



Amyloidosis Support Group Meeting
ALN-TTR02 and ALN-TTRsc
Transthyretin Amyloidosis Programs

Jared Gollob, M.D.
October 26, 2013

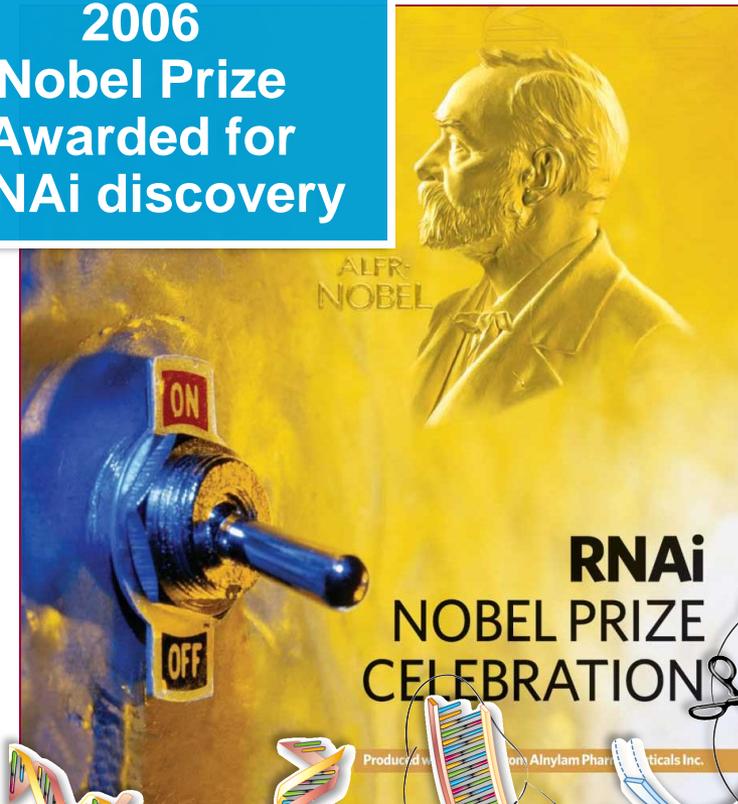
Anylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches, successfully demonstrate the efficacy and safety of our drug candidates, obtain, maintain and protect intellectual property, enforce our patents and defend our patent portfolio, obtain regulatory approval for products, establish and maintain business alliances; our dependence on third parties for access to intellectual property; and the outcome of litigation, as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

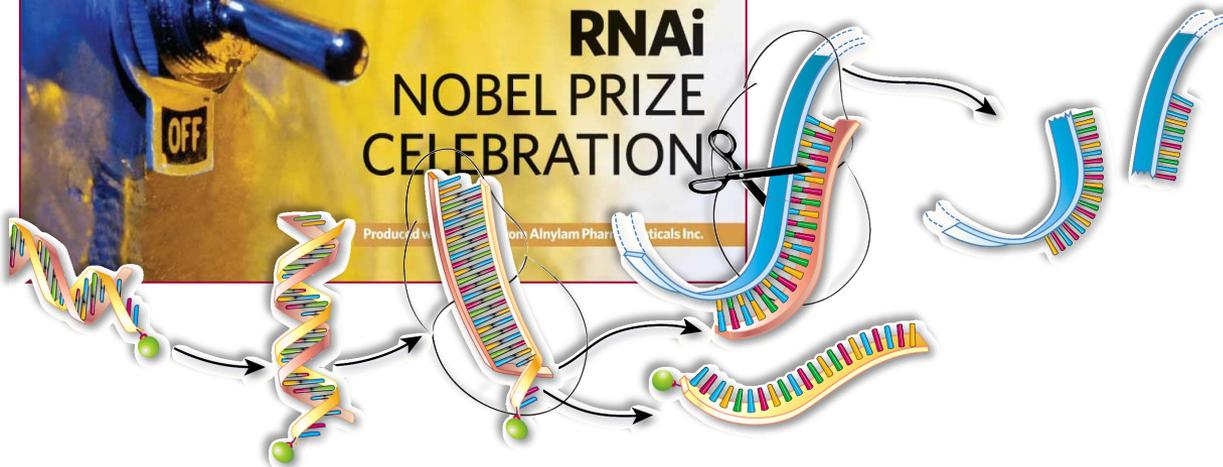
RNA Interference (RNAi)

A Breakthrough Discovery in Biology

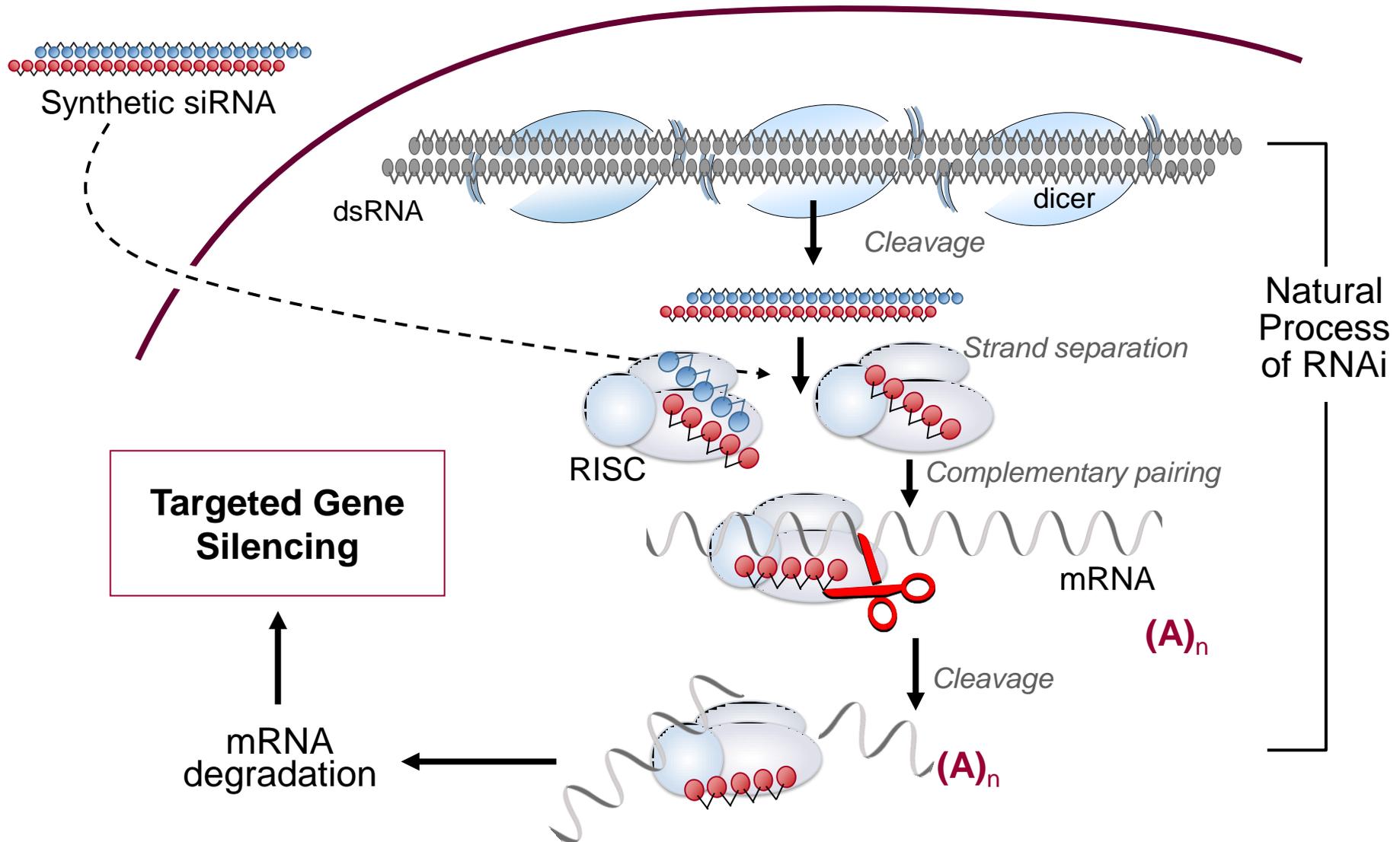
2006
Nobel Prize
Awarded for
RNAi discovery



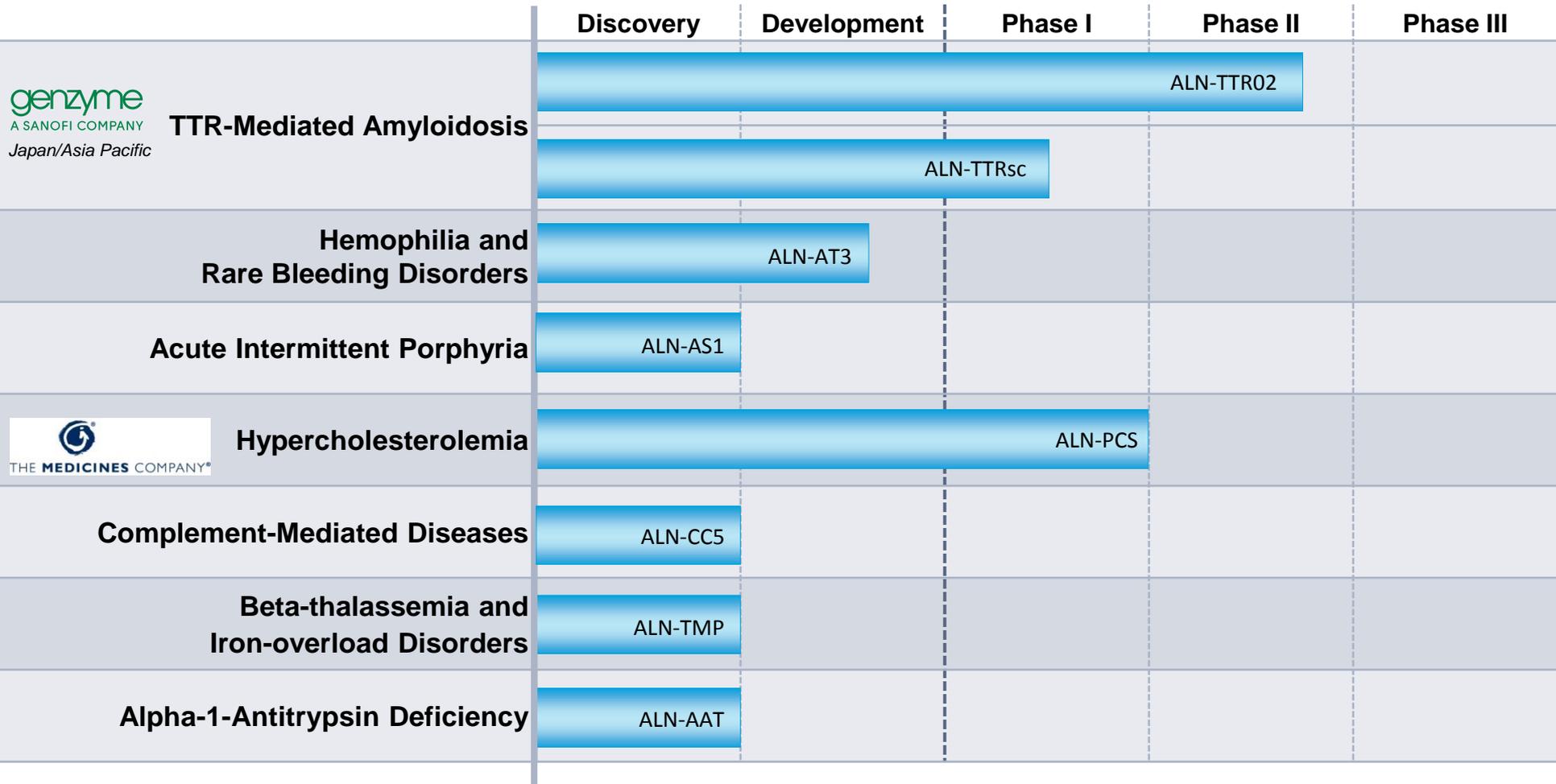
- “Silence” disease-causing genes
- Create whole new class of medicines



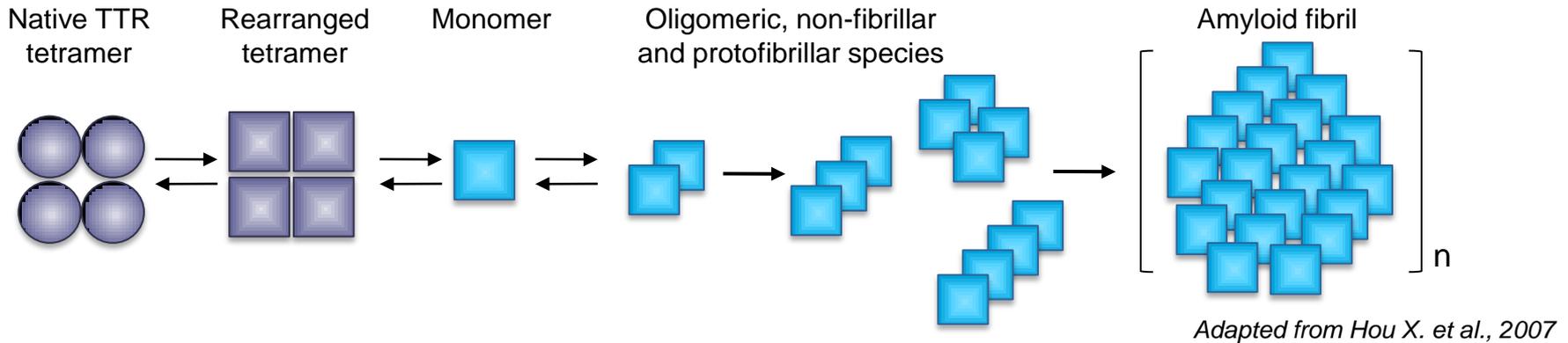
Therapeutic Approach to Harnessing RNAi



Alnylam Development Pipeline



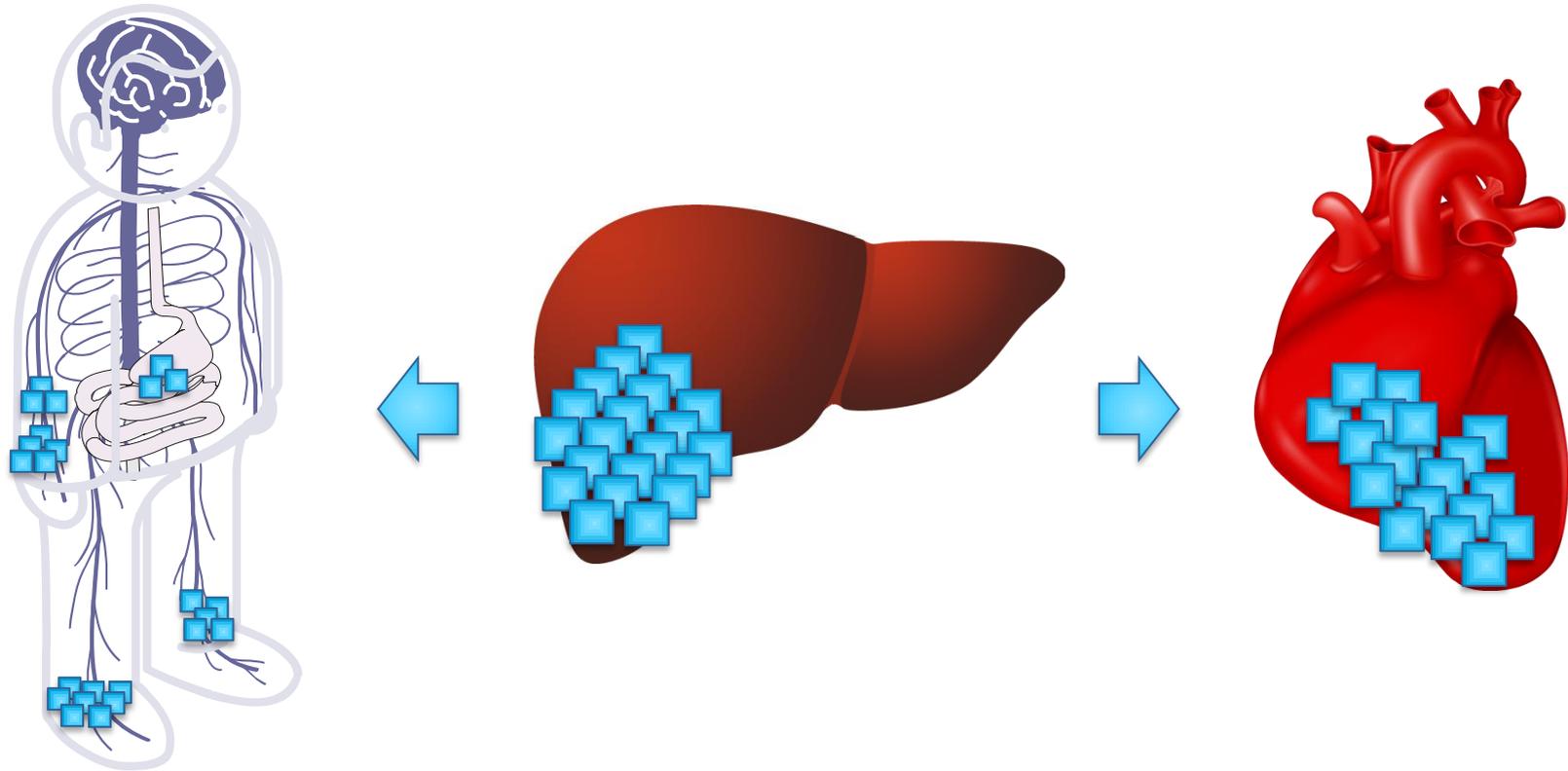
Transthyretin (TTR)



- TTR amyloidosis is a fatal, autosomal dominant, multisystem disease caused by abnormal extracellular deposits of TTR amyloid (mutant and WT)
 - » TTR is a primarily liver-expressed tetrameric protein that binds and transports serum retinol binding protein (RBP)/Vitamin A and minor fraction of serum thyroxine (T4)
 - » Mutations in TTR gene lead to destabilization of TTR tetramer with deposition of mutant and WT protein and fibril/amyloid formation in a variety of tissues, including:
 - Nerves (FAP): 10,000 patients, commonly associated with Val30Met (V30M) mutation
 - Heart (FAC): 40,000+ patients
 - » Therapeutic options for early stage FAP
 - Liver transplantation: eliminate mutant protein
 - Tafamidis: stabilize TTR tetramer

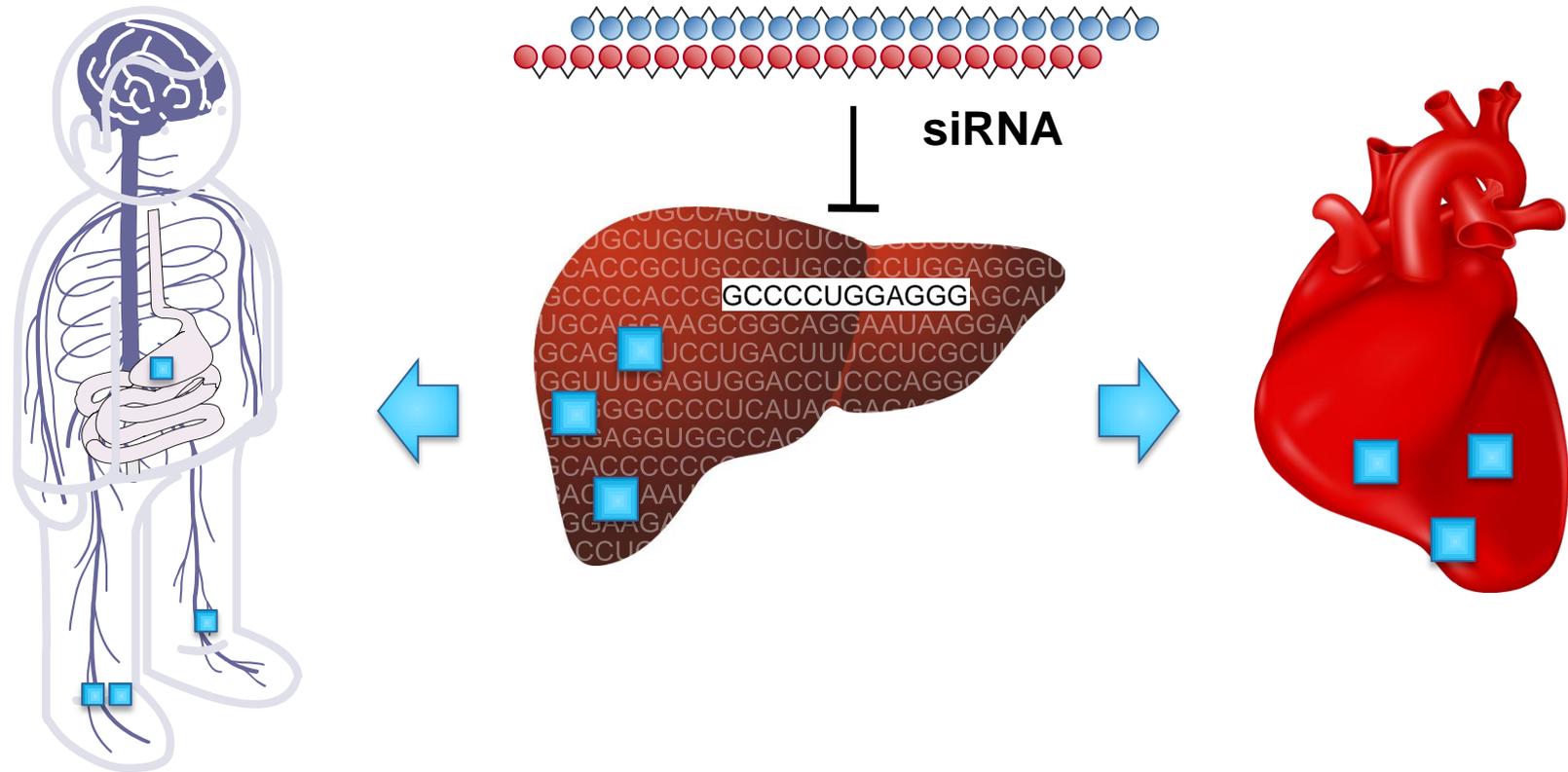
RNAi Therapeutic Approach

Blocking Liver Production of TTR



RNAi Therapeutic Approach

Blocking Liver Production of TTR

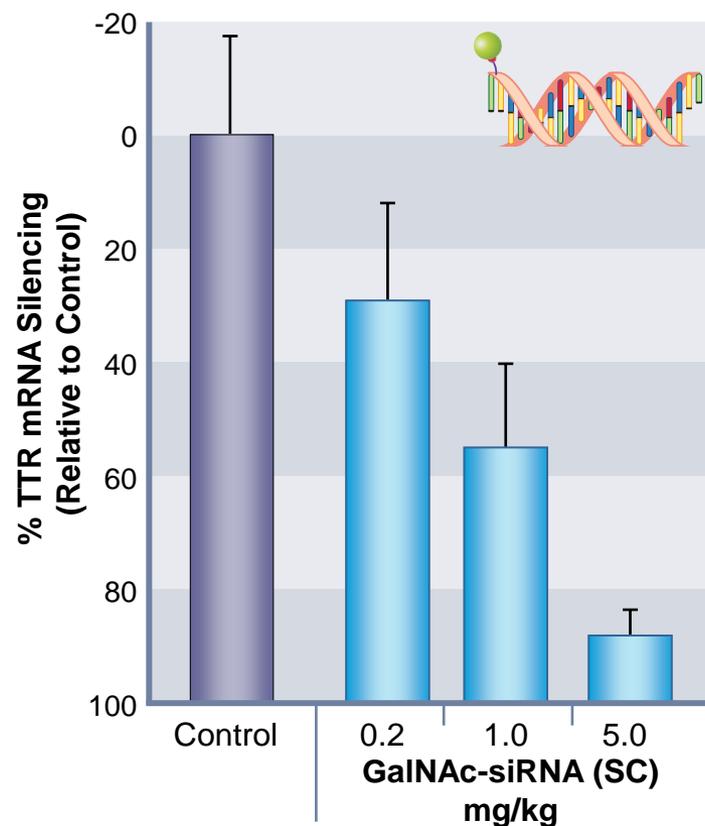
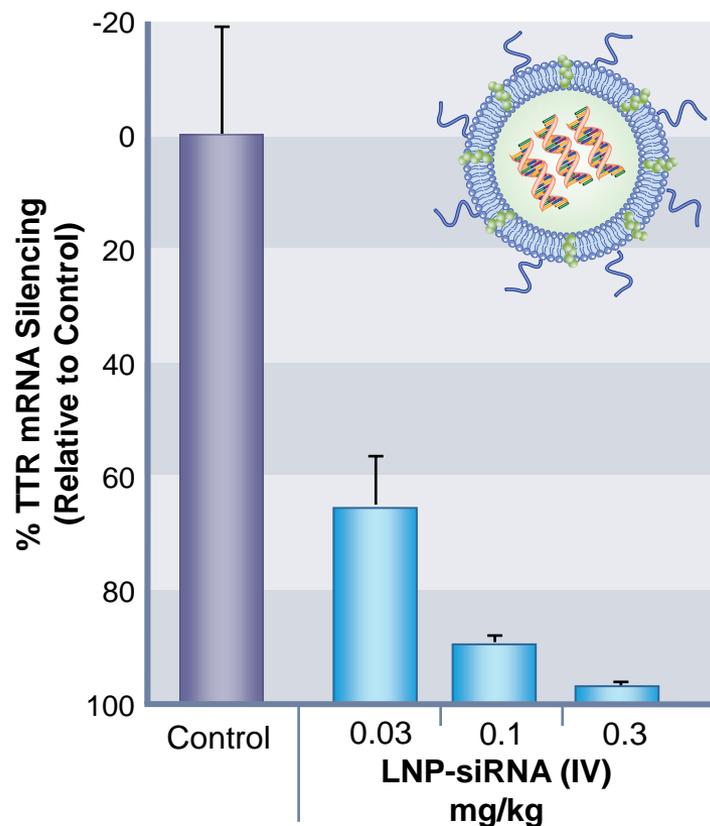


RNAi Delivery to Liver Solved

IV and SC Platforms: Pre-clinical

Enables advancement of innovative medicines to patients

- Potent, rapid, and durable target gene silencing with lipid nanoparticle (LNP) technology and IV dosing
- Potent, rapid, and durable target gene silencing with proprietary GalNAc-conjugate technology and SC dosing with wide therapeutic index



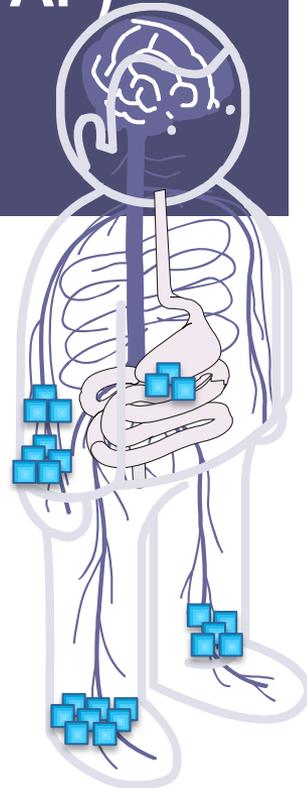
ALN-TTR Programs

For the Treatment of Transthyretin Amyloidosis

ALN-TTR02

Familial Amyloidotic Polyneuropathy (FAP)

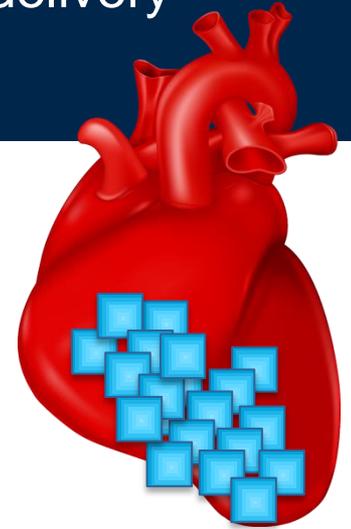
- Intravenous delivery



ALN-TTRsc

Familial Amyloidotic Cardiomyopathy (FAC)

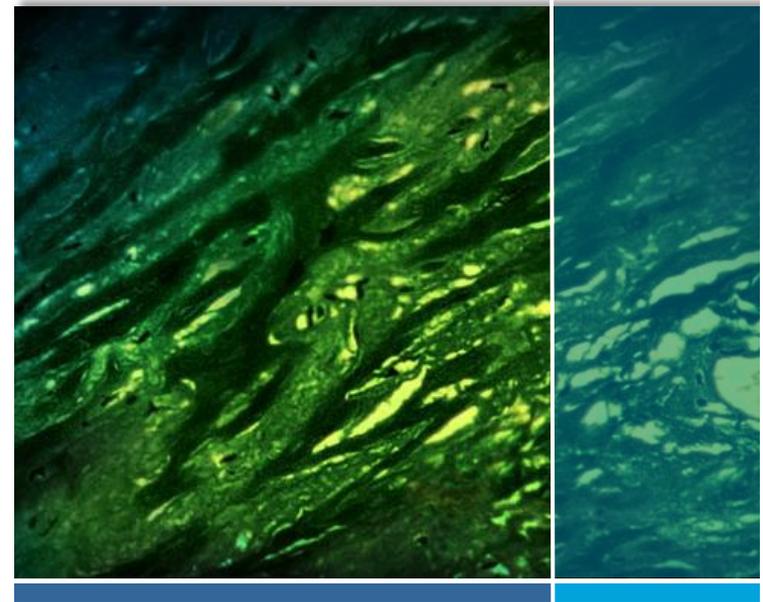
- Subcutaneous delivery



Familial Amyloidotic Polyneuropathy (FAP)

ALN-TTR02 in clinical development

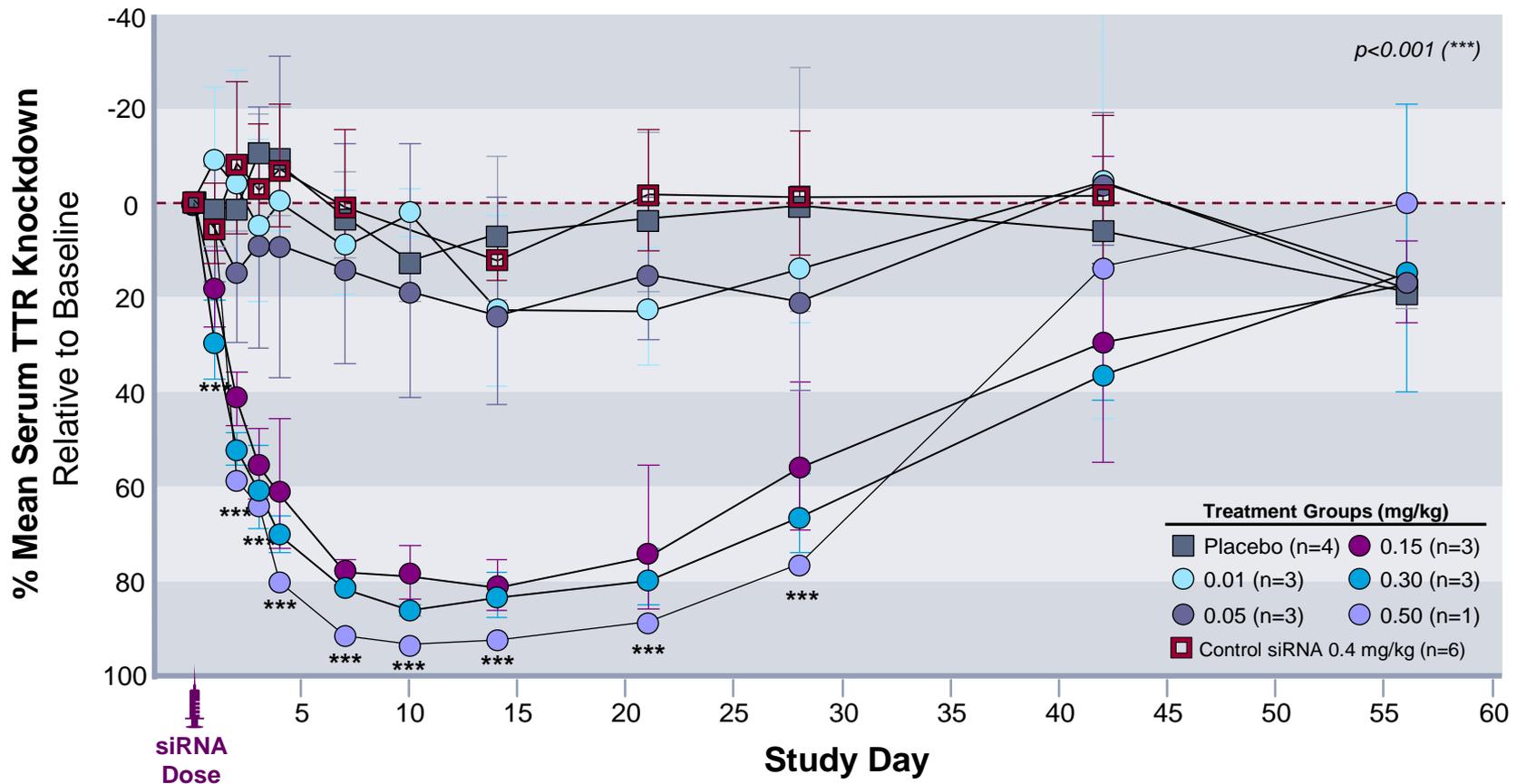
- Positive Phase I results in human volunteers
 - » Data published in *New England Journal of Medicine*
- Positive Phase II results in FAP patients
 - » Interim data at Peripheral Nerve Society, June 30, 2013
 - » Final data at FAP Symposium
 - November 10–13, 2013 in Rio de Janeiro, Brazil
- Open-label Phase II extension study initiated
 - » Includes clinical endpoints measured every 6 months
- Phase III start planned for late 2013
 - » Successful completion of long-term non-clinical studies supporting chronic dosing in humans



ALN-TTR02 Phase I Study Results

RNAi-Mediated TTR Knockdown

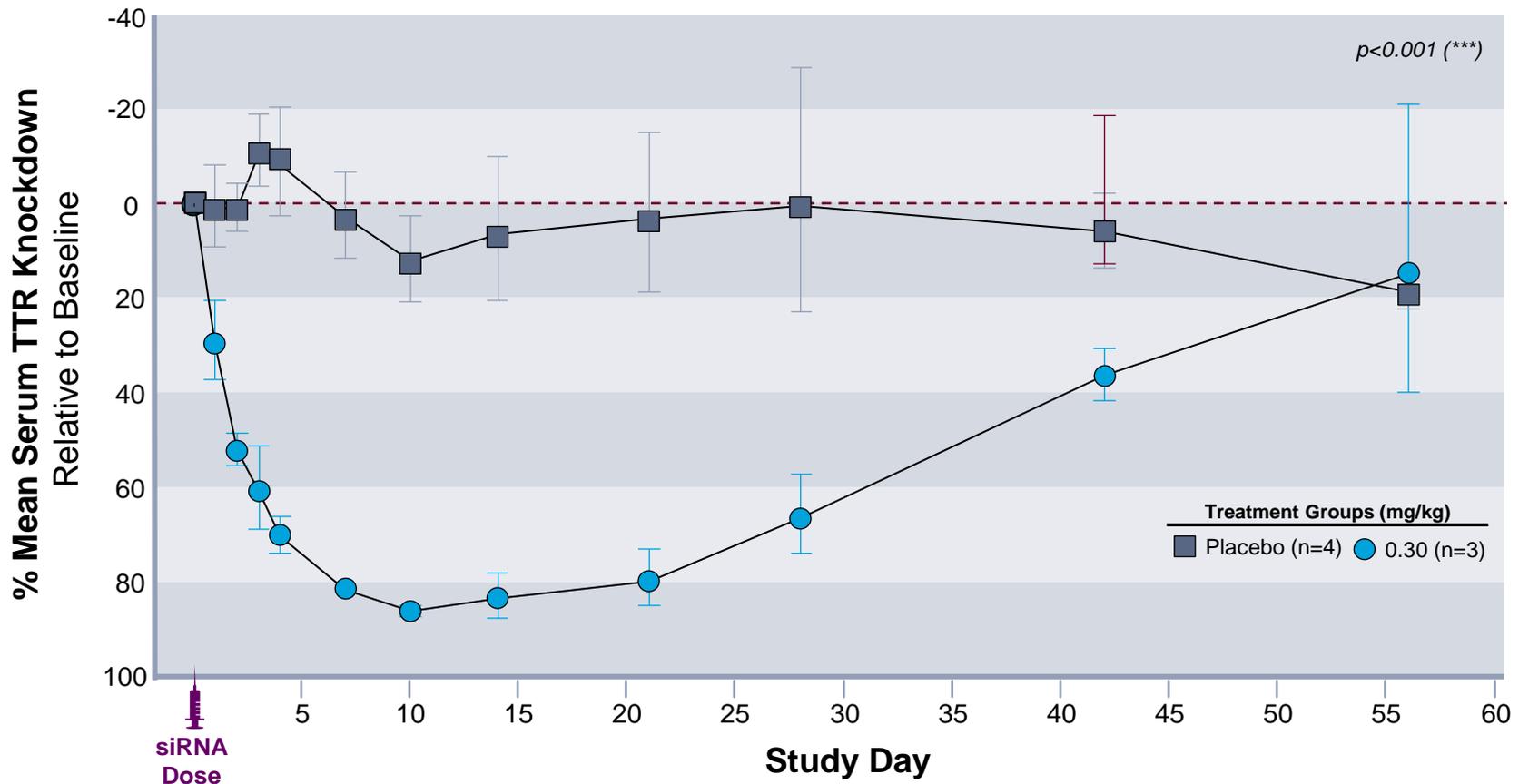
- Randomized, placebo-controlled, single-blind, single-dose escalation study in healthy volunteers (n=17)
- Up to 94% TTR knockdown at nadir and 77% knockdown sustained at 28 days
- RNAi mechanism of action confirmed by 5'RACE analysis of circulating mRNA



ALN-TTR02 Phase I Study Results

RNAi-Mediated TTR Knockdown

- Randomized, placebo-controlled, single-blind, single-dose escalation study in healthy volunteers (n=17)
- Up to 94% TTR knockdown at nadir and 77% knockdown sustained at 28 days
- RNAi mechanism of action confirmed by 5'RACE analysis of circulating mRNA

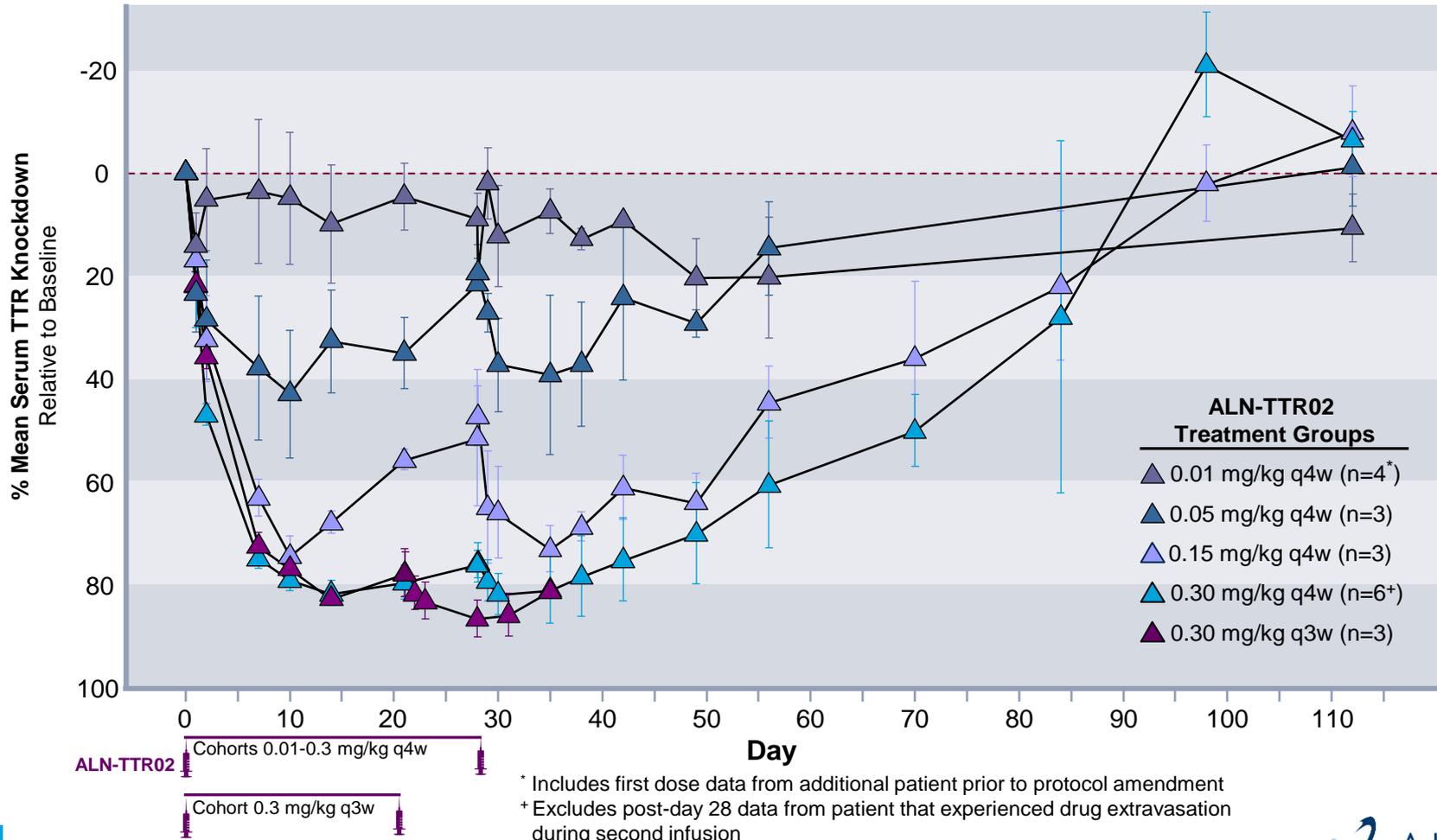


ALN-TTR02 Phase II Study Results

Dose Response and Duration of TTR Knockdown in FAP Patients

Knockdown of both wild-type and mutant TTR in ATTR patients

- Open label, multi-center, multi-dose, dose escalation study (n~30)
- Interim results (n=19) show up to 93% TTR knockdown; 83% and 87% mean TTR knockdown after 1st and 2nd doses in 0.3 mg/kg q3w cohort (p<0.001 vs. 0.01 mg/kg)

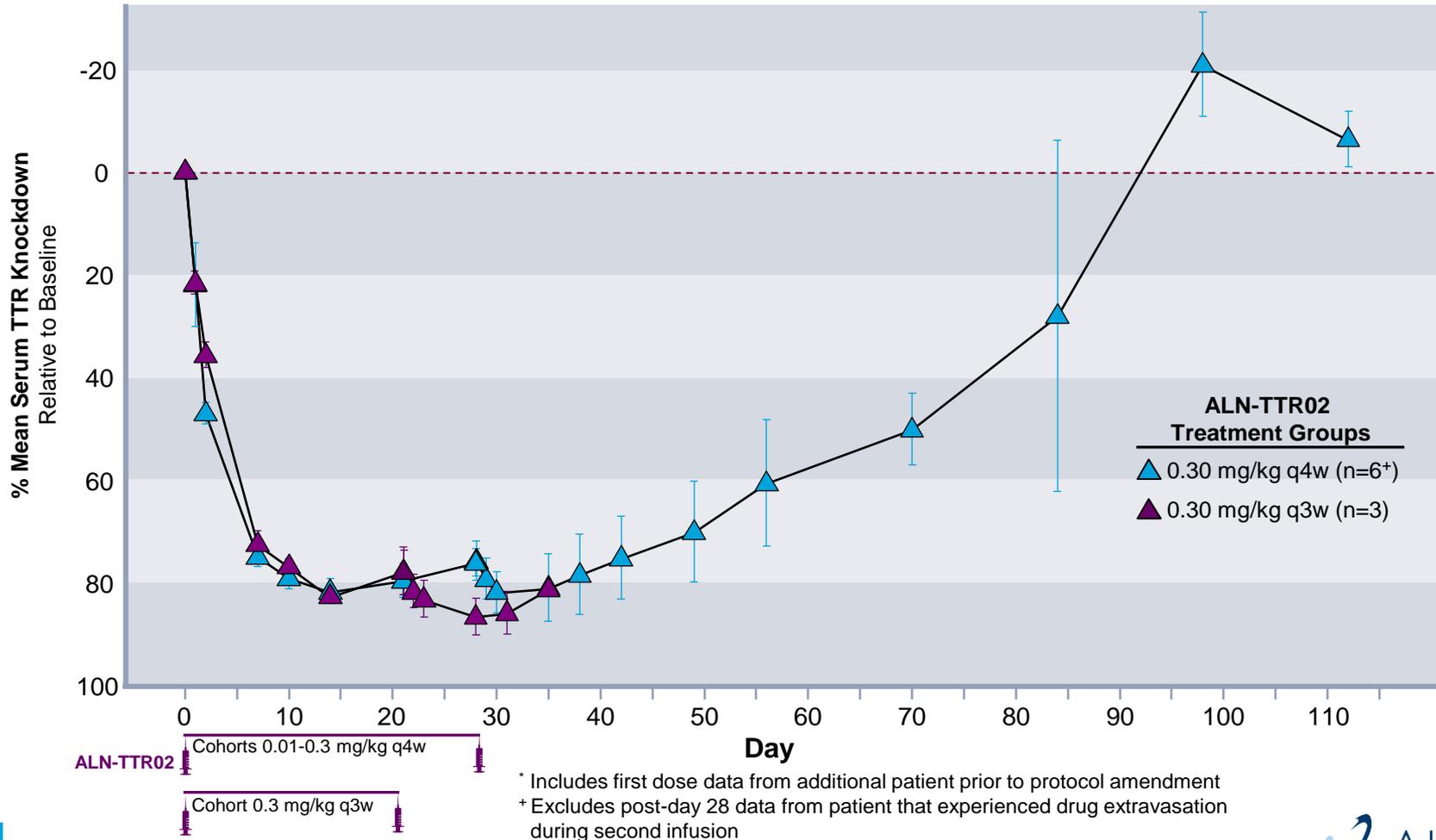


ALN-TTR02 Phase II Study Results

Dose Response and Duration of TTR Knockdown in FAP Patients

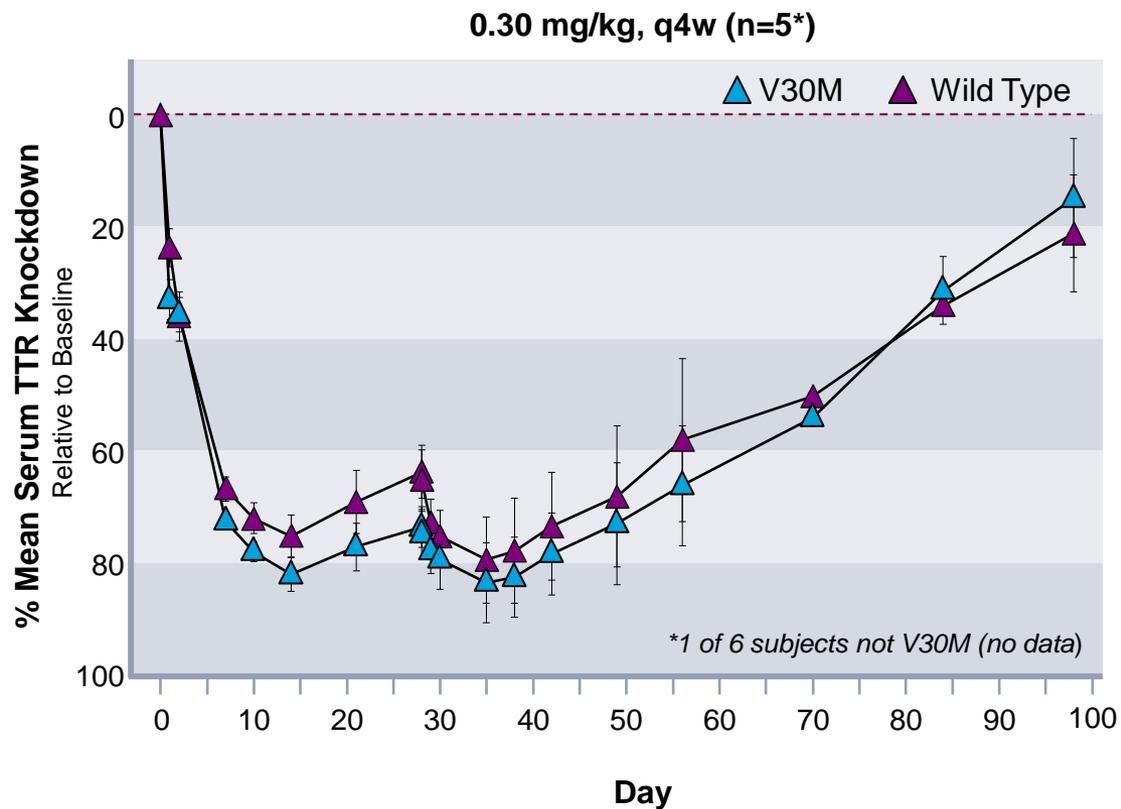
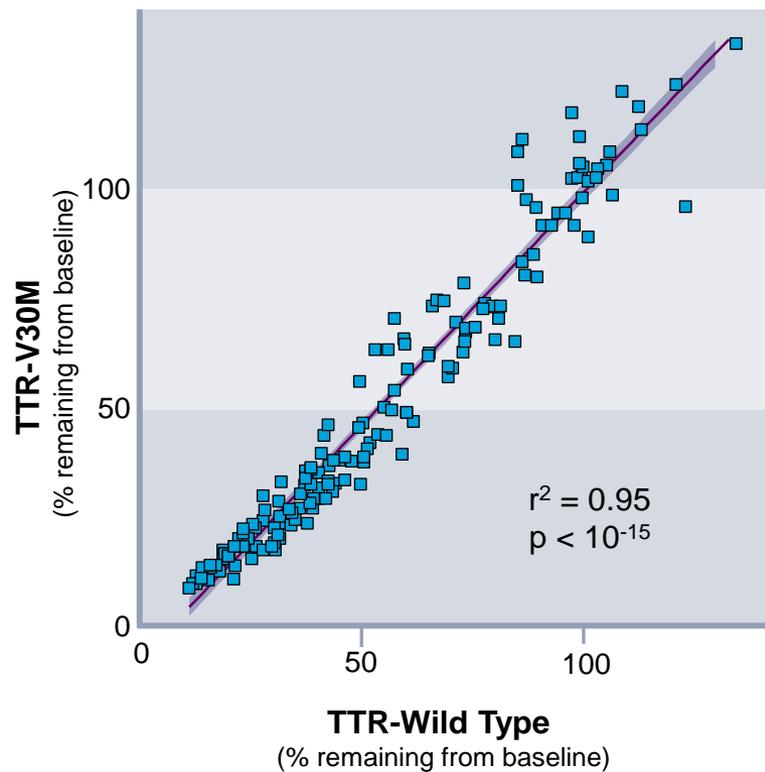
Knockdown of both wild-type and mutant TTR in ATTR patients

- Open label, multi-center, multi-dose, dose escalation study (n~30)
- Interim results (n=19) show up to 93% TTR knockdown; 83% and 87% mean TTR knockdown after 1st and 2nd doses in 0.3 mg/kg q3w cohort (p<0.001 vs. 0.01 mg/kg)



ALN-TTR02 Phase II Study Results

TTR Knockdown in V30M Patients: WT vs Mutant



ALN-TTR02 Safety and Tolerability

Results from Phase I and II Studies

Generally safe and well tolerated in human volunteers (n=17) with single dose¹

- All AEs associated with drug administration mild or moderate in severity
 - » Moderate infusion reaction in one subject at 0.5 mg/kg
- No SAEs, no discontinuations due to study drug
- No laboratory abnormalities
 - » LFTs, renal function, or hematologic parameters

Generally safe and well tolerated in ATTR patients (n=19) with multi-dose^{2, 3}

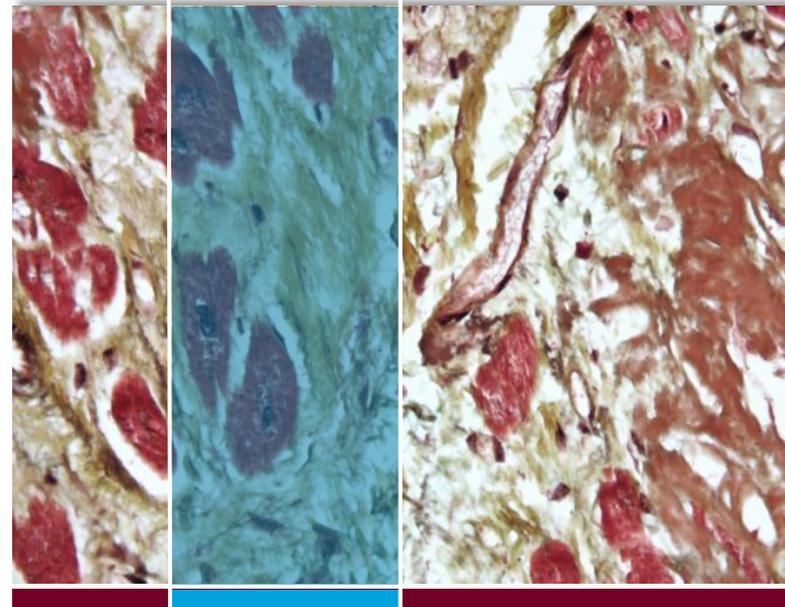
- All AEs associated with drug administration mild or moderate in severity
 - » Mild infusion reaction in one patient at 0.3 mg/kg
- Self-limiting episode of upper limb cellulitis due to drug extravasation at infusion site in a patient with poor IV access (SAE)
- No laboratory abnormalities
 - » LFTs, renal function, or hematologic parameters
- Additional safety data reported at PNS meeting
 - » No additional AEs reported in 6 additional patients dosed at 0.3 mg/kg with simplified/reduced pre-medication regimen

¹Coelho et al., *N Engl J Med*;369:819-29 (2013);

²Peripheral Nerve Society, June 2013; ³Data as of PNS presentation date

ALN-TTRsc in clinical development

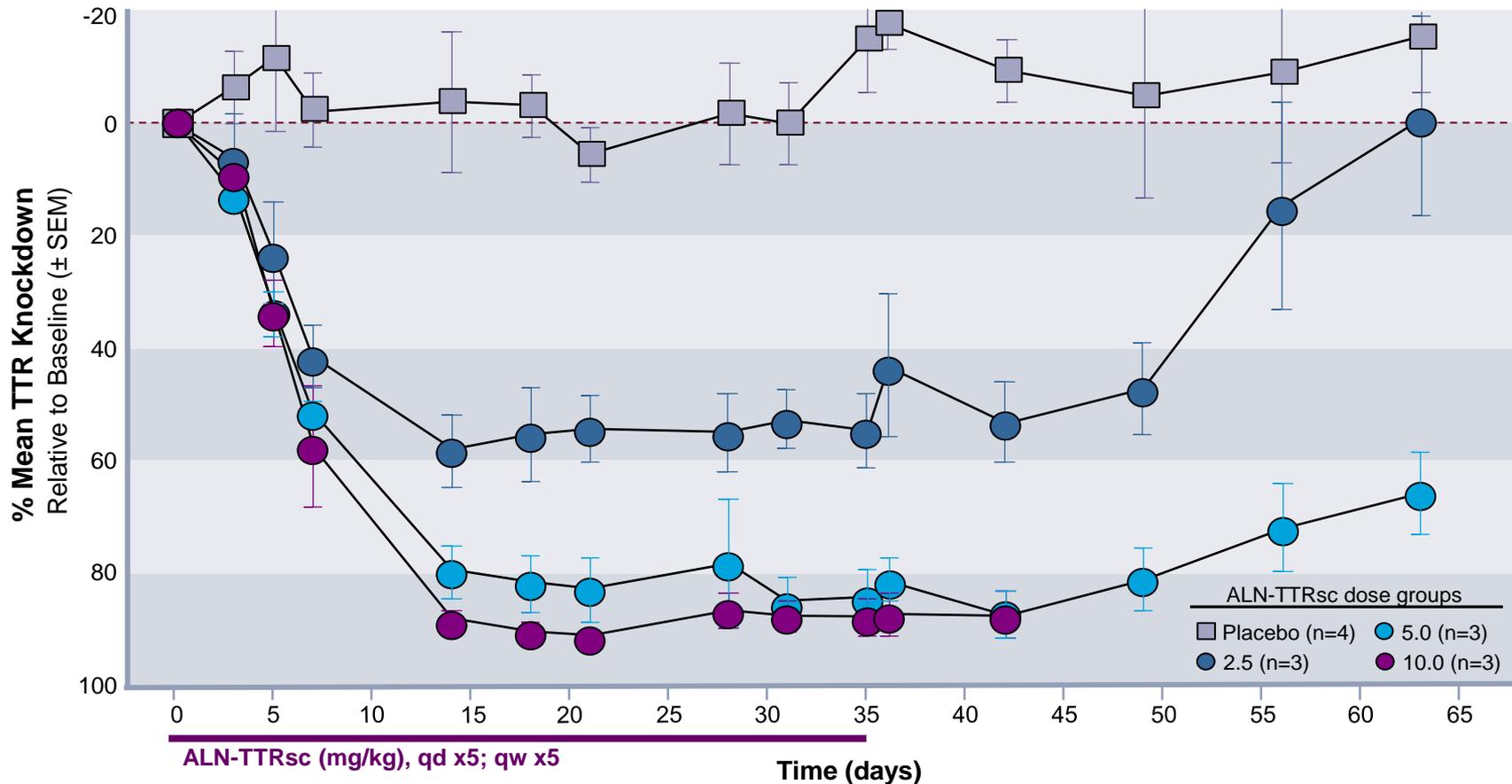
- Positive Phase I study results
 - » Normal healthy volunteer study in UK
 - » Data presented at Annual Scientific Meeting of Heart Failure Society of America, September 23, 2013
- Pilot Phase II study start expected in late 2013
- Phase III start planned for 2014



ALN-TTRsc Phase I Study

TTR Knockdown in Multi-Dose Cohorts

- Statistically significant knockdown of serum TTR at all doses evaluated ($p < 0.01$)
- Consistent level of TTR knockdown with weekly dosing; durable effects lasting weeks after last dose
- Mean TTR knockdown of 87.5% and 92.4% at 5.0 and 10.0 mg/kg, respectively
 - » Maximum TTR knockdown of up to 94%



ALN-TTR02 Safety and Tolerability

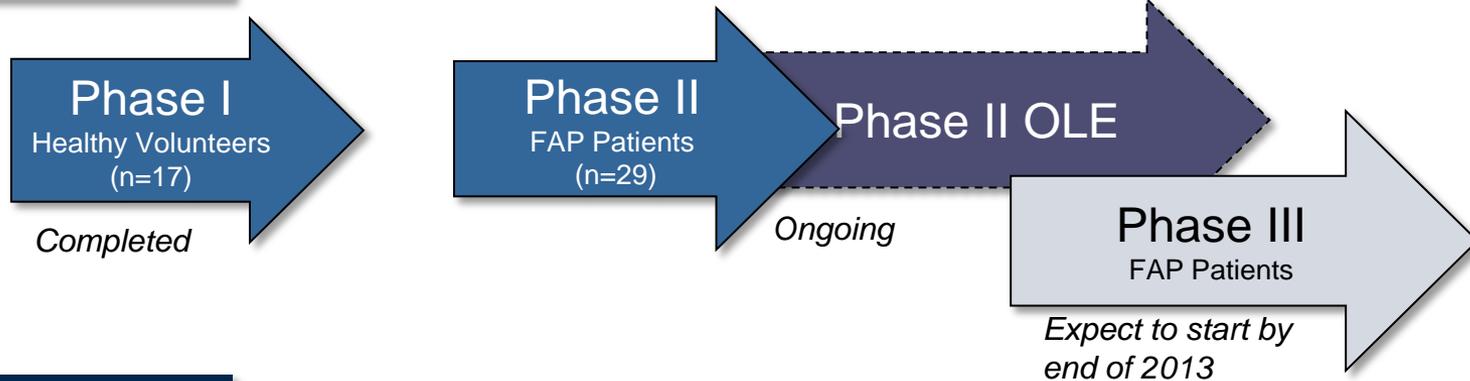
Results from Phase I Study

Multiple doses of ALN-TTRsc generally safe and well tolerated

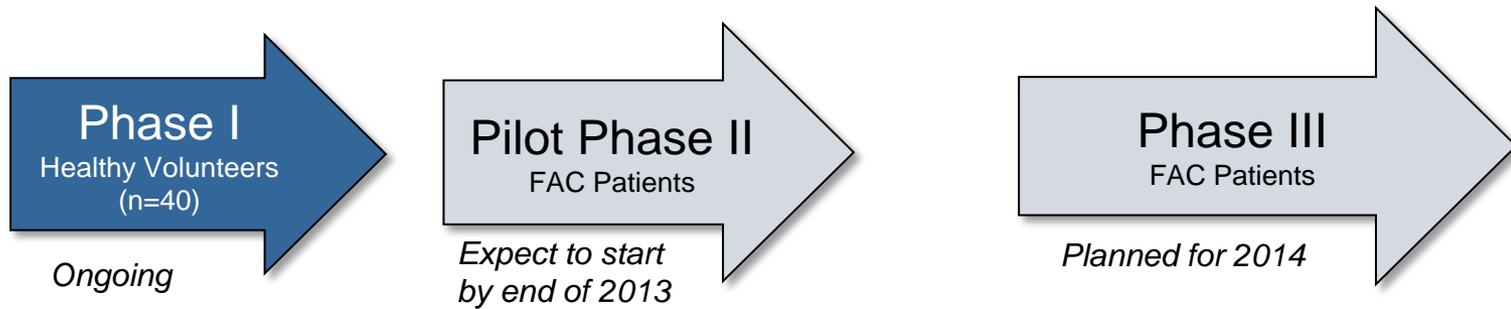
- Transient (<2 h), clinically mild erythema at injection site in minority of subjects
- No abnormalities in liver function tests, renal function, or hematologic parameters
- No evidence of inflammation (cytokines, CRP)

ALN-TTR Programs in Clinical Development

ALN-TTR02/FAP



ALN-TTRsc/FAC



Acknowledgments

ALN-TTR02 Phase II Investigators

- David Adams
 - » Hospital de Bicetre, Le Kremlin-Bicetre, France
- Teresa Coelho, Ana Silva
 - » Hospital de Santo Antonio, Porto, Portugal
- Ole Suhr
 - » Umea University Hospital, Umea, Sweden
- Isabel Conceicao
 - » Centro Hospitalar Lisboa Norte-Hospital de Santa Maria, Lisboa, Portugal
- Juan Buades
 - » Hospital Son Llatzer, Palma de Mallorca, Spain
- Josep Campistol
 - » Hospital Clinic Barcelona Instituto, Barcelona, Spain
- Jean Pouget
 - » Hôpital de La Timone, Marseille, France
- Hartmut Schmidt
 - » University Hospital of Muenster, Muenster, Germany
- Marcia Waddington-Cruz
 - » Hospital Universitário, Rio de Janeiro, Brazil
- John Berk
 - » Boston University, Boston, MA USA

TTR Program - Scientific Collaborators

- Maria Saraiva
 - » Institute of Cellular and Molecular Biology, Porto, Portugal
- Yukio Ando and Hiro Jono
 - » Kumamoto University, Japan

Our Commitment to the Treatment of Transthyretin Amyloidosis

We understand the impact that FAP or FAC can have on you and your family. Improving the understanding and treatment of this condition is one of our highest commitments.

Help us continue learning about your experience as an ATTR patient
<https://www.surveymonkey.com/s/ATTRPatientSurvey>

Keep up to date with status of our programs
www.Alnylam.com/connect-attr