Delivering on RNAi Therapeutics: Patisiran and Beyond

TIDES, May 8, 2018

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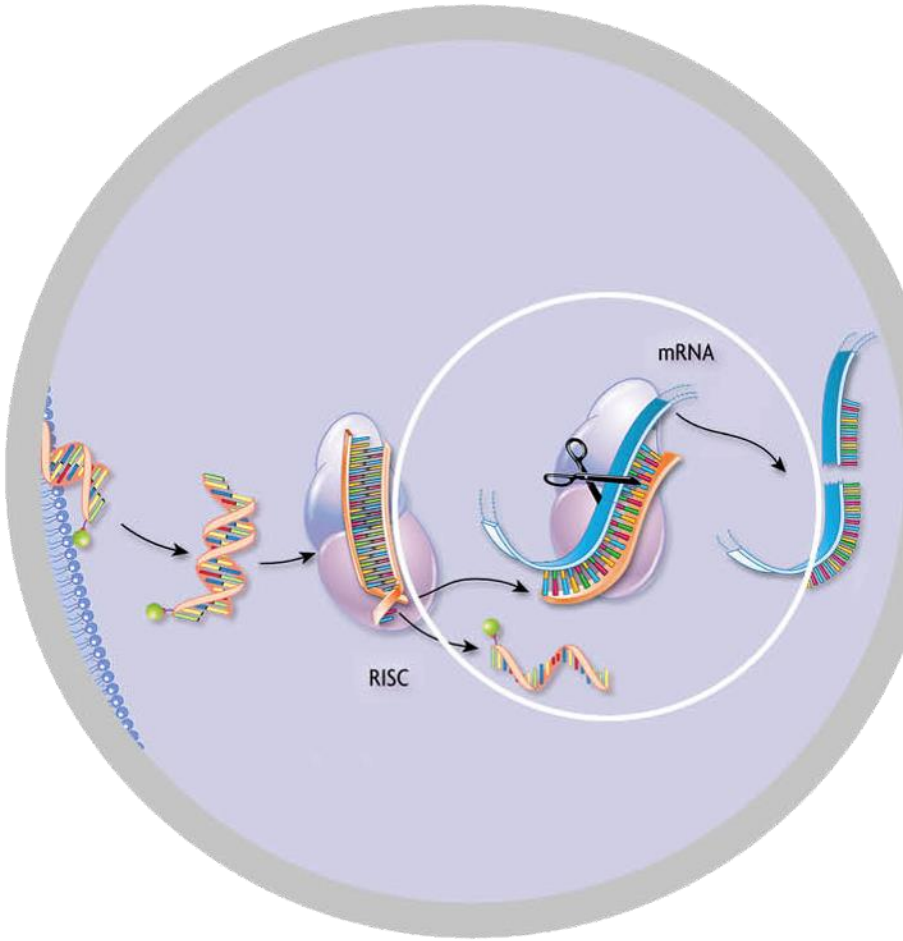
Alnylam Forward Looking Statements

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 and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent report on Form 10-K 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.

RNAi Therapeutics: New Class of Innovative Medicines

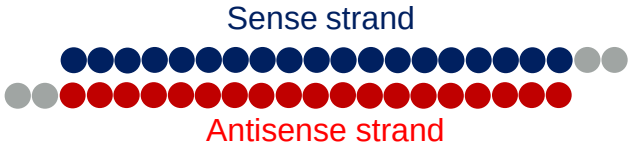
Clinically Proven Approach with Transformational Potential

- Nobel Prize-winning science
- Silence any gene in genome
- Potent and durable mechanism of action
- Product engine for sustainable pipeline
- Now entering commercial stages



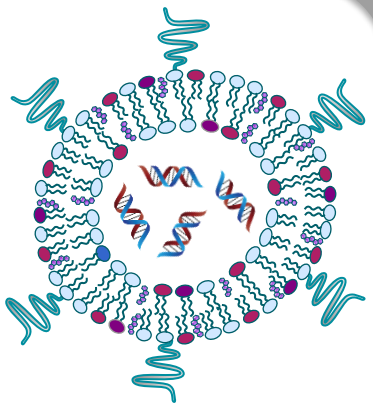
Addressing Delivery Challenge

Alnylam Platforms for Functional siRNA Delivery to Target Tissue

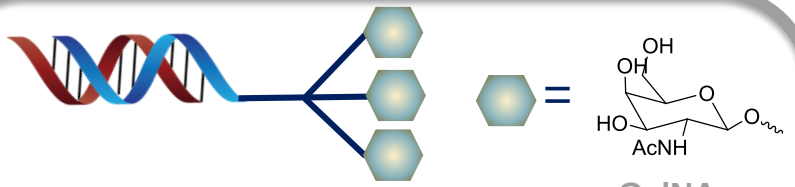


Lipid Nanoparticles (LNPs)

- Multi-component lipid formulation (~100 nm in size)
- Encapsulated siRNA
- Highly efficient for targeted delivery to liver
- Administered intravenously (IV)
- Clinically validated



Patisiran



GalNAc

GalNAc-siRNA Conjugates

- Single chemical entity
- GalNAc ligand conjugated to extensively modified siRNA
- Targeted delivery to liver
- Administered subcutaneously (SC)
- Clinically validated

Complementary Approaches for Efficient siRNA Delivery to Liver

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Alnylam R&D Strategy

Building a Pipeline of Potentially Transformative Medicines

Genetically validated, liver-expressed target gene

Biomarker for POC in Phase 1

Definable path to approval and patient access

Alnylam Clinical Development Pipeline

Focused in 3 Strategic Therapeutic Areas (STARs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Hepatic Infectious Diseases

		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	EARLY STAGE *(IND or CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[2]	COMMERCIAL RIGHTS
Patisiran	*Hereditary ATTR Amyloidosis*	✓	✓			●	Global
Givosiran	*Acute Hepatic Porphyrias*	✓	✓		● → 2018		Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*	✓			●		15-30% Royalties
Inclisiran	*Hypercholesterolemia*	✓			●		Milestones & up to 20% Royalties
ALN-TTRsc02	*ATTR Amyloidosis*	✓		● → 2018			Global
Lumasiran	*Primary Hyperoxaluria Type 1*	✓	✓	● → 2018			Global
Cemdisiran	*Complement-Mediated Diseases*	✓		●			Global

[1]POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2]Includes marketing application submissions

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Extensive Human Safety Experience

Encouraging Results to Date

Number of Programs	Number of Clinical Studies	Total Patients or Volunteers Dosed	Greatest Duration of Exposure
>10	>25	>1200	>48 months

Minimal platform related findings*

- Low incidence (2.9%) of generally mild, asymptomatic, reversible LFT increases >3x ULN
- Injection site reactions (24%) generally mild, transient and rarely led to discontinuation
  - No events of ulceration, necrosis or tissue damage
- One report of anaphylaxis (<0.05%) in patient with prior history of atopy**
  - No anti-drug antibodies (ADA) detected against GalNAc-siRNA

Revusiran program discontinued in October 2016

- Extensive evaluation showed no clear reason for mortality imbalance
- While possible that imbalance was a chance finding, role for revusiran cannot be excluded
- Revusiran exposure is 12-140 times greater than other pipeline programs

Favorable emerging profile for ESC-GalNAc platform compared with competing oligo platforms†

- No evidence of thrombocytopenia, renal toxicity, or systemic inflammatory effects

*Experience as of December 2017 – Data estimated based on available safety data
** Givosiran OLE study, reported April 2018
† Not based on direct comparative studies

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Agenda

- RNAi Therapeutics for hATTR Amyloidosis
- RNAi Therapeutics for Other Rare and Common Diseases
- New Frontiers for RNAi Therapeutics

Dane
Living with hATTR Amyloidosis

Hereditary ATTR (hATTR) Amyloidosis

Patisiran and ALN-TTRsc02

Description

Mutations in TTR gene lead to deposition of misfolded protein as amyloid, causing multi-system disease manifestations[1]

Significant morbidity and fatal within

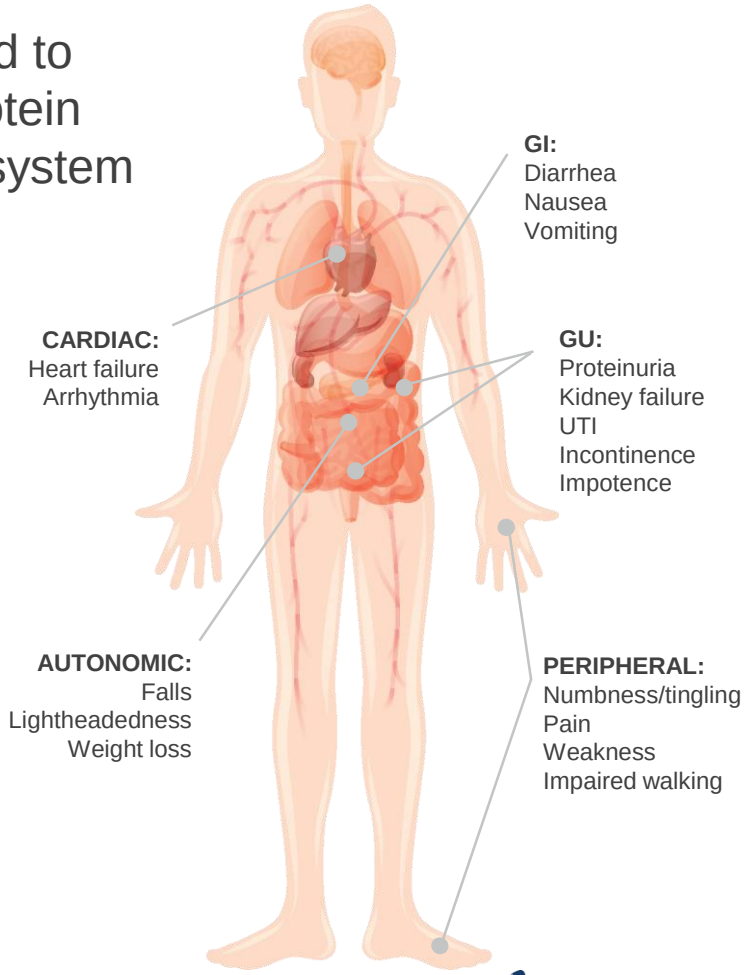
2-15

years from symptom onset

Patient Population*

~50,000

worldwide



[1]Coelho T, et al. *N Engl J Med.* 2013;369(9):819-829
*Ando *et al., Orphanet J Rare Dis,* 2013; Ruberg *et al., Circulation,* 2012

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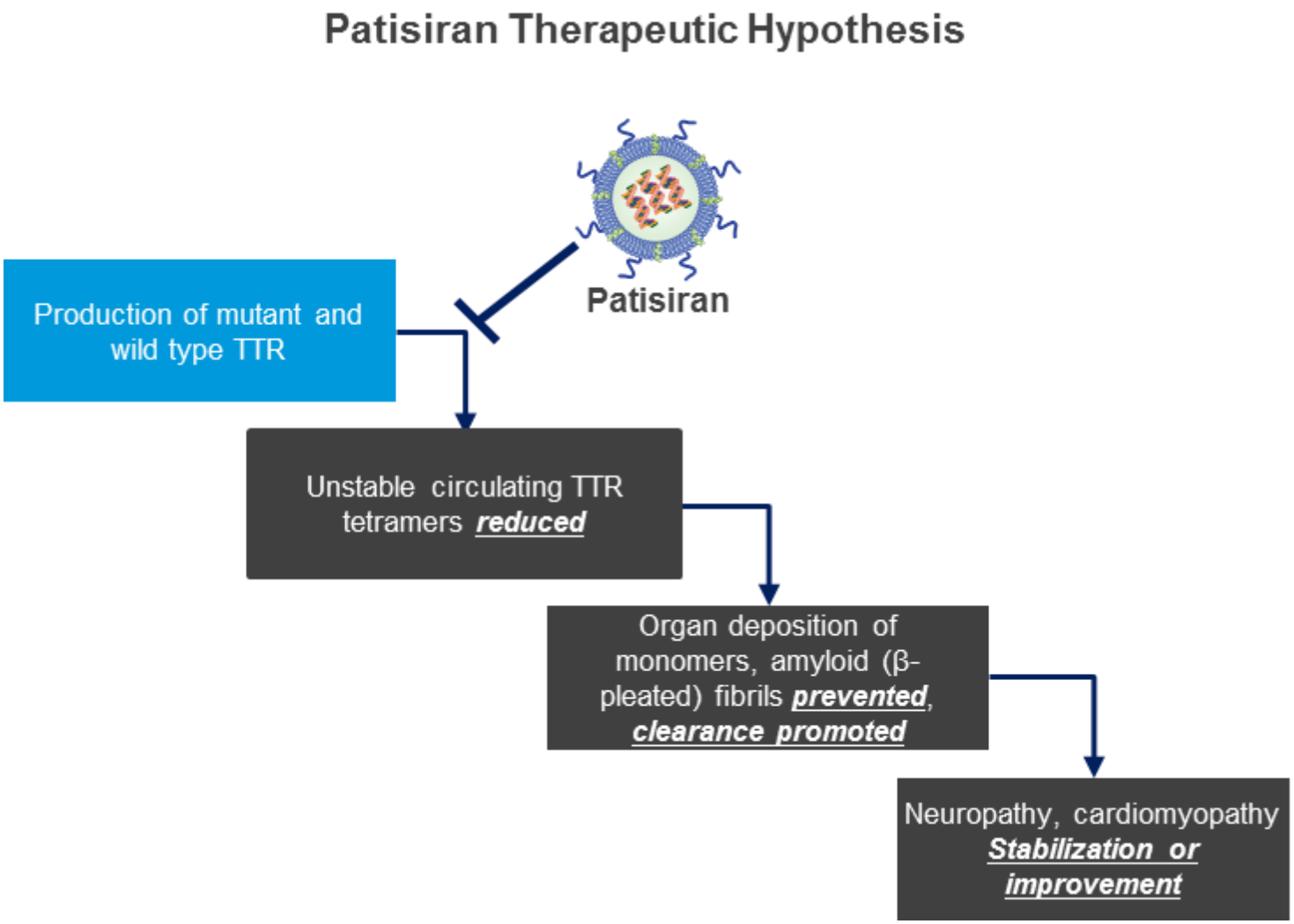
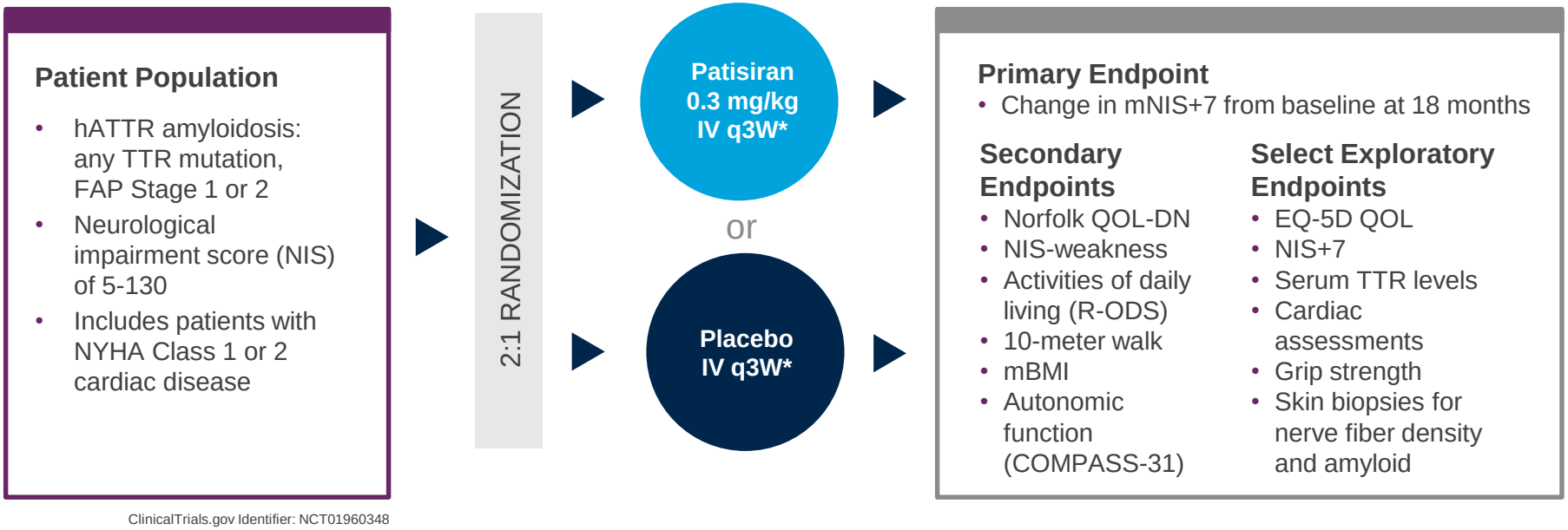
TTR Knockdown for hATTR Amyloidosis



APOLLO Phase 3 Study Design

Randomized, Double-Blind, Placebo-Controlled Study in hATTR Amyloidosis Patients with Polyneuropathy



ClinicalTrials.gov Identifier: NCT01960348

*To reduce likelihood of infusion-related reactions, patients received following premedication or equivalent at least 60 min before each study drug infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers.

99% of patients who completed APOLLO study enrolled in Global OLE study

OLE, open-label extension; ClinicalTrials.gov Identifier: NCT02510261
Adams D, et al. BMC Neurology 2017

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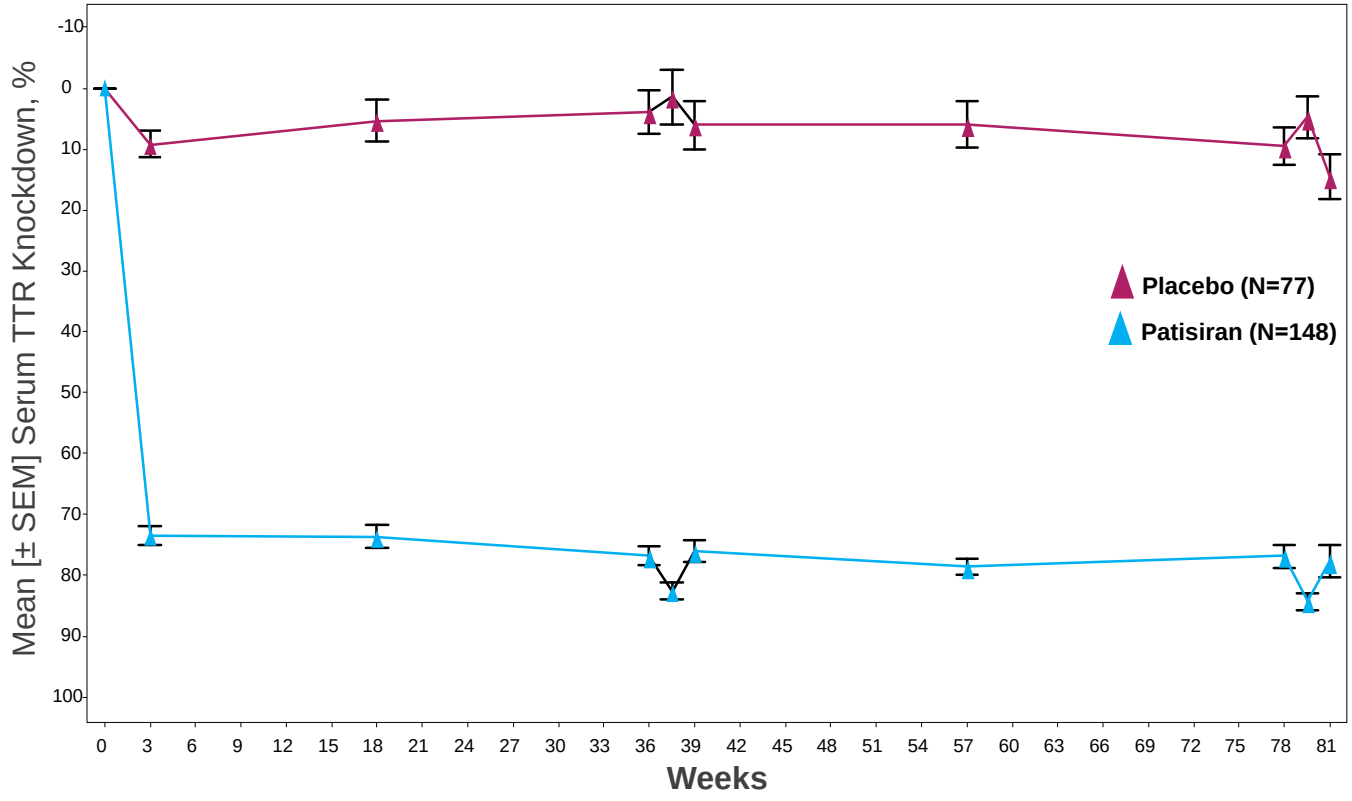
APOLLO Phase 3 Study Results

Serum TTR Knockdown

87.8% mean max serum TTR knockdown from baseline for patisiran over 18 months



TTR Change	Change from Baseline at 9 Months		Change from Baseline at 18 Months	
	Placebo (N=77)	Patisiran (N=148)	Placebo (N=77)	Patisiran (N=148)
Mean (SEM) Serum TTR Knockdown	1.5% (4.47)	82.6% (1.36)	4.8% (3.38)	84.3% (1.48)

SEM, standard error of the mean

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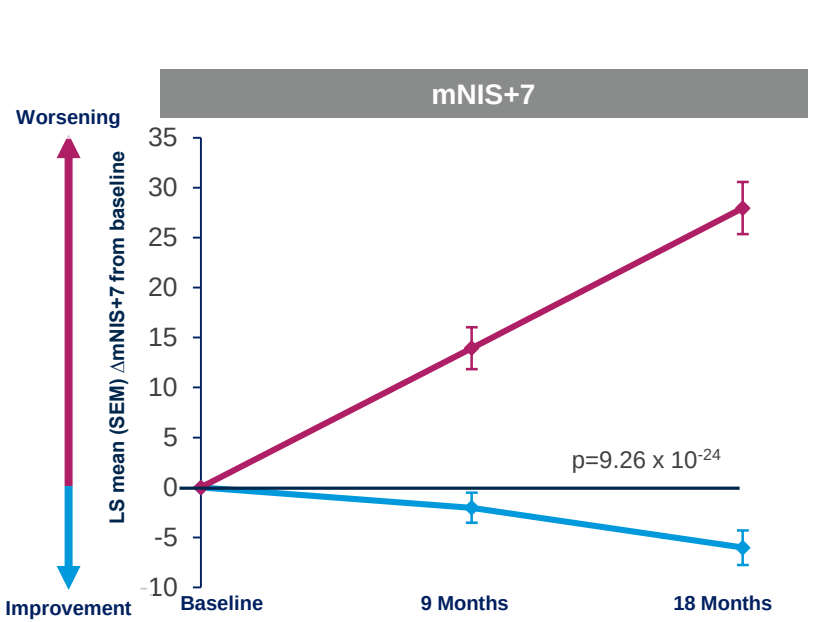
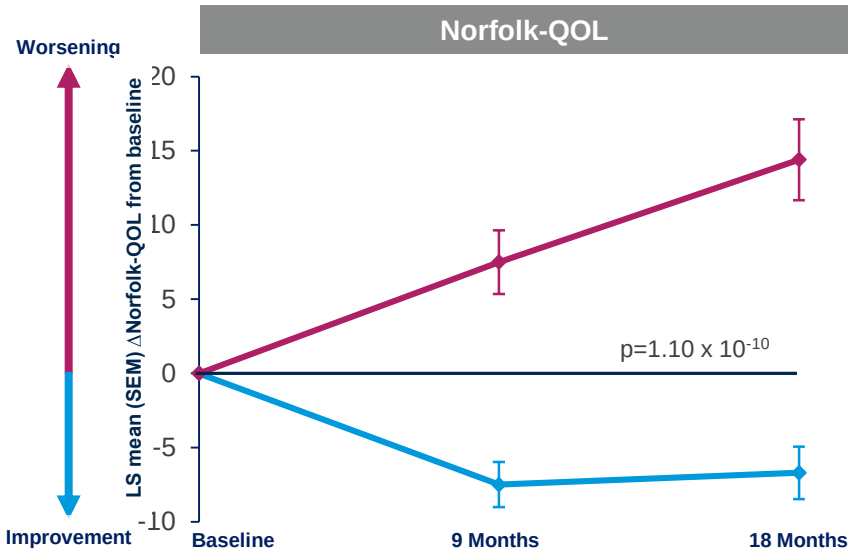
APOLLO Phase 3 Study Results

Patisiran Met Primary and all Secondary Endpoints





At 18 months

- -6.0 point change relative to baseline
- 34.0 point difference relative to placebo
- 56.1% of patients improved*

At 18 months

- -6.7 point change relative to baseline
- 21.1 point difference relative to placebo
- 51.4% of patients improved*

All secondary endpoints encompassing QOL, walk speed, activities of daily living and autonomic dysfunction met

Adams *et al*., EU-ATTR Meeting, Nov 2017
*Improvement defined as patients with <0 point increase from baseline to 18 months

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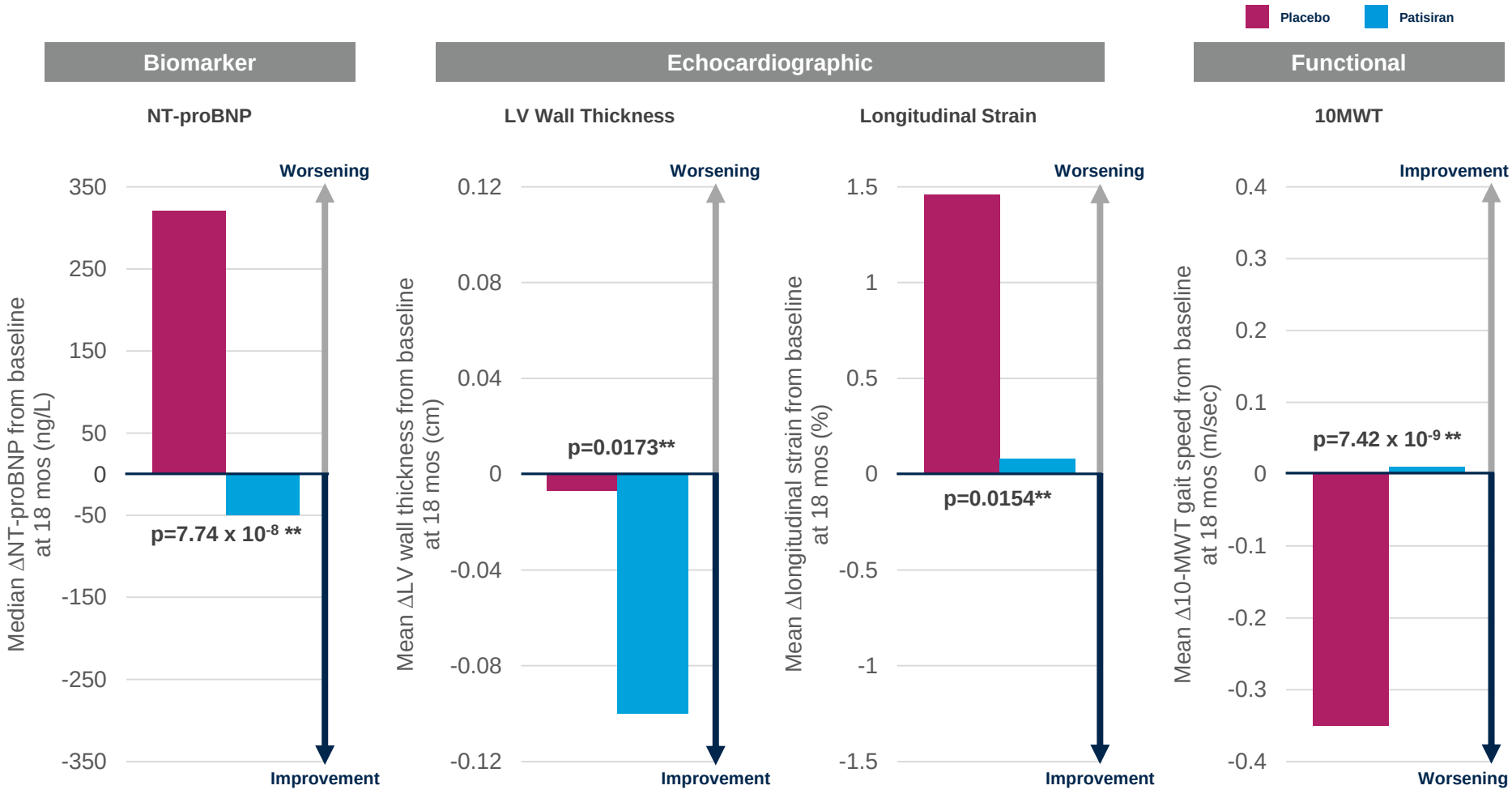
APOLLO Phase 3 Study Results

Patisiran Met Key Exploratory Endpoints in Cardiac Subpopulation*



Adams *et al*., EU-ATTR Meeting, Nov 2017

*Cardiac subpopulation: patients with pre-existing cardiac amyloid involvement without confounding medical conditions (i.e., patients with baseline LV wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history)

**p-values are nominal

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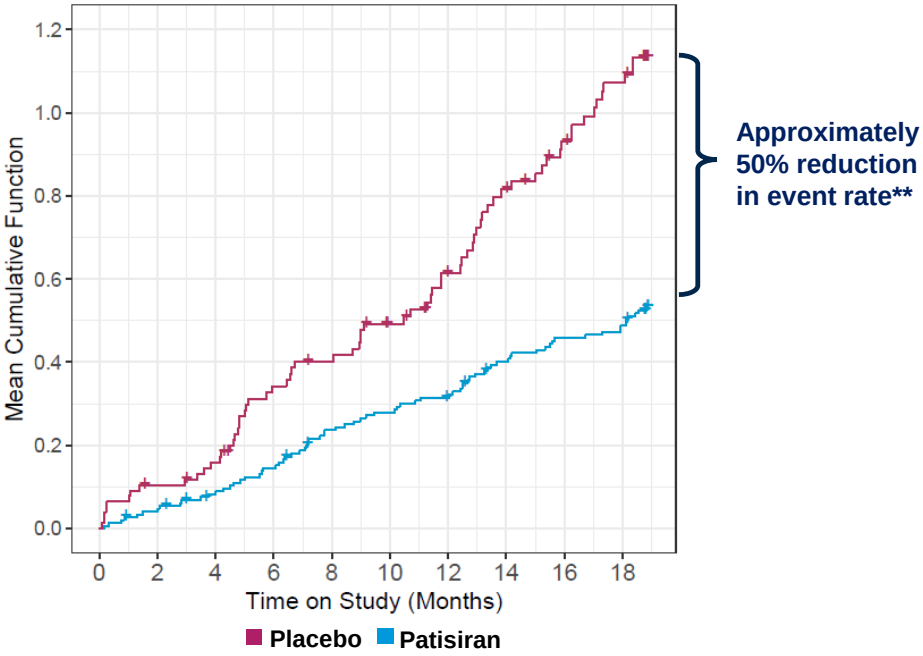
APOLLO Phase 3 Study Results

Recurrent Hospitalization and Death Events by Treatment Arm (Post-Hoc Analysis)*

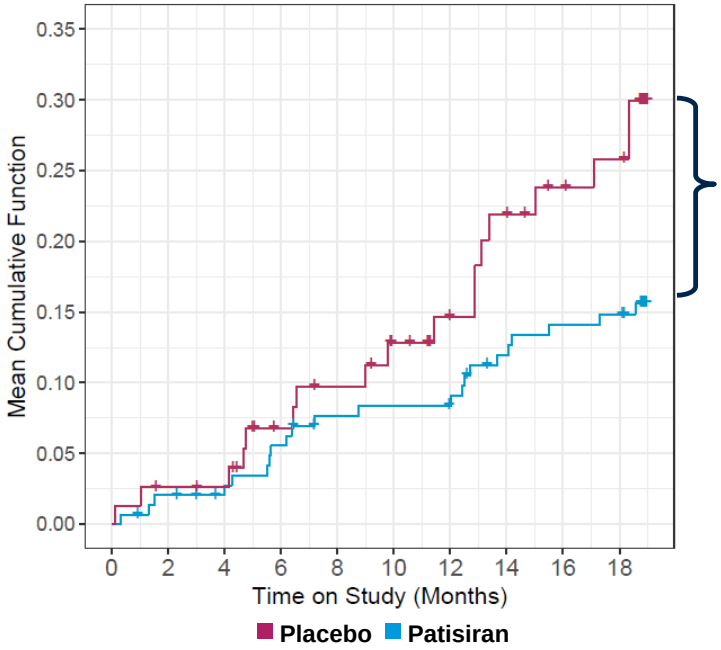
Mean Cumulative Function: average number of events per patient by a certain time

Composite Rate of All-Cause Hospitalization and Mortality



Approximately 50% reduction in event rate**

Composite Rate of Cardiac Hospitalization and All-Cause Mortality



Approximately 45% reduction in event rate†

Analysis of hospitalization/death data was conducted post-hoc based on data collected from AE CRFs; hospitalization/death events caused by SAEs within 28 days of last dose of study drug were included; hospitalization events caused by SAEs within SOC of cardiac disorder were classified as cardiac hospitalization

Adams *et al*., AAN Meeting, Apr 2018
*mITT population
**For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio (HR) 0.48 [0.34, 0.69]
†For cardiac hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.54 [0.25, 1.16]; Anderson-Gill hazard ratio HR) 0.54 [0.28, 1.01]
AE, adverse event; CRF, case report forms; SAEs, serious adverse events; SOC, system organ class

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APOLLO Phase 3 Study Results

Encouraging Safety & Tolerability Profile

Overall, 13 deaths in APOLLO study; no deaths considered related to study drug

- Lower percent deaths in patisiran vs. placebo treatment groups
- Causes (e.g., cardiovascular, infection) consistent with NH

Majority of AEs mild or moderate in severity

- Most common AEs more frequently observed in patisiran arm vs. placebo included peripheral edema (29.7% vs. 22.1%) and infusion-related reactions (18.9% vs. 9.1%)
  - Both AEs decreased over time; IRRs led to discontinuation in only 1 patient (0.7%); peripheral edema led to no discontinuations

Additional notable safety findings

- Encouraging safety & tolerability in cardiac subpopulation
  - Lower percent deaths in patisiran (5.6%) vs. placebo (11.1%) treatment groups
- No safety signals related to steroid pre-medication regimen or TTR KD
- No safety signals regarding liver function tests, hematology including thrombocytopenia, or renal dysfunction related to patisiran

Type of Adverse Event, Number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Adverse event (AE)	75 (97.4)	143 (96.6)
Severe AE	28 (36.4)	42 (28.4)
Serious AE (SAE)	31 (40.3)	54 (36.5)
AE w/ discontinuation	11 (14.3)	7 (4.7)
AE w/ withdrawal	9 (11.7)	7 (4.7)
Death	6 (7.8)	7 (4.7)

Adams *et al.*, EU-ATTR Meeting, Nov 2017

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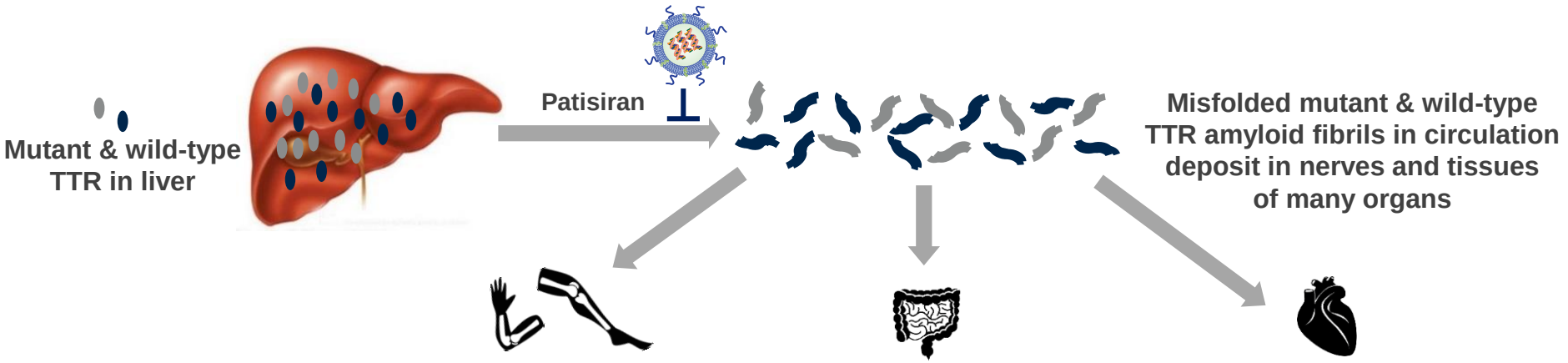
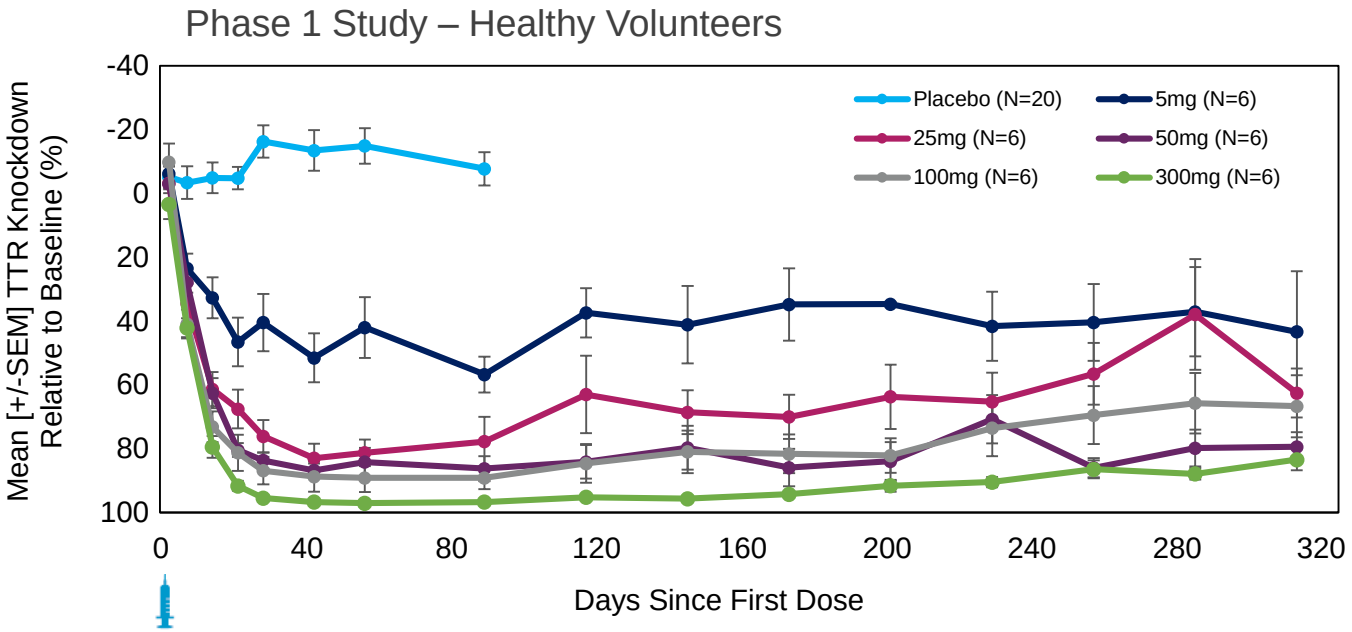
hATTR Amyloidosis and APOLLO Assessments



	Sensorimotor Nerves	Autonomic Nerves	Heart
Clinical Manifestations	• Loss of sensation • Muscle weakness • Impaired ambulation	• Orthostatic hypotension • Syncope/falls • Constipation/diarrhea • Urinary retention/UTIs	• Heart failure • Arrythmias/syncope • Impaired exercise tolerance
APOLLO Assessments	• mNIS+7 • NIS-W subdomain • QST subdomain • Reflexes subdomain • Norfolk-QOL • R-ODS disability • 10-MWT • Grip strength • AE profile	• mNIS+7 • Postural BP subdomain • Norfolk-QOL • Autonomic subdomain • mBMI • COMPASS-31 • Orthostatic hypotension • GI & bladder subdomains • AE profile	• NT-proBNP • Echo longitudinal strain • Echo LV thickness • 10-MWT • AE profile

ALN-TTRsc02 Opportunity

Advancing Continued Innovation for Patients with ATTR Amyloidosis



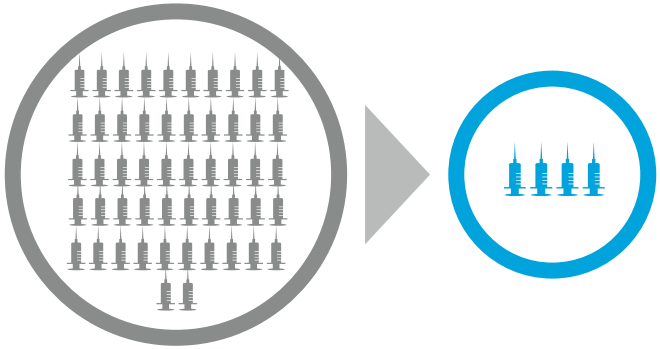
Mean max TTR KD of 97.1%; ~80% TTR KD at nearly 1 year after single 50 mg dose*

Safety (N=80):

- No SAEs and no discontinuations due to AEs
- All AEs mild or moderate in severity

Inotersen

52 DOSES PER YEAR



ALN-TTRsc02

4 DOSES PER YEAR ANTICIPATED

Expect to initiate Phase 3 study in **Late 2018**

*As of data cutoff on 31May2017

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Agenda

- RNAi Therapeutics for hATTR Amyloidosis
- RNAi Therapeutics for Other Rare and Common Diseases
- New Frontiers for RNAi Therapeutics

Acute Hepatic Porphyrias

Givosiran

Description

Family of ultra-rare orphan diseases causing incapacitating and potentially fatal attacks, leading to frequent hospitalizations and chronic pain

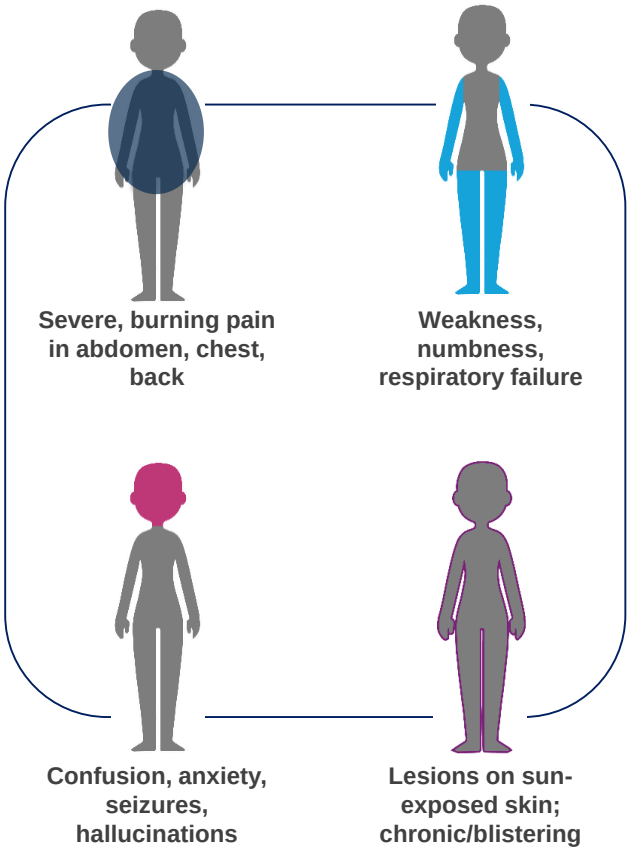
Predominantly

female,

commonly misdiagnosed

Patient Population*

~5,000	~1,000
Patients with **sporadic attacks** in U.S./EU	Patients with **recurrent attacks** in U.S./EU



*ORPHANET; The Porphyria Consortium

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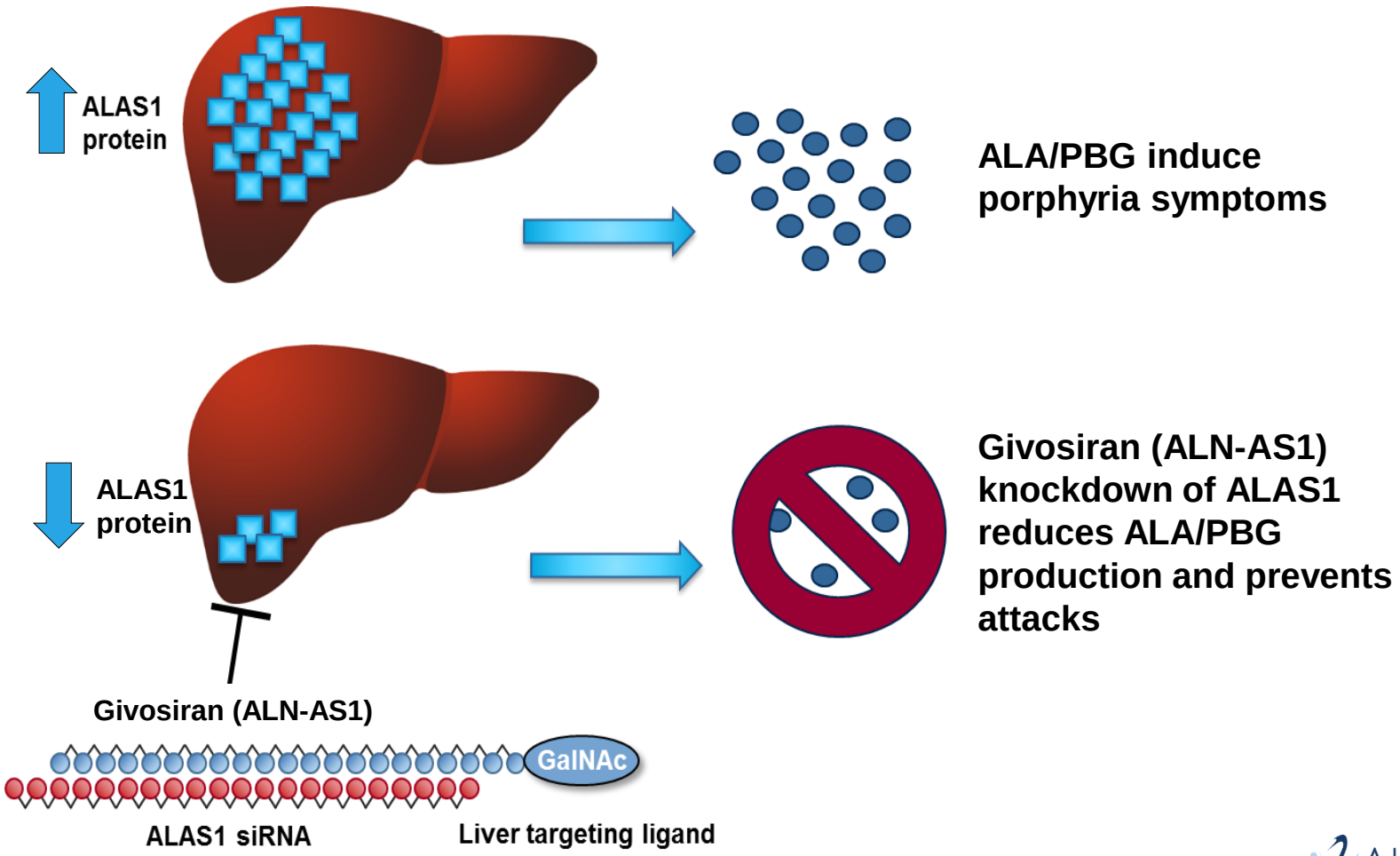
Givosiran: Investigational RNAi Therapeutic

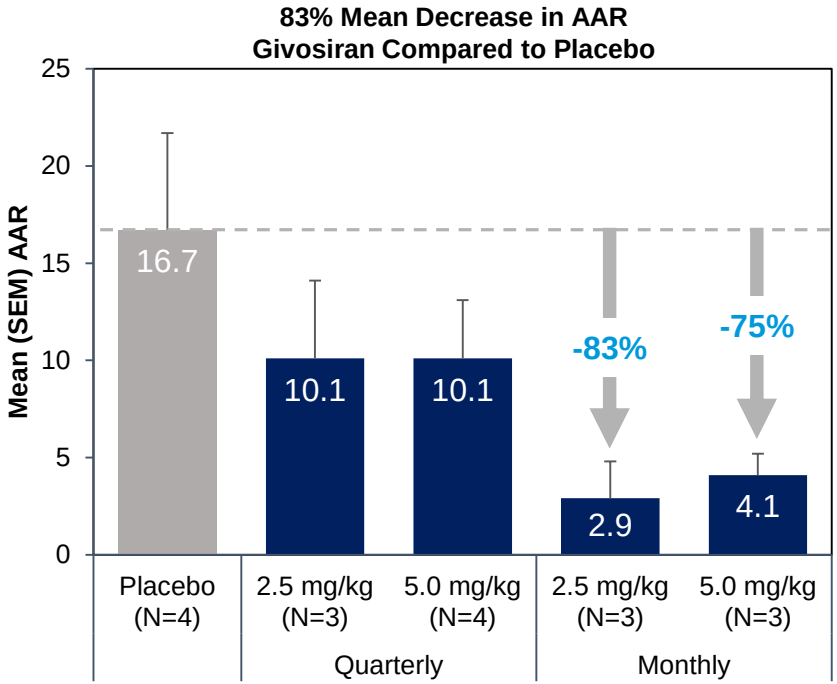
Therapeutic Hypothesis

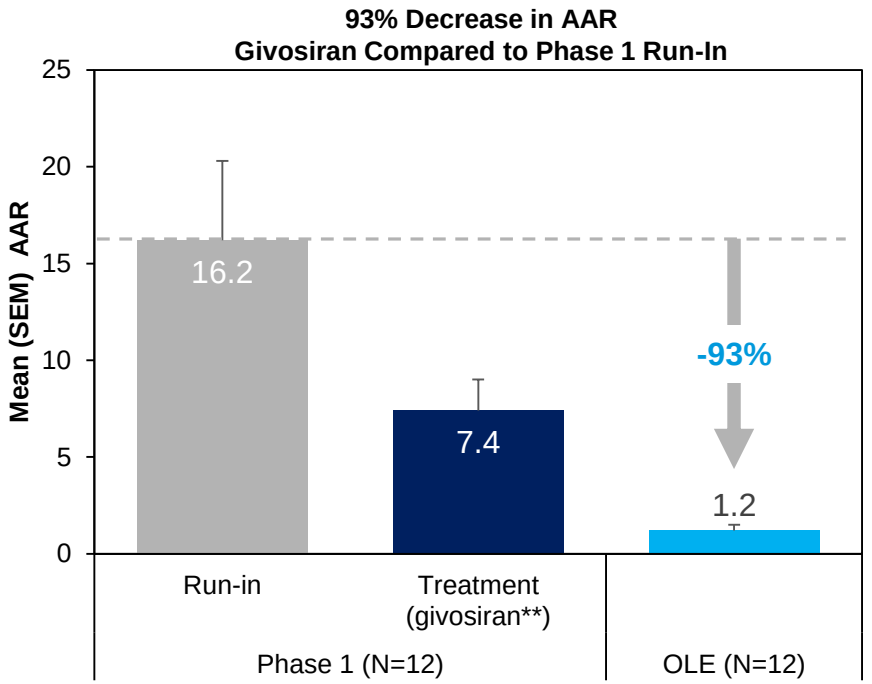
Knockdown of Liver ALAS1 Protein to Reduce ALA/PBG



Givosiran Interim Phase 1 and OLE Study Results†

Decreased Annualized Attack Rates (AAR)* Observed with up to 22 Months of Total Treatment in Phase 1 and OLE





Phase 1 and OLE Safety:
In OLE study (N=16):
- Two patients with SAEs, including one with anaphylactic reaction, assessed as definitely related to study drug. Patient had past history of asthma, oral allergy syndrome, and prior allergic reactions to acne cream and possibly latex gloves; patient discontinued from study
- Most common AEs: abdominal pain, nausea, injection site erythema, headache, injection site pruritis, fatigue, nasopharyngitis

In Phase 1 (N=40):
- Six patients with SAEs, including one who developed acute pancreatitis complicated by pulmonary embolism resulting in death, considered unlikely related to study drug
- Majority of AEs mild-moderate in severity

DURABILITY
Monthly SC dose regimen

†Phase 1 and interim OLE study results as of Feb 26, 2018; Sardh *et al*., *EASL*, April 2018
*Includes attacks treated in healthcare facility or with hemin
**Aggregated across all dose groups
Mean time in Phase 1 run-in and treatment of 103 days and 165 days, respectively; mean time in OLE of 322 days

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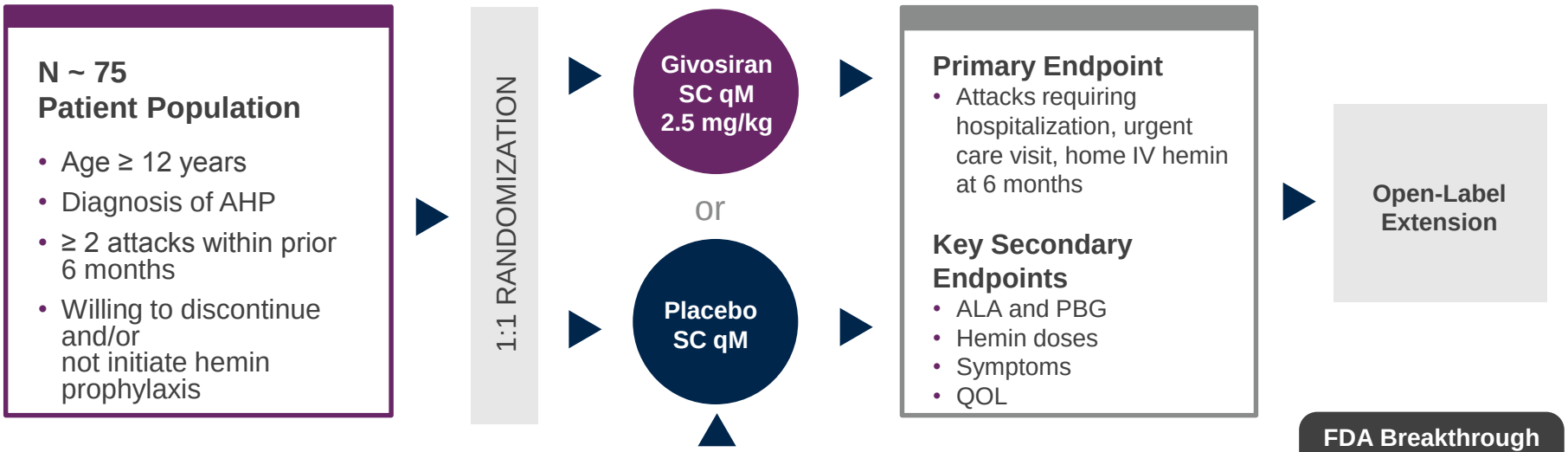
ENVISION Phase 3 Study Design

Randomized, Double-Blind, Placebo-Controlled Study in Acute Hepatic Porphyria Patients



Statistical Considerations:

- 70 patients will have at least 90% power to detect 45% reduction in annualized attack rate at 2-sided alpha of 0.05
- Unblinded interim analysis of urinary ALA levels in 30 patients at 3 months
  - Includes blinded assessment to adjust sample size for primary endpoint

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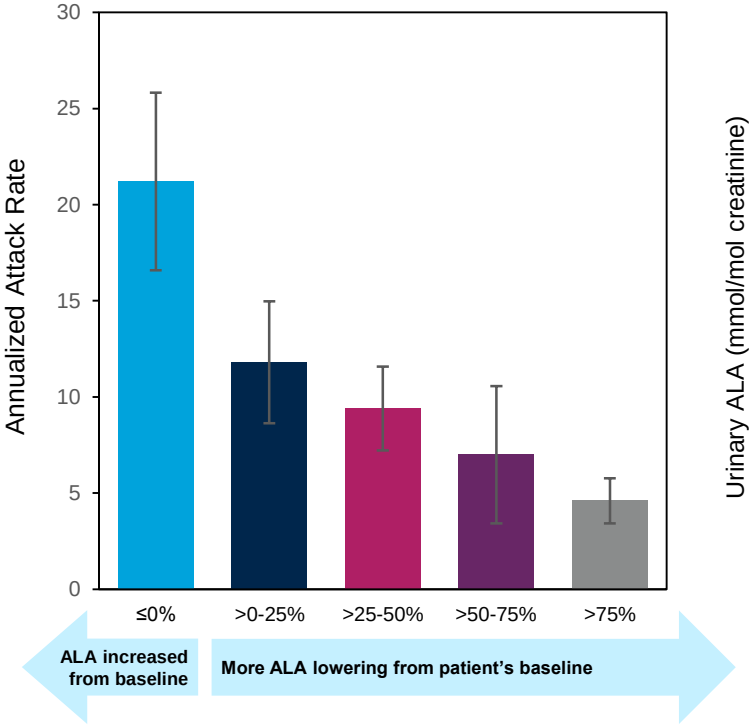
ENVISION Phase 3 Study

Interim Analysis for Potential Accelerated Approval

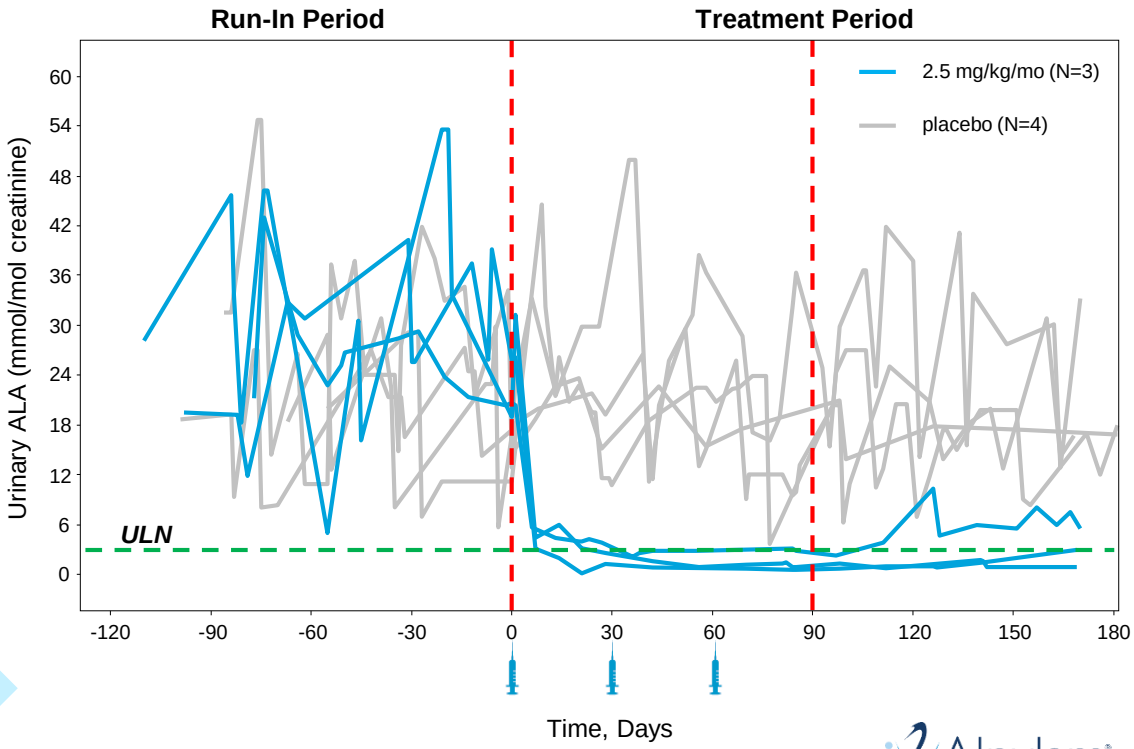
Alignment with FDA that reduction of urinary ALA is reasonably likely to predict clinical benefit

- Interim analysis with ~30 patients after 3 mo dosing; expect topline data in mid-2018
- Expect NDA submission in late 2018 and potential FDA approval in mid-2019

Relationship of ALA Lowering with Annualized Attack Rate in Recurrent Attack Patients*



ALA Lowering in Recurrent Attack Patients at 2.5 mg/kg qM**



*Sardh *et al.*, *EASL*, April 2018; Includes attacks treated in healthcare facility or with hemin
**Sardh *et al.*, *ICPP*, June 2017


PCSK9
Inclisiran
Alnylam
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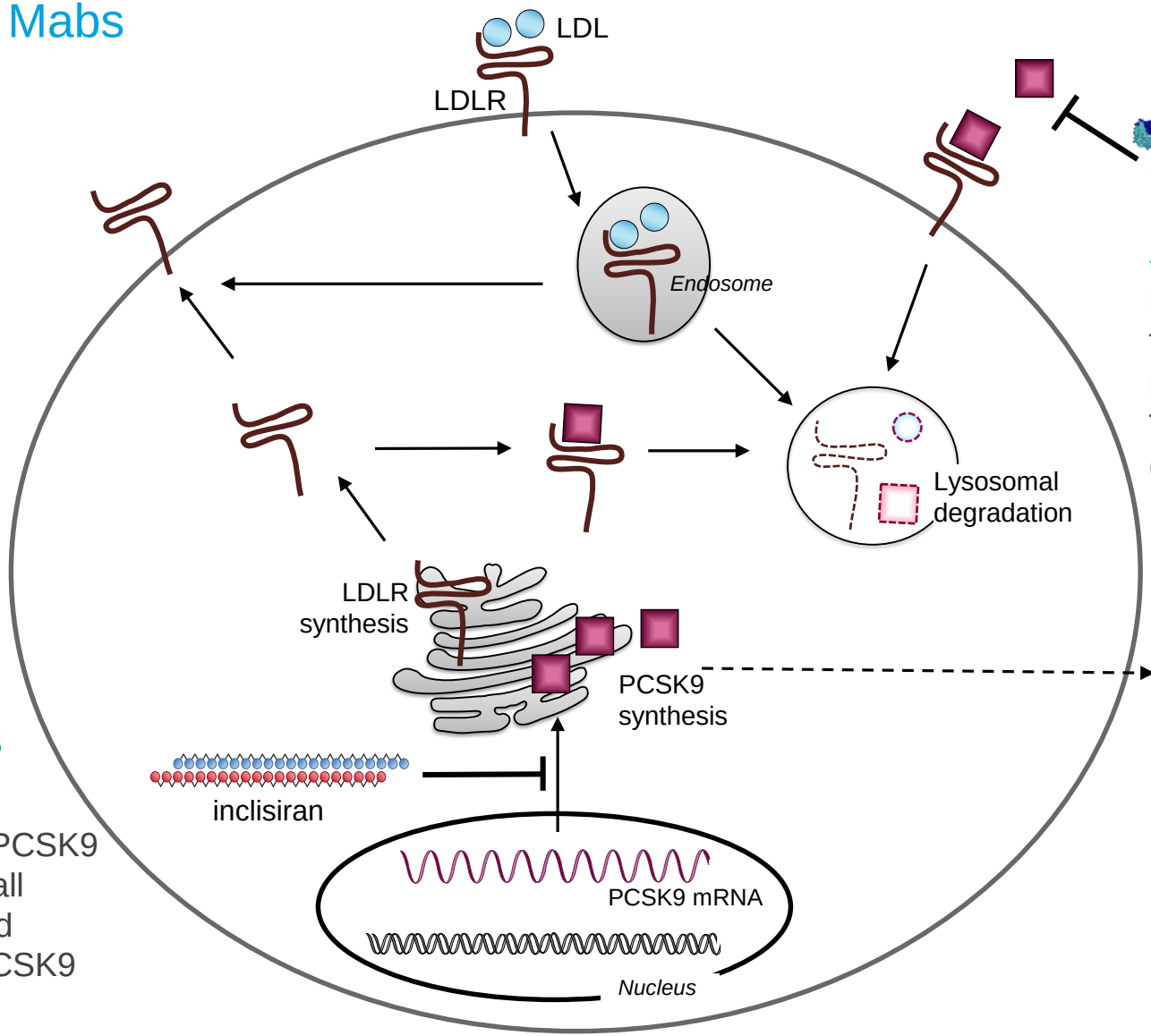
PCSK9 Therapeutic Hypothesis

RNAi vs. Mabs

The Medicines Company



Anti-PCSK9 Mabs

Transiently block PCSK9 binding To LDL receptor (LDLR)

PCSK9 Synthesis Inhibitors

Durably block PCSK9 synthesis and all intracellular and extracellular PCSK9 functions

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ORION-1 Phase 2 Clinical Study

The Medicines Company

501 ASCVD subjects with elevated LDL-C on maximal lipid lowering therapy

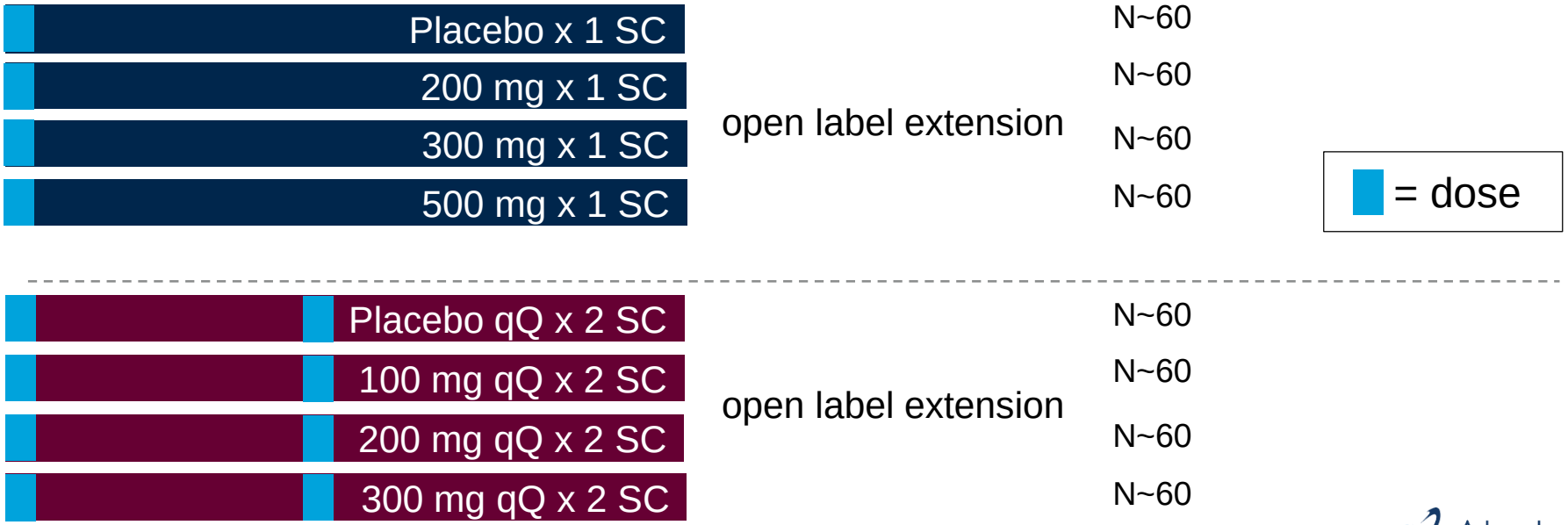
Primary objectives

- LDL-C levels at day 180

Secondary objectives

- Safety and tolerability, PCSK9 and LDL-C reduction and duration of effect qQ vs Bi-annual, proportion of patients reaching global lipid guidelines, changes in other lipoprotein levels

Randomized 3:1, Double blind, Placebo controlled



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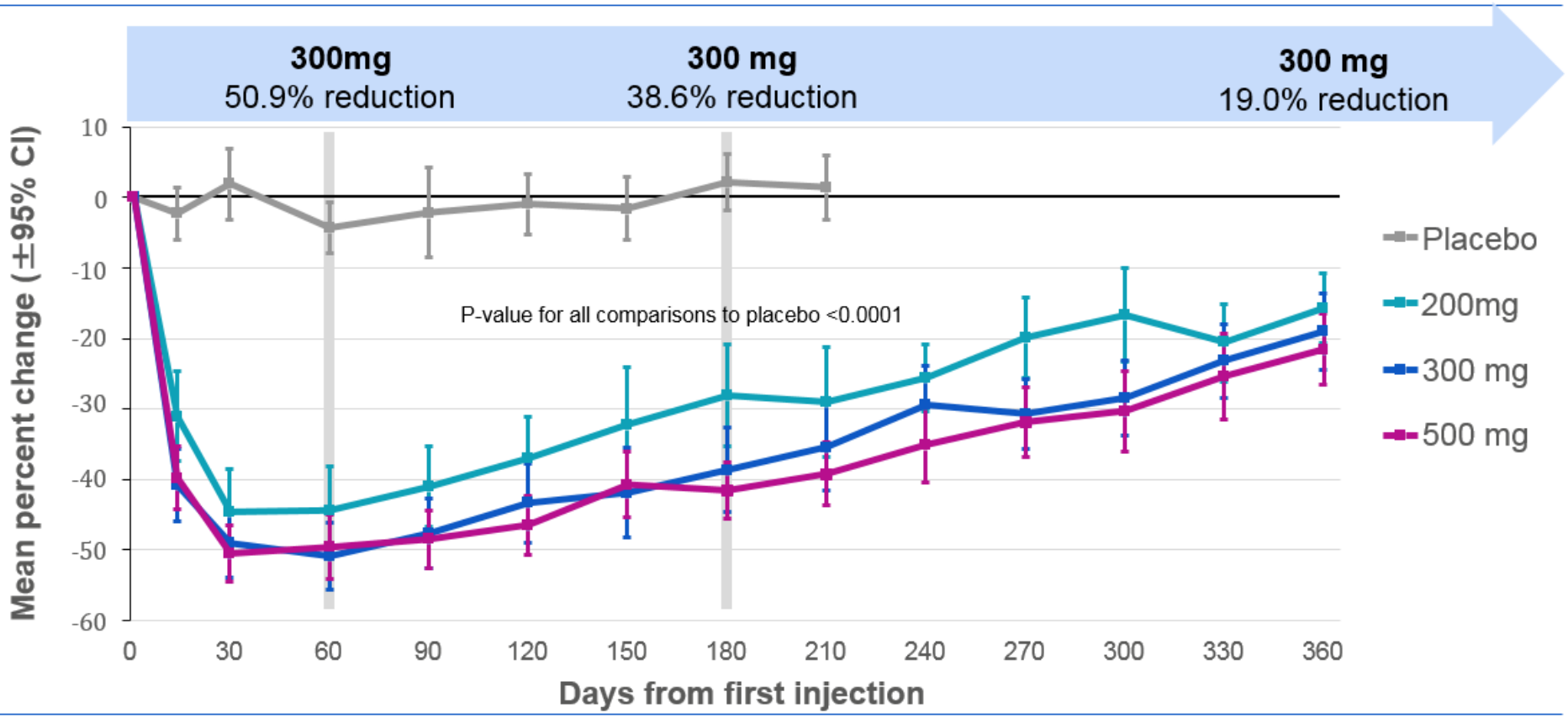
Robust and Sustained LDL-C Reductions with Inclisiran*

Results to Day 360 Following One Dose



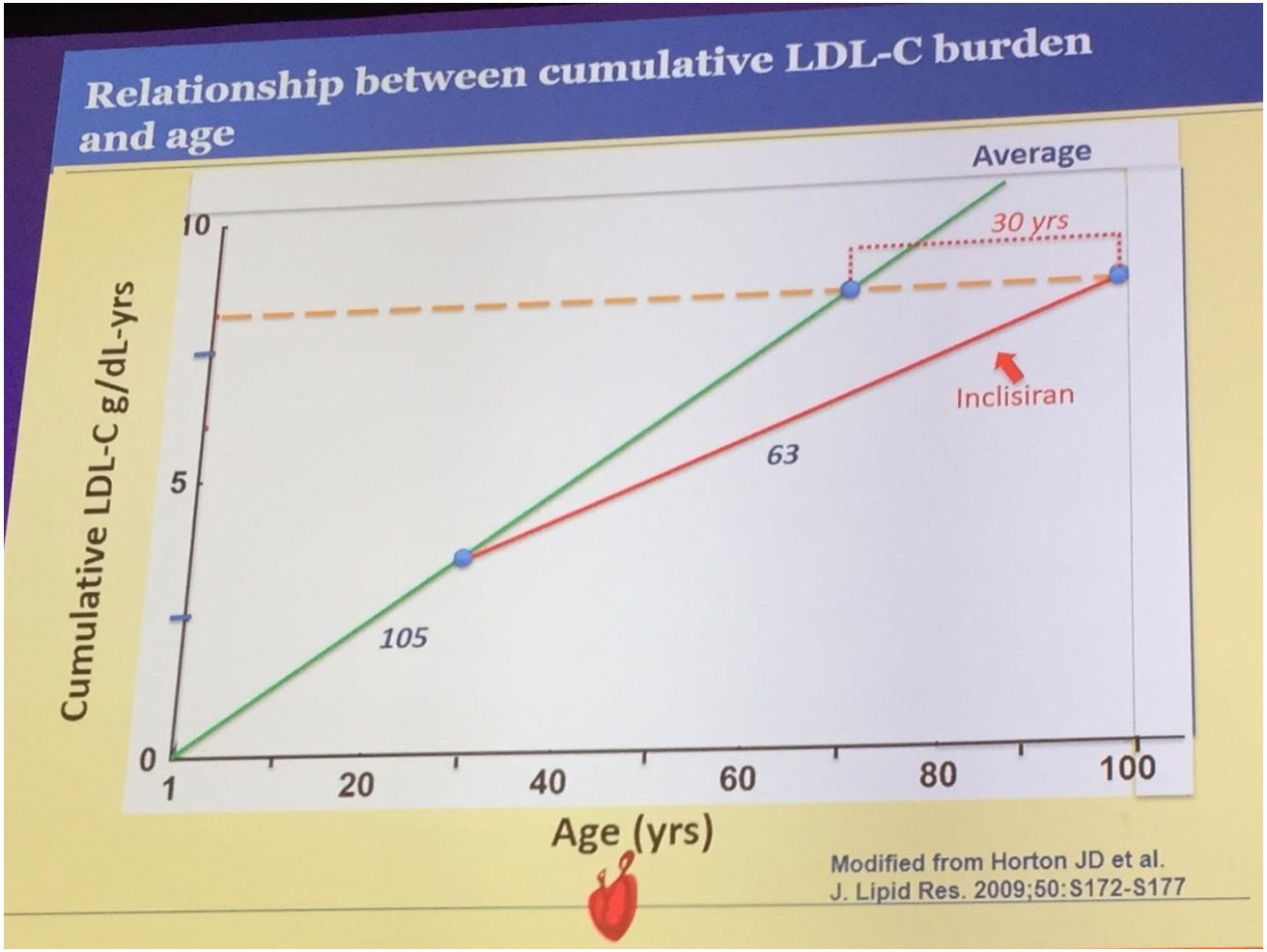
*Phase 2 study results; Ray *et al., ESC*, Aug 2017

Inclisiran also known as “ALN-PCSsc” and “PCSK9si”

The Medicines Company is leading and funding development of inclisiran from Phase 2 onward and will commercialize the program, if successful

Free from CVD for 100 Years?

Hypothesis on Inclisiran Primary Prevention by E. Braunwald, ACC 2018



ORION-1 Phase 2 Study of Inclisiran*

Safety Summary

The Medicines Company

Generally safe and well tolerated (N=501)

- Overall incidence of treatment emergent adverse events (TEAE) 76% both in patients randomized to placebo and in patients randomized to inclisiran
  - No significant differences in TEAEs between inclisiran doses
- Two deaths on study, both unrelated to study drug
  - One fatal MI in patient w/ prior MI and unstable angina >3 months after single inclisiran dose
  - One death in patient w/ complications of aortic aneurysm surgery including sepsis and stroke
- No elevations of liver enzymes related to study drug
  - One SAE of elevated ALT and AST attributed to increased dose of statin therapy which resolved upon lowering to original dose
- No thrombocytopenia, neuropathy, or changes in renal function
- Injection site reactions (ISRs) infrequent and transient
  - Observed in 5.1% of patients
  - Mild or moderate

*Phase 2 study results; Ray *et al.,* ACC, March 2017

Inclisiran also known as “ALN-PCSsc” and “PCSK9si”

The Medicines Company is leading and funding development of inclisiran from Phase 2 onward and will commercialize the program, if successful

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ORION Phase 3 Program

The Medicines Company

- 3,660 patients (1:1 inclisiran or placebo) dosed across ORION-9, ORION-10 and ORION-11
  - Baseline data and demographics consistent with ASCVD and ASCVD Risk Equivalents including HeFH
- Encouraging safety results to date with >1000 patient years exposure
  - Including, ORION-3, ORION-2 and ORION-7 open label studies
- ORION-4 CVOT study in ~15,000 patients with ASCVD and Risk Equivalents to start in mid-2018

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Agenda

- RNAi Therapeutics for hATTR Amyloidosis
- RNAi Therapeutics for Other Rare and Common Diseases
- New Frontiers for RNAi Therapeutics

UK Biobank Consortium

World-leading effort to connect genotype to full medical records for phenome-wide association studies

- Goal to generate 500K exome sequences linked to medical records by end-2019
  - 50K exomes sequenced to date
- Consortium members receive broad, ongoing access to UK Biobank data linked to exome sequences
  - Exclusive for 1 year after generation

Substantial value to Alnylam R&D efforts

- Modern drug discovery must incorporate human genetics
- Provides additional genetic validation for existing programs
- Identify/de-risk new programs
- *In silico* natural history data for new and existing programs
- Patient finding efforts

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science to medicine®

biobank uk
Improving the health of future generations

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Nonalcoholic Steatohepatitis (NASH)

HSD17B13 Target

Description

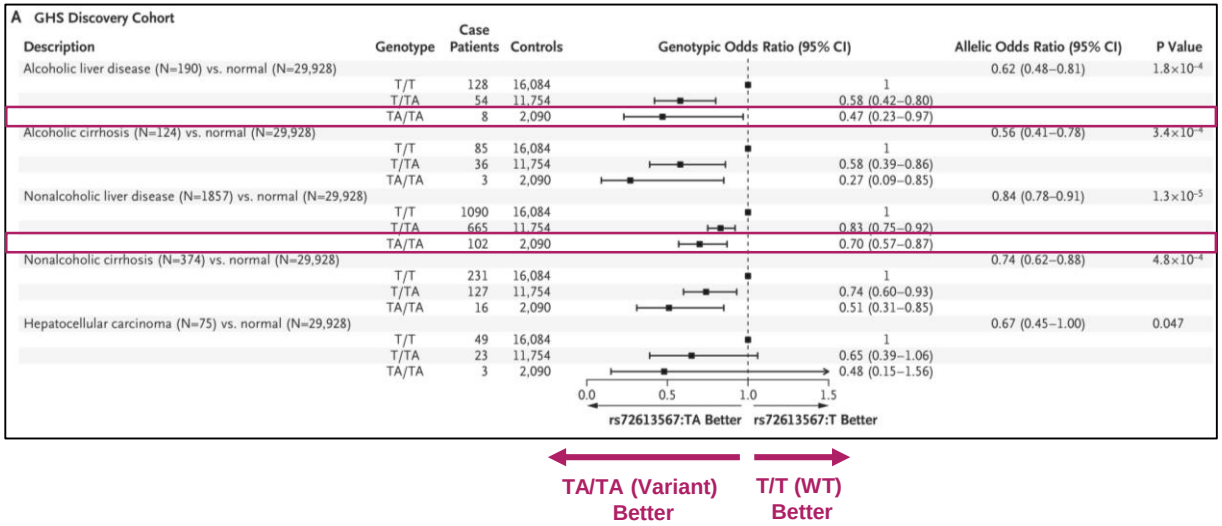
Progressive disease characterized by hepatic fat buildup and inflammation, potentially leading to cirrhosis

PATIENT POPULATION[2]

>9 million

adults in U.S.

HSD17B13 as a novel target[1]



- Hepatocyte expressed intracellular target amenable to RNAi therapeutic approach
- Loss-of-function variant (TA) associated with reduced risk of chronic liver disease, including NASH

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[1]Abul-Husn et al. NEJM 2018 378;12, 1096
[2]Spengler et al. Mayo Clinic Proceedings. 2015;90(9):1233-1246

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RNAi Therapeutics for CNS Diseases

No Current Therapies to Prevent or Reverse Neurodegenerative Disease

- Dominantly inherited neurodegenerative diseases include
  - Alzheimer's disease
  - Parkinson's disease
  - Frontotemporal dementia
  - Huntington's disease
  - Amyotrophic lateral sclerosis (ALS)
  - Spinocerebellar ataxia
  - Prion disease
  - Many other orphan genetic diseases with CNS component

- Many genetically validated targets known but no current disease modifying therapies for these devastating, life threatening disorders
- RNAi therapeutics directed to disease-causing, CNS-expressed genes represent next great frontier
- Expect superior potency, duration and systemic safety profile vs. ASOs

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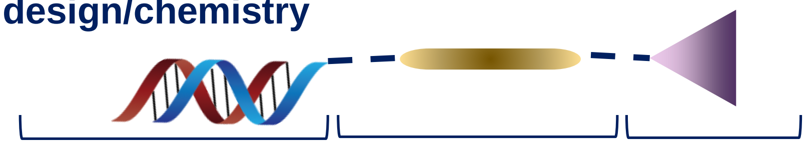
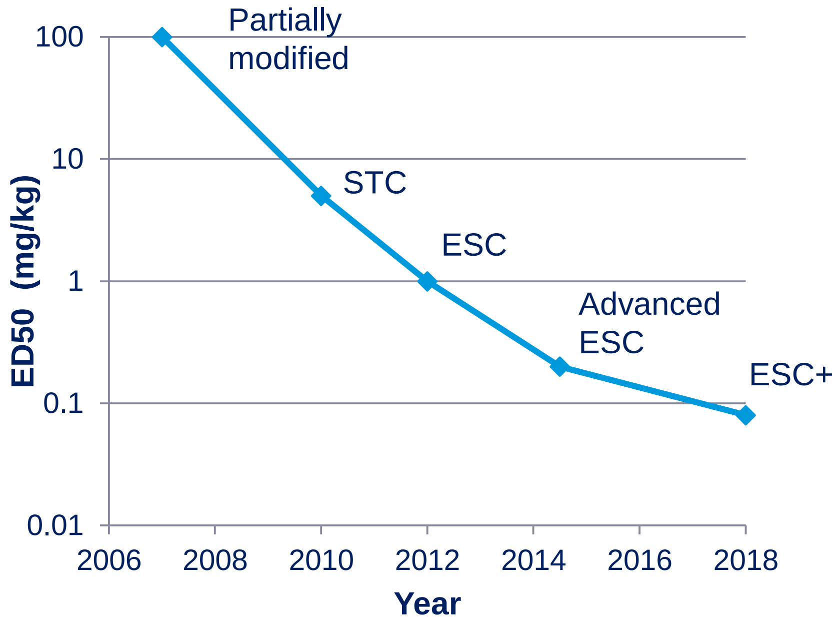
Alnylam Advancements in Conjugate-Based Delivery



Evolution of conjugate potency (mouse, SD ED_{50})



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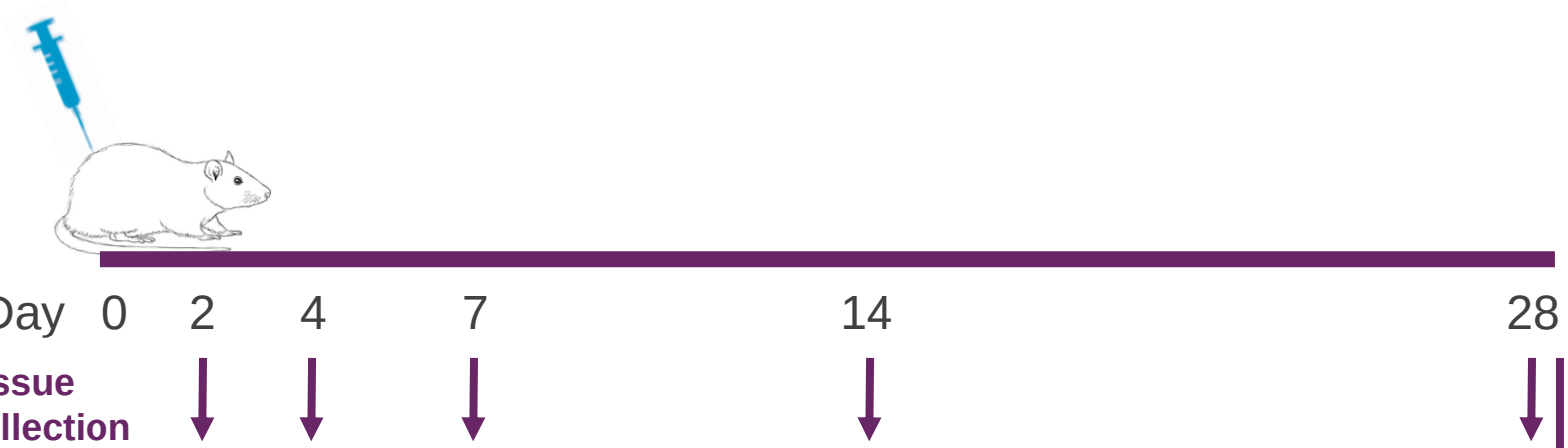
Intrathecal Delivery of Novel siRNA Conjugates

Single Dose Time Course in Rat

Two targets tested to demonstrate sequence specificity
siRNA conjugate dose of 0.9 mg



Tissues: Spinal cord: lumbar, thoracic and cervical
Brain: prefrontal cortex, cerebellum and remaining brain
Fluids: CSF and plasma

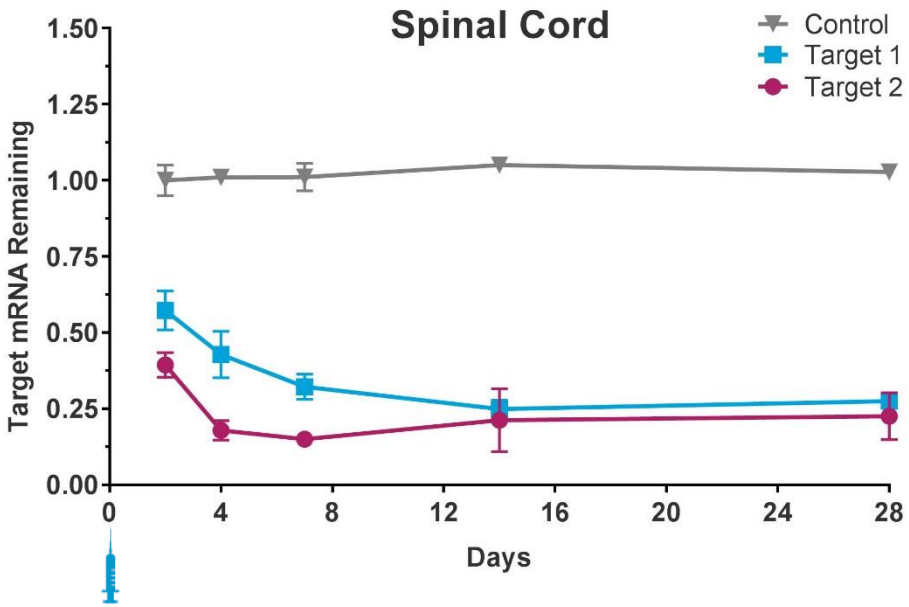
Assays: mRNA, tissue siRNA levels, RISC loaded siRNA

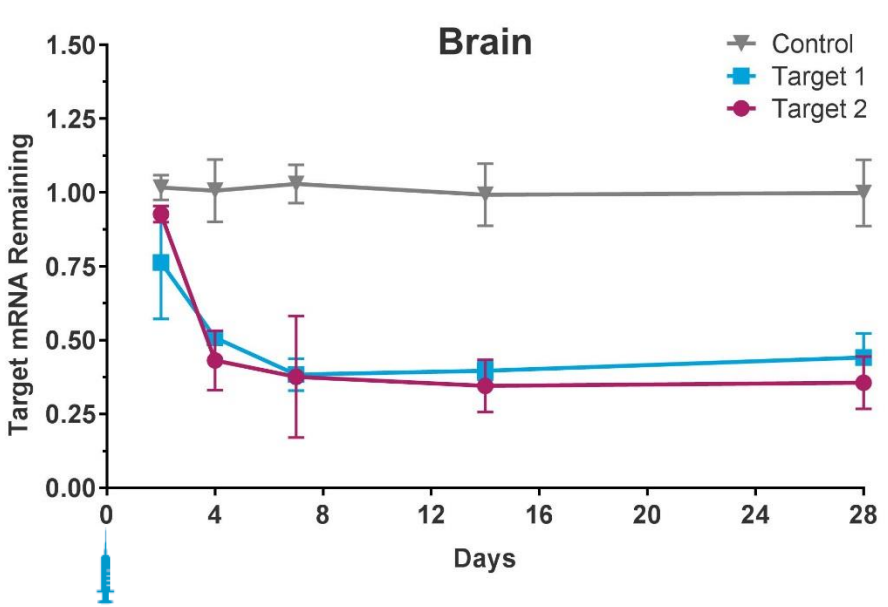
Histology

Robust, Durable CNS Silencing by Novel siRNA Conjugates

Single Intrathecal Dose in Rats

Sequence specific target knockdown across the brain and spinal cord for both targets





- Confirmed siRNA uptake in several different cell types
- Widespread distribution and knockdown in all key anatomical regions of brain and spinal cord tissue

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Alnylam CNS Pipeline Strategy

Expanding a Pipeline of Potentially Transformative Medicines

Genetically validated, CNS-expressed target gene

Biomarker for POC in Phase 1

Definable path to approval and patient access

Alnylam CNS Objectives

- 1st DC in 2018
- 1st IND in late ’19/early ’20
- 1-2 INDs/yr starting in ’20

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Summary

- RNAi therapeutics are in advanced stages of clinical development and at cusp of commercialization
  - Patisiran poised to emerge as industry's 1st RNAi therapeutic to reach market
  - RNAi therapeutics emerge as high impact, transformational medicines
- Many RNAi therapeutic opportunities advancing for rare and common diseases
  - E.g., Givosiran for acute hepatic porphyrias
  - E.g., Inclisiran for hypercholesterolemia
  - Many significant opportunities for breakthrough medicines and high patient impact
- New frontiers for future expansion of RNAi therapeutics opportunity
  - Convergence of RNAi and genetic data to advance highly innovative medicines across many diseases (e.g., NASH)
  - Delivery of RNAi therapeutics to CNS achieved!
    - Novel siRNA conjugate approach
    - Opens advancement of MANY new opportunities for high impact medicines