTR01

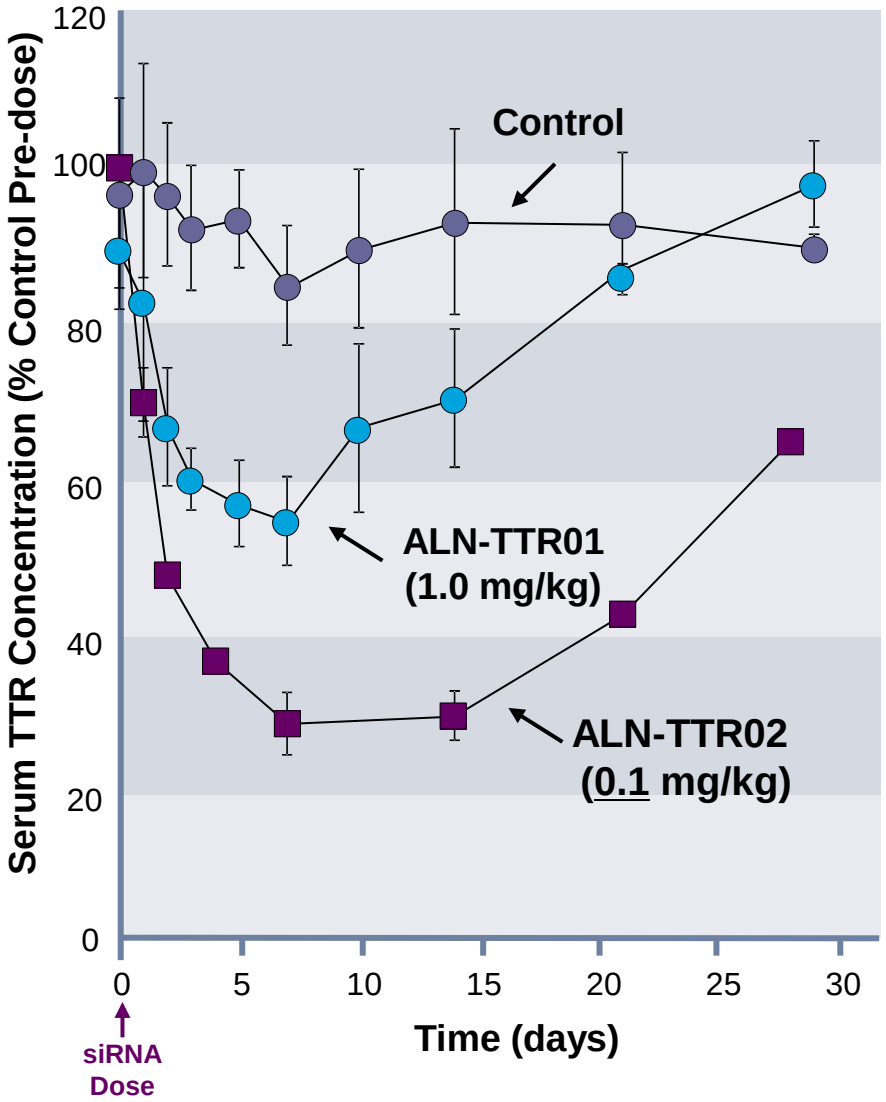
- Phase I study to be completed

ALN-TTR02

- 2nd generation LNP with >10-fold enhanced potency *in vivo*
- On-track for clinical development
  - » IND/IND equivalent ~YE ’11
  - » Planned development to commercialization

2nd Generation ALN-TTR Program

ALN-TTR02



Oligo Ther Soc., Sep 2011

ALN-TTR02 shows >10-fold improved *in vivo* efficacy in animal models

- ALN-TTR02 uses 2nd generation MC3 LNP formulation
- Single i.v. infusion; Serum TTR levels post-dosing
- Potent, dose-dependent, and durable TTR silencing
- On track to file IND/IND equivalent ~YE ’11

Acknowledgments

- ALN-TTR01 Clinical Investigators
  - David Adams, Pierre Lozeron
    - CHU Hospital Bicetre, Le Kremlin-Bicetre, France
  - Teresa Coelho, Ana Silva
    - Hospital Geral de Santo Antonio, Porto, Portugal
  - Philip Hawkins
    - National Amyloidosis Centre, Royal Free Hospital, London, U.K.
  - Tim Mant
    - Quintiles Drug Research Unit at Guy's Hospital, London, U.K.
  - Ole Suhr
    - Umea, Sweden
- TTR Program - Scientific Collaborators
  - Maria Saraiva
    - Institute of Cellular and Molecular Biology, Porto, Portugal
  - Yukio Ando and Hiro Jono
    - Kumamoto University, Japan
- Medpace
- Tekmira Pharmaceuticals
- Alnylam Pharmaceuticals

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Thank you