



# Early Stage RNAi Therapeutics Pipeline



July 17, 2020

# Agenda

## Welcome

- Joshua Brodsky – Director, Investor Relations & Corporate Communications

## Introduction

- Vasant Jadhav, Ph.D. – Vice President, Research

## NASH Overview and ALN-HSD Development Program

- Josh Friedman, M.D., Ph.D. – Senior Director, Clinical Research

## RNAi Therapeutics for CNS Diseases

- Tanya Fischer, M.D., Ph.D. – Vice President, Clinical Development

## Q&A Session

# Reminders

**Event will run for approximately 60 minutes**

**Q&A session at end of presentation**

- Questions may be submitted at any time via the 'Ask a Question' field on the webcast interface

**Replay, slides and transcript available at [www.alnylam.com/capella](http://www.alnylam.com/capella)**

# 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: the direct or indirect impact of the COVID-19 global pandemic or a future pandemic, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by our products, or in patient enrollment in clinical trials, potential supply chain disruptions, and other potential impacts to our business, the effectiveness or timeliness of steps taken by us to mitigate the impact of the pandemic, and our ability to execute business continuity plans to address disruptions caused by the COVID-19 or a future pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates, including ALN-APP and ALN-HSD; pre-clinical and clinical results for our product candidates, including ALN-APP and ALN-HSD; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates, including ALN-APP and ALN-HSD, and our marketed products; intellectual property matters including potential patent litigation relating to our platform, products or product candidates; our and our partner's ability to obtain regulatory approval for our product candidates, including lumasiran and inclisiran, and our ability to maintain regulatory approval and obtain pricing and reimbursement for products, including ONPATTRO<sup>®</sup> (patisiran) and GIVLAARI<sup>®</sup> (givosiran); our progress in continuing to establish a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally, including ONPATTRO and GIVLAARI, and achieve net product revenues for ONPATTRO within our revised expected range during 2020; our ability to successfully expand the indication for ONPATTRO in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses within the reduced ranges of guidance provided by us through implementation of further discipline in operations to moderate spend and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to establish and maintain business alliances, including completing an agreement for funding by Blackstone of certain R&D activities for vutrisiran and ALN-AGT; our dependence on third parties, including Novartis, for the development, manufacture and commercialization of inclisiran, Regeneron, for development, manufacture and commercialization of certain products, including eye and CNS products and ALN-APP and ALN-HSD, Ironwood, for assistance with the education about and promotion of GIVLAARI, and Vir for the development of ALN-COV and other potential RNAi therapeutics targeting SARS-CoV-2 and host factors for SARS-CoV-2; the outcome of litigation; and the risk of government investigations; as well as those risks and other factors more fully discussed in our most recent annual, quarterly and current reports filed with the SEC. 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.

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# RNAi Therapeutics: New Class of Innovative Medicines

Clinically Proven Approach with Transformational Potential

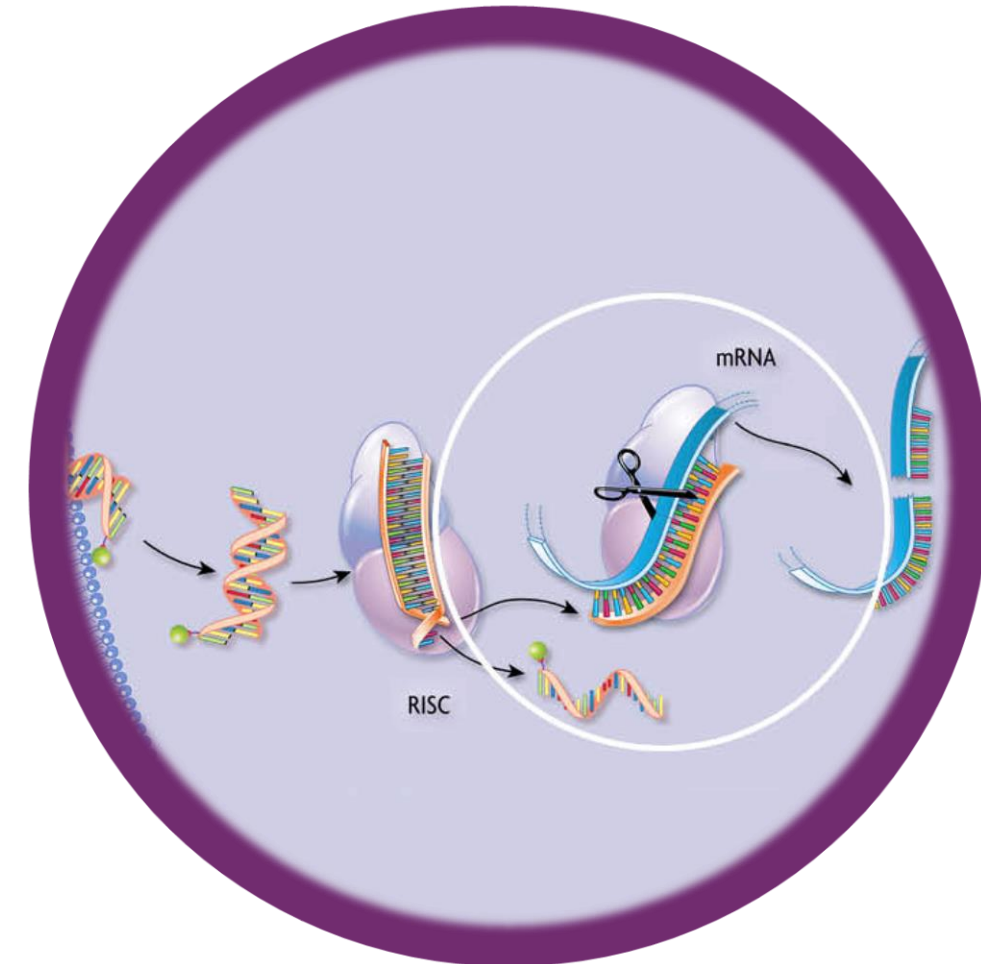
**Nobel Prize-winning science**

**Silence any gene in genome**

**Potent and durable mechanism of action**

**Product engine for sustainable innovation**

**Multiple products impacting patients globally**



# Anylam Commercial Products and Late Stage Clinical Development Pipeline

## Focused in 4 Strategic Therapeutic Areas (STARs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

**BREAKTHROUGH  
DESIGNATION**

**LATE STAGE**  
(Phase 2-Phase 3)

**REGISTRATION**

**COMMERCIAL**

**COMMERCIAL  
RIGHTS**



*hATTR Amyloidosis<sup>1</sup>*



Global



*Acute Hepatic Porphyria<sup>2</sup>*



Global

**Lumasiran**

*Primary Hyperoxaluria Type 1*



Global

**Inclisiran**

*Hypercholesterolemia*



Milestones & up to  
20% Royalties<sup>3</sup>  
(Novartis)

**Patisiran**

*ATTR Amyloidosis  
Label Expansion*



Global

**Fitusiran**

*Hemophilia and Rare  
Bleeding Disorders*



15-30% Royalties  
(Sanofi)

**Vutrisiran**

*ATTR Amyloidosis*



Global

<sup>1</sup> Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy

<sup>2</sup> Approved in the U.S. for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older












<sup>3</sup> As part of Blackstone strategic financing collaboration, 50% of inclisiran royalty revenue will be payable to Blackstone



# Alnylam Early Stage Clinical Development and 2020 IND Pipeline

## Focused in 4 Strategic Therapeutic Areas (STArS):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		HUMAN POC <sup>1</sup>	BREAKTHROUGH DESIGNATION	2020 IND CANDIDATES	EARLY STAGE (Phase 1-Phase 2)	COMMERCIAL RIGHTS
<b>Cemdisiran</b>	<i>Complement-Mediated Diseases</i>					50-50 (Regeneron)
<b>Cemdisiran/Pozelimab Combo<sup>2</sup></b>	<i>Complement-Mediated Diseases</i>					Milestone/Royalty (Regeneron)
<b>ALN-AAT02 (DCR-A1AT)<sup>3</sup></b>	<i>Alpha-1 Liver Disease</i>					Ex-U.S. option post-Phase 3 (Dicerna)
<b>ALN-HBV02 (VIR-2218)</b>	<i>Hepatitis B Virus Infection</i>					50-50 option post-Phase 2 (Vir)
<b>ALN-AGT</b>	<i>Hypertension</i>					Global
<b>ALN-HSD</b>	<i>NASH</i>					50-50 (Regeneron)
<b>ALN-COV (VIR-2703)</b>	<i>COVID-19</i>					50-50 option post-Phase 2 (Vir)

**2-4** *INDs per year planned from organic product engine*

<sup>1</sup> POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies

<sup>2</sup> Cemdisiran is currently in Phase 2 development and pozelimab is currently in Phase 1 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics

<sup>3</sup> Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development



# Robust Next Wave Pipeline: 2-4 INDs/Year on Average Planned Through 2025

Over 20 Pre-Clinical Programs Across 4 Tissues

## LIVER



### Alnylam

- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

### Alnylam/Regeneron

- ALN-HSD
- ALN-REGN-L2
- ALN-REGN-L3
- ALN-REGN-L4

## CNS



### Alnylam/Regeneron

- ALN-APP
- ALN-HTT
- ALN-REGN-C3
- ALN-REGN-C4
- ALN-REGN-C5
- ALN-REGN-C6

## EYE



### Alnylam

- ALN-TTRoc

### Alnylam/Regeneron

- ALN-REGN-E1
- ALN-REGN-E2
- ALN-REGN-E3
- ALN-REGN-E4

## LUNG



### Alnylam/Vir

- ALN-COV
- ALN-VIR2 (ACE2)
- ALN-VIR3 (TMPRSS2)

# Pipeline Expanding To Highly Prevalent Diseases

Supported by Growing Safety Database with Conjugates and ESC+ Human Translation

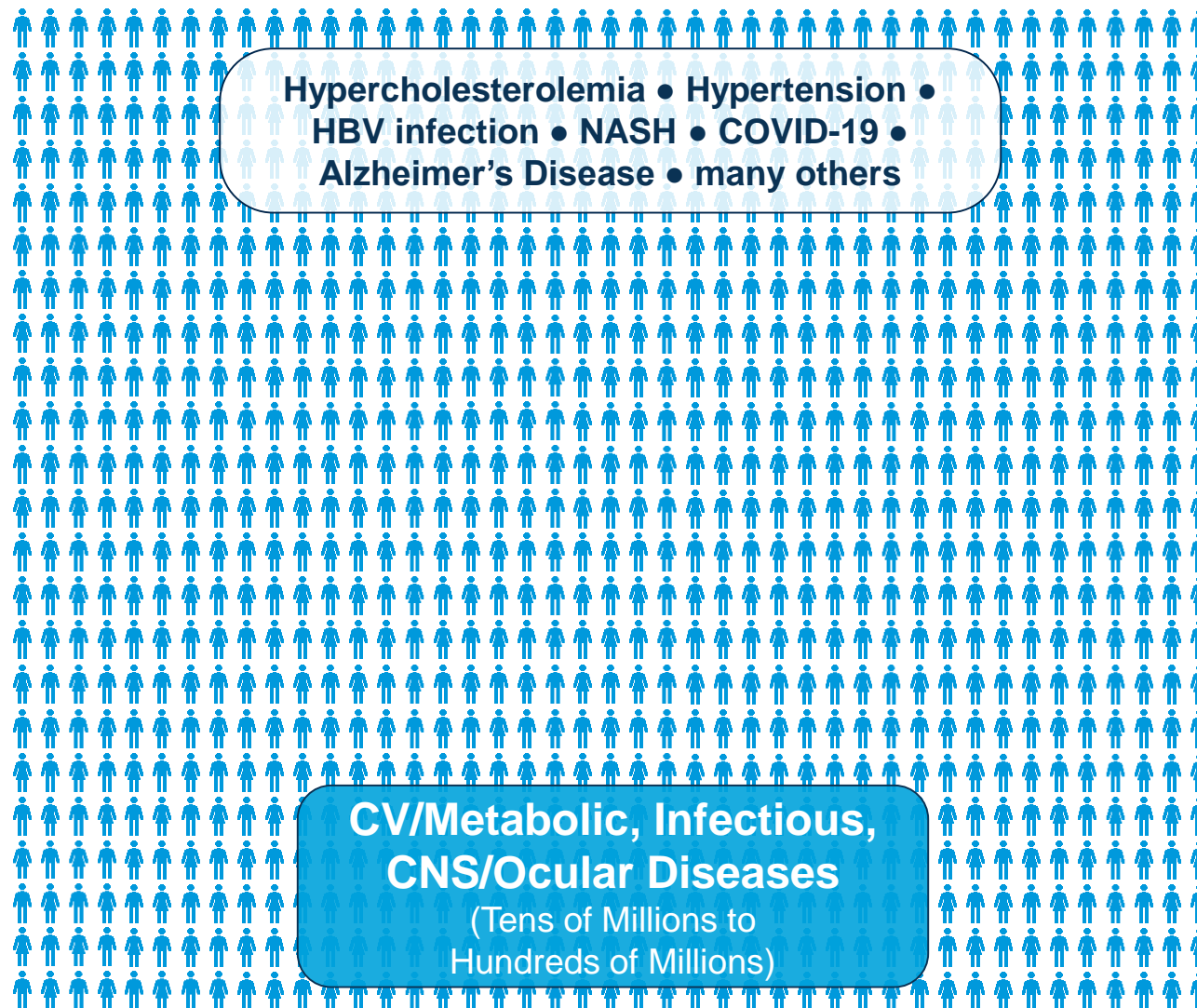
ATTR amyloidosis • Hemophilia •  
Acute hepatic porphyria • PH1 •  
Complement-mediated diseases •  
AATD liver disease • hCAA • others



**Genetic Medicines**  
(Thousands to  
Hundreds of Thousands)



Hypercholesterolemia • Hypertension •  
HBV infection • NASH • COVID-19 •  
Alzheimer's Disease • many others



**CV/Metabolic, Infectious,  
CNS/Ocular Diseases**  
(Tens of Millions to  
Hundreds of Millions)

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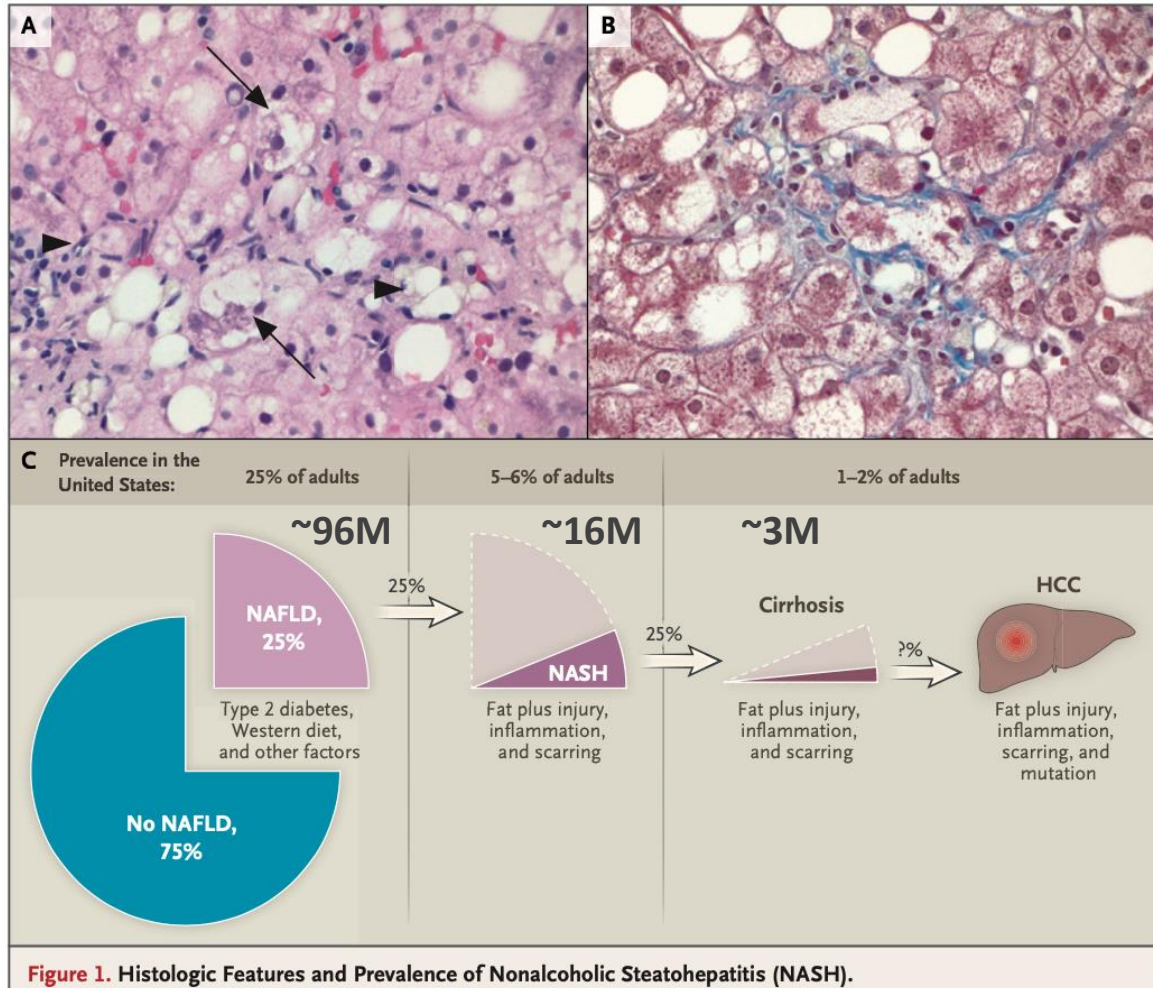
## RNAi Therapeutics for CNS Diseases

- Tanya Fischer, M.D., Ph.D. – Vice President, Clinical Development

## Q&A Session

# Nonalcoholic Fatty Liver Disease (NAFLD)

Disorder of Over-Nutrition Leading to Accumulation of Hepatic Fat



**Figure 1.** Histologic Features and Prevalence of Nonalcoholic Steatohepatitis (NASH).

- **Nonalcoholic steatohepatitis (NASH)**
  - Subset of NAFLD defined by presence of liver cell injury and inflammation
  - Associated with progressive fibrosis, cirrhosis, and hepatocellular carcinoma
  - Co-morbidities include obesity, metabolic syndrome, and type 2 diabetes
- **NASH treatment**
  - Weight loss is effective but difficult to achieve and not durable
  - No approved medical therapies

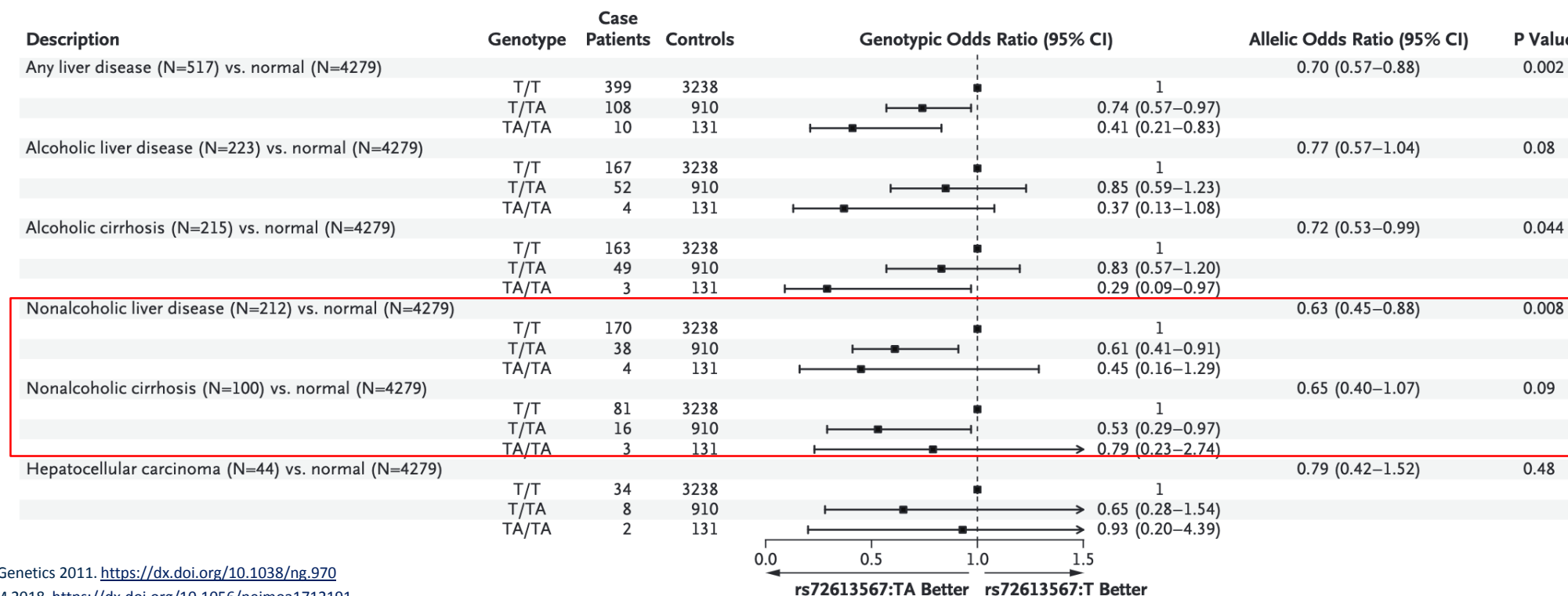
# HSD17B13 Identified as Novel Target for NASH

## Genome-Wide Association Identifies HSD17B13 as Driver of Liver Disease

### Loss-of-function variants in HSD17B13 associated with reduced risk of:

- Elevated ALT
- Non-alcoholic and alcoholic liver disease; cirrhosis across liver diseases (ALD, NAFLD, HCV, Wilson's)
- Inflammation and liver injury among patients with NAFLD<sup>1-3</sup>

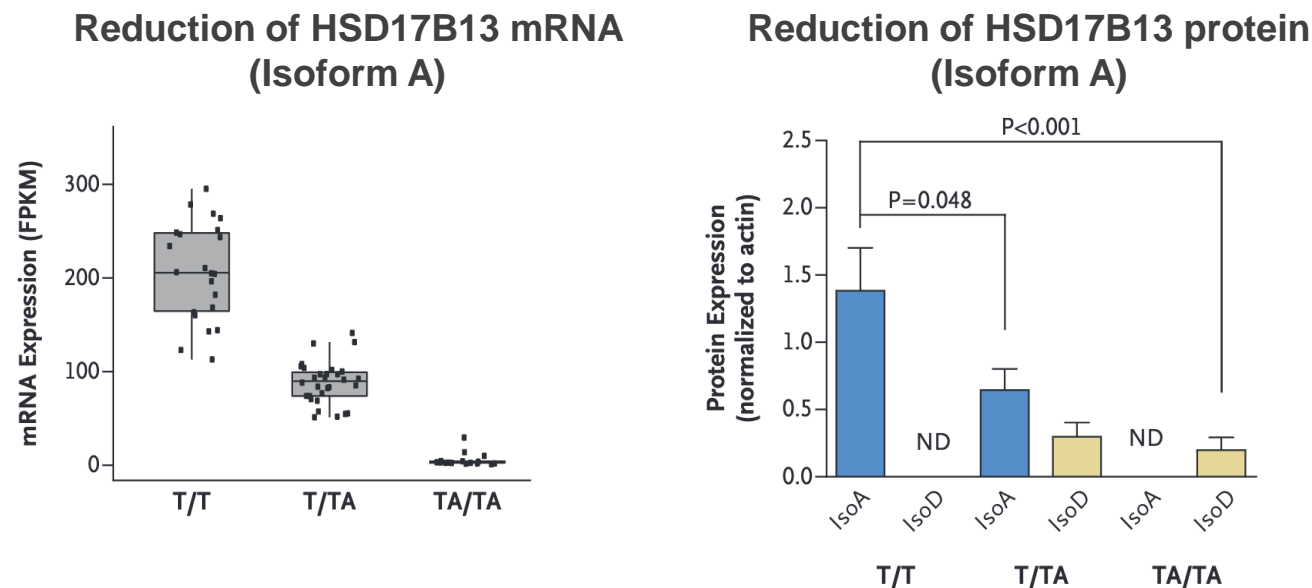
### HSD17B13 is a hydroxysteroid dehydrogenase with unknown in vivo substrates



1. Nat Genetics 2011. <https://dx.doi.org/10.1038/ng.970>  
2. NEJM 2018. <https://dx.doi.org/10.1056/nejmoa1712191>  
3. Hepatology 2019. <https://dx.doi.org/10.1002/hep.30350>

## ALN-HSD Scientific Rationale

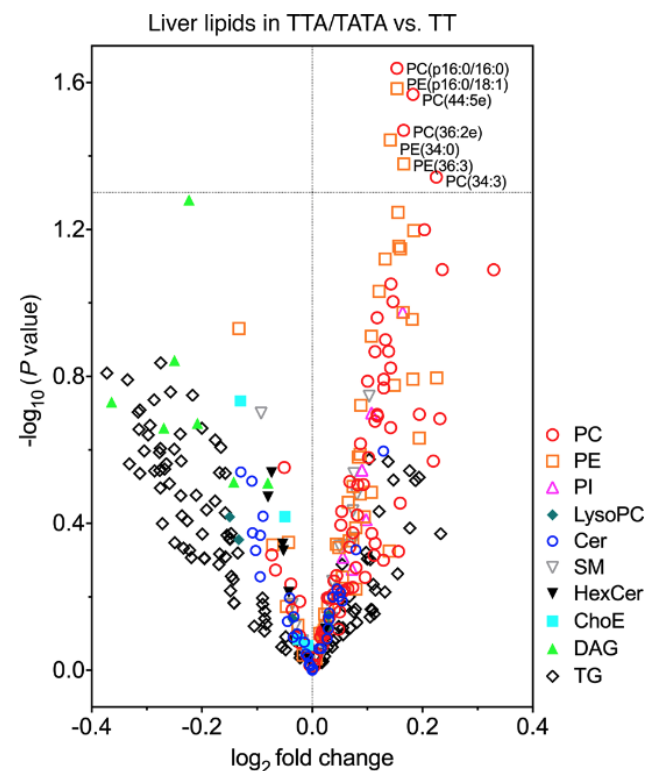
- Protective *HSD17B13* variant (rs72613567) disrupts splice site at exon 6
- As a result, wild-type mRNA isoform A is replaced with isoform D
- Isoform D protein is expressed at low levels in vivo and has minimal enzymatic activity in vitro
- **Conclusion: *HSD17B13* is a driver of NASH through an unknown mechanism of action**



- **Hypothesis:** siRNA-mediated knockdown of *HSD17B13* will mimic genetic loss of function, reducing hepatic inflammation, injury, and fibrosis in NASH patients

# Recent Findings Relevant to ALN-HSD Mechanism of Action

## Protective HSD17B13 Variant is Associated with Elevated Phosphatidylcholine and Phosphatidylethanolamine



**Figure 2. Increased hepatic phospholipids in carriers of the HSD17B13 rs72613567 variant.** Liver lipids are visualized as a volcano plot, in which y axes denote the  $-\log_{10}$  of  $P$  value of the  $t$  test between individual lipid species in the TTA/TATA ( $n = 38$ ) as compared with the TT group ( $n = 48$ ) and x axes denote the  $\log_2$  fold change of mean concentrations of an individual lipid species between the HSD17B13 groups. Differences were tested using independent 2-sample Student's  $t$  test. Each symbol denotes an individual lipid species. PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; LysoPC, lyso-phosphatidylcholine; Cer, ceramide; SM, sphingomyelin; HexCer, hexosylceramide; ChoE, cholesteryl ester; DAG, diacylglycerol; TG, triacylglycerol.

### Other findings (+/- protective variant)

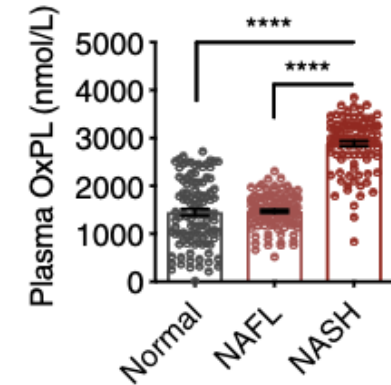
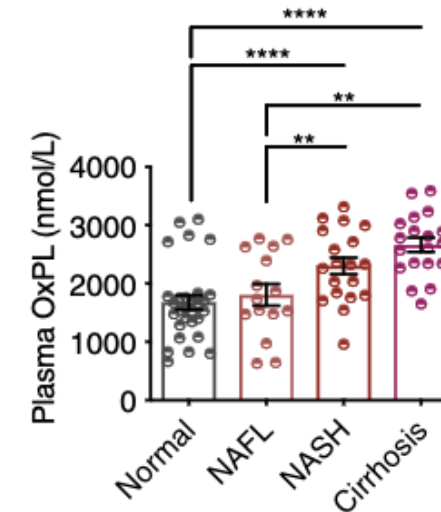
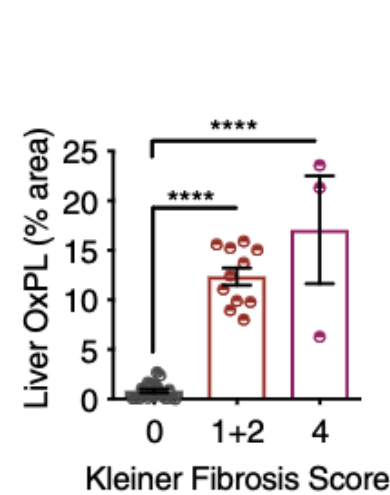
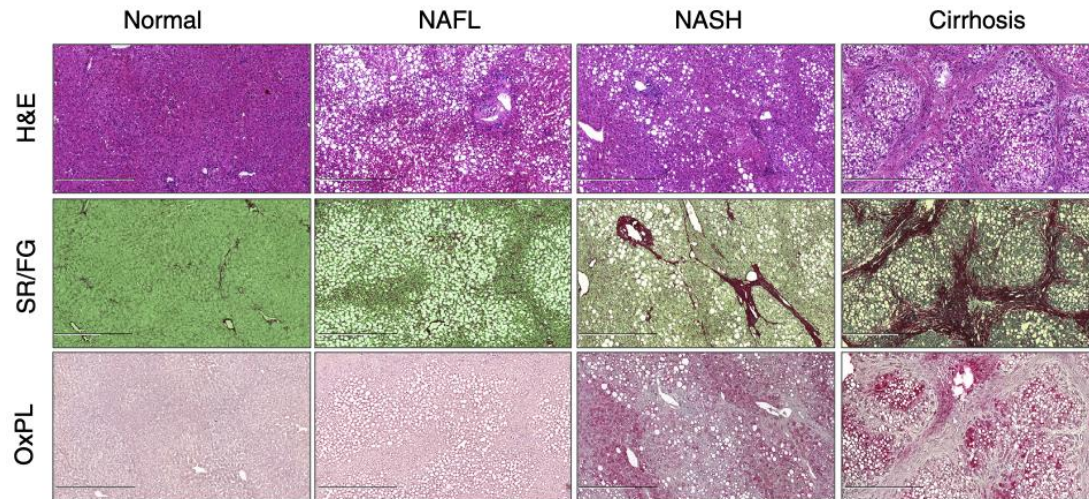
- RNA-seq: decreased inflammatory pathways, increased mitochondrial protein targeting pathways
- Plasma cytokines: slightly decreased IL-6, IL-1 $\beta$ , IL-10
- No differences in hepatic free fatty acids, de novo lipogenesis, adipose tissue lipolysis, or insulin sensitivity



# Recent Findings Relevant to ALN-HSD Mechanism of Action

Oxidized Phospholipids (OxPL) are Elevated in NASH and Neutralization is Protective in Mouse NASH Models

## Elevated OxPL in NASH: liver and plasma

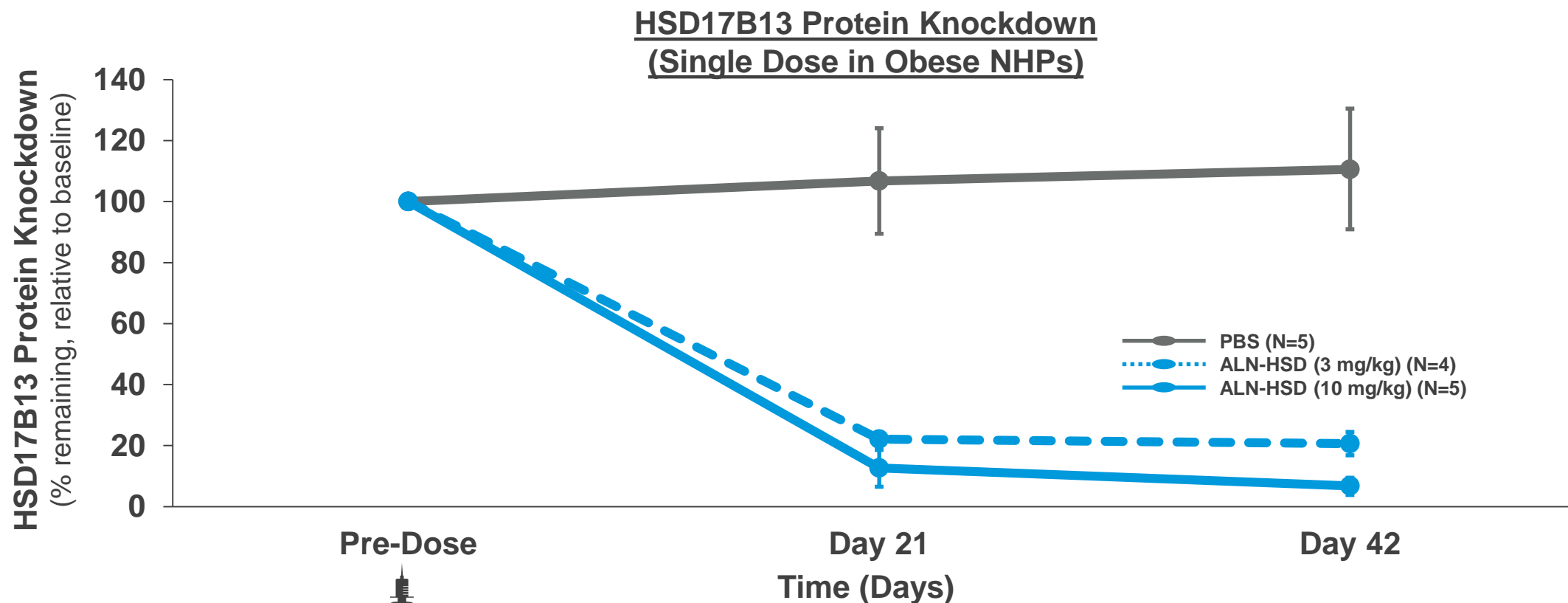


## Neutralization of OxPL:

- Protects mitochondrial function and number in NASH models and oxidative stress
- Reduces inflammation (macrophage number and activation) in NASH model

# ALN-HSD Pre-Clinical Development Highlights

Potent Dose-Dependent HSD17B13 Knockdown in Non-Human Primates



- ALN-HSD suppresses HSD17B13 both *in vitro* and *in vivo* (rodents and healthy and obese NHPs)
- Preliminary evidence suggesting highly durable pharmacodynamic profile
- No pre-clinical toxicity of concern observed, with high safety margins demonstrated

## Planned Next Steps for ALN-HSD

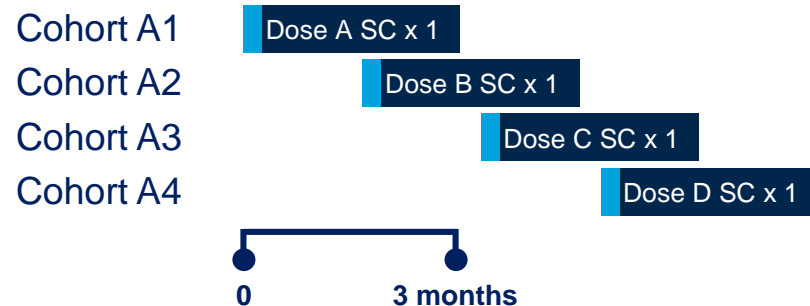


# ALN-HSD Proposed Phase 1 Design

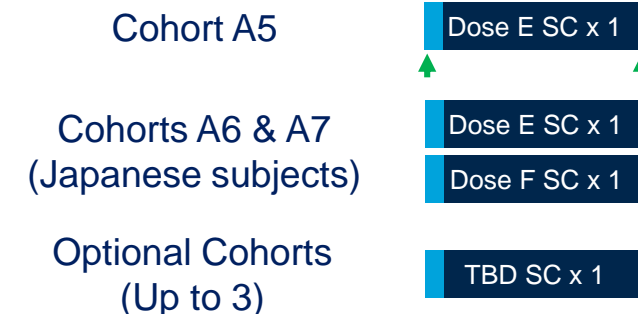
## Part A: Healthy Volunteers

- Single-ascending dose
- Planned liver biopsy in one cohort
- Two cohorts of Japanese subjects
- Up to 3 optional cohorts, including option of liver biopsy

### SAD Cohorts



### Other Cohorts

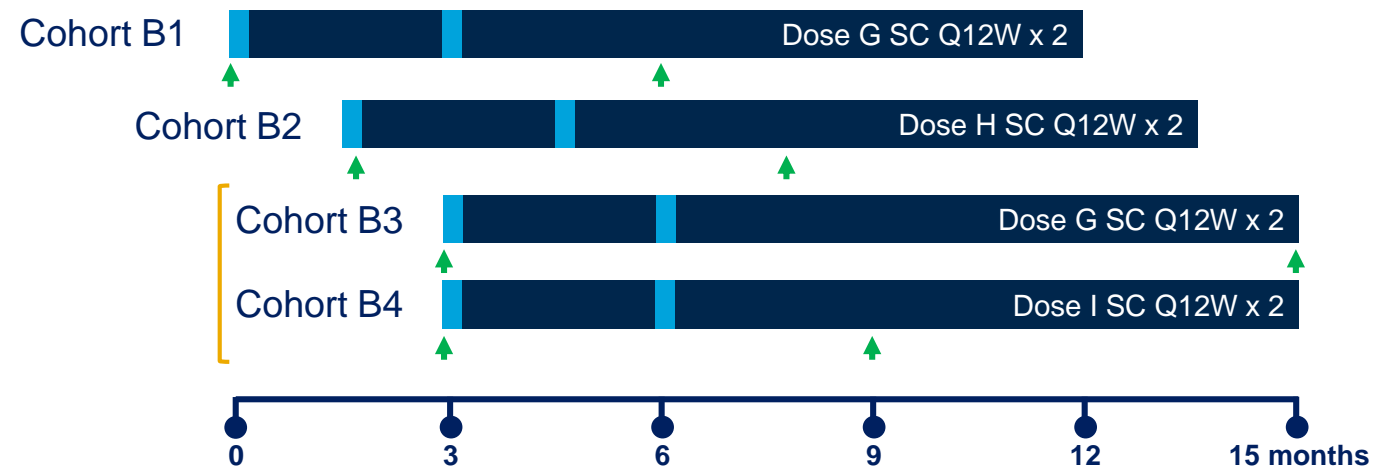


■ = study drug administration ▲ = planned liver biopsy

## Part B: NASH Patients

- Multiple-dose (2 doses)
- Baseline and post-dose liver biopsies
- Designed to:
  - Test doses predicted to result in 50, 80, and 90% maximal KD
  - Assess kinetics of recovery from maximal KD

### MD Cohorts



■ = study drug administration ▲ = planned liver biopsy

**Primary Endpoint:** Safety and tolerability of ALN-HSD

**Key Secondary Endpoints:** ALN-HSD PK/PD

**Exploratory Endpoints:** Identify potential biomarkers of HSD; Assess effects of ALN-HSD on histologic and circulating biomarkers of NASH

# ALN-HSD Summary

**Nonalcoholic steatohepatitis (NASH) is subset of nonalcoholic fatty liver disease (NAFLD) that can lead to progressive fibrosis, cirrhosis, and hepatocellular carcinoma**

- Represents significant unmet need: Approximately 16M people in U.S. live with NASH, with about 3M progressing to liver cirrhosis
- No medical therapies currently approved to treat NASH

**HSD17B13 identified as novel target for treatment of NASH**

- Loss-of-function variants in HSD17B13 associated with reduced risk of elevated ALT, non-alcoholic and alcoholic liver disease, cirrhosis, inflammation, and liver injury among patients with NAFLD

**ALN-HSD is an ESC+ GalNAc-siRNA conjugate targeting HSD17B13 with goal of reducing hepatic inflammation, injury, and fibrosis in NASH patients**

**CTA-enabling pre-clinical work completed with no pre-clinical toxicity of concern observed, with high safety margins demonstrated**

- CTA filing on track for mid-2020
- Phase 1 start planned for late 2020

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## RNAi Therapeutics for CNS Diseases

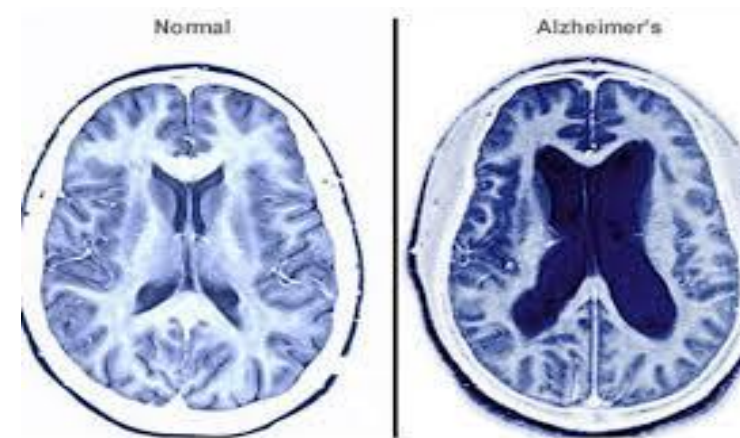
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# RNAi Therapeutics for CNS Diseases

No Current Therapies to Prevent or Restore Neurodegenerative Disease

- Dominantly inherited neurodegenerative diseases include
  - Alzheimer's disease
  - Amyotrophic lateral sclerosis (ALS)
  - Frontotemporal dementia
  - Huntington's disease
  - Parkinson's disease
  - Prion disease
  - Spinocerebellar ataxia
  - Many other orphan genetic diseases with CNS component
- Number of 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
- Based on pre-clinical studies, expect superior potency, duration and systemic safety profile vs. ASOs

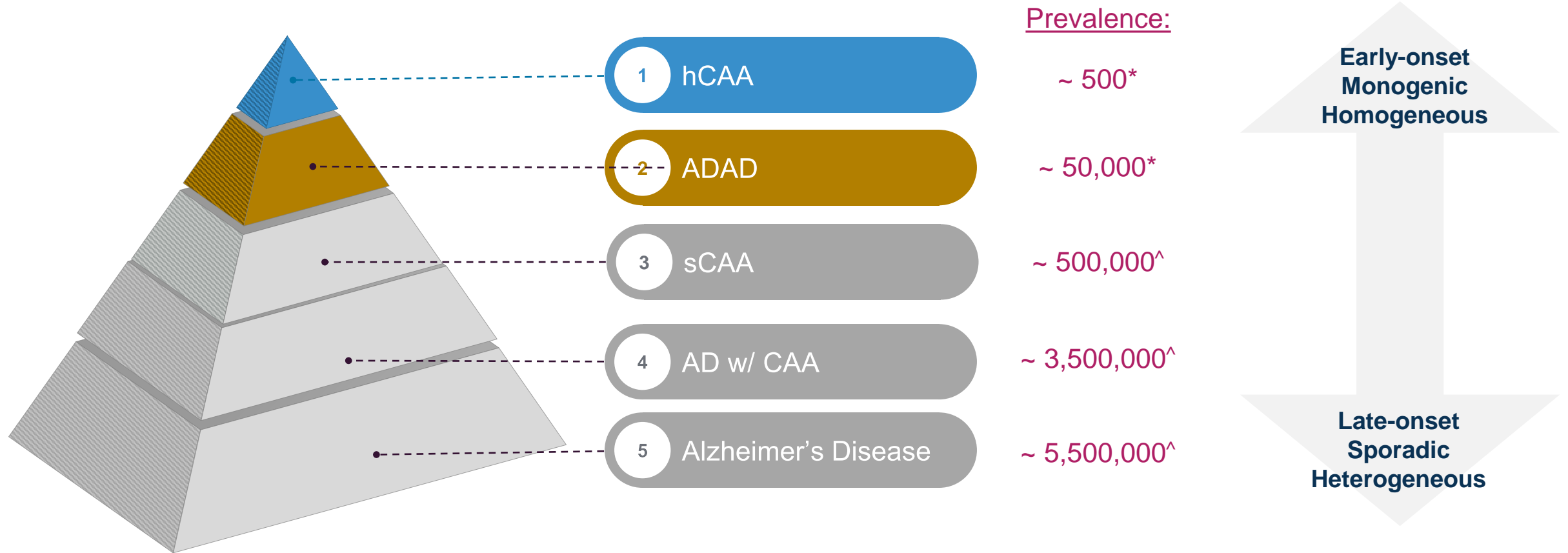




A woman with dark, wavy hair is looking out a window. She is wearing a dark red top and a gold necklace with a circular pendant. The background is a bright window with a dark frame.

## Amyloid Precursor Protein (APP) Program

# Study of hCAA and ADAD Provides Potential Gateway to Larger Indications

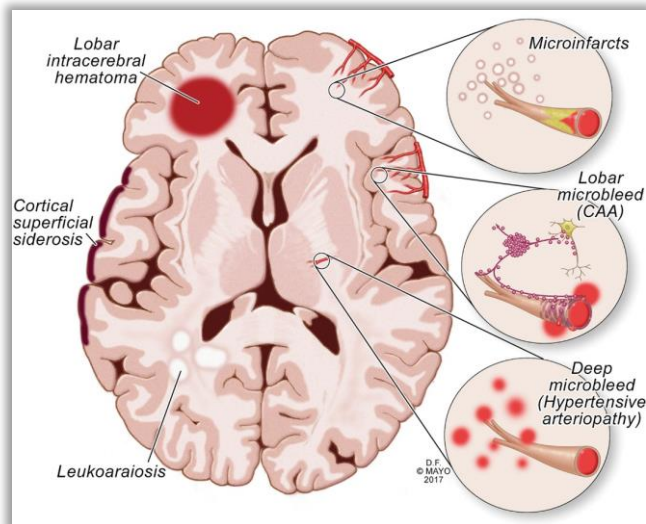


hCAA: hereditary cerebral amyloid angiopathy; ADAD: autosomal-dominant Alzheimer's Disease; sCAA: sporadic cerebral amyloid angiopathy; AD: Alzheimer's Disease; CAA: cerebral amyloid angiopathy  
^ U.S. \* global

# APP Targeting for Hereditary Cerebral Amyloid Angiopathy (hCAA)

## hCAA

Patients present with stroke-like presentation (intracerebral hemorrhage)



## BURDEN

- 100% of affected individuals share a common ancestor from the Netherlands
- Mean age of onset 54 years

## TARGET IDENTIFICATION

- Missense substitution in *APP* (p.Glu693Gln) increases production of A $\beta$ 40 and causes 100% of known cases of Dutch-type cerebral amyloid angiopathy
- Autosomal dominant, 100% penetrant genetic syndrome

## THERAPEUTIC HYPOTHESIS

- A $\beta$ 40 is made in neurons but then undergoes extracellular transit before deposition in the perivascular space
- RNAi-mediated knockdown of *APP* transcript in neurons may potentially lower production of A $\beta$ 40, halting toxic protein build-up

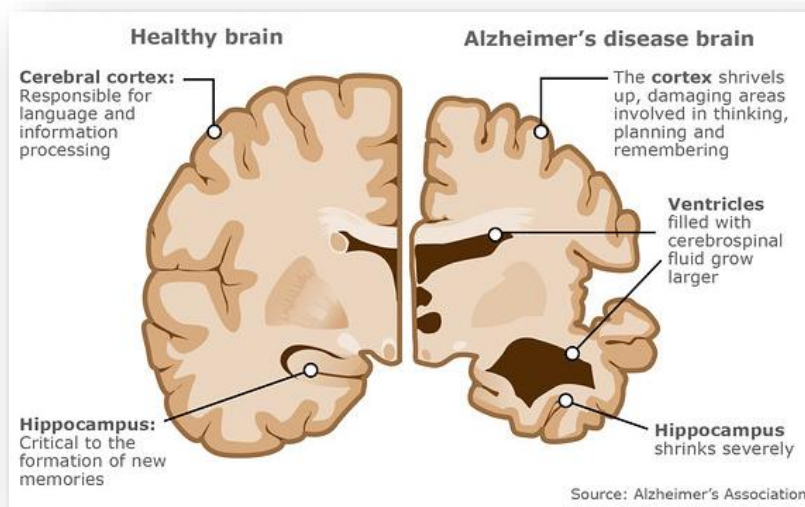
## OPPORTUNITY

- Application of Alnylam's CNS platform to reduce perivascular *APP*-derived amyloid in hCAA with no existing disease-modifying treatment
- Potential for expansion into sporadic CAA, a very common age-related cause of common hemorrhagic stroke

# APP Targeting for Autosomal Dominant Alzheimer's Disease (ADAD)

## ADAD

Patients develop rapidly progressive Alzheimer's-type dementia



## BURDEN

- ~50,000 affected globally
- Mean age of onset 44 years with rapid progression over 6-8 years

## TARGET IDENTIFICATION

- All ADAD causative genes identified to date (*APP*, *PSEN1*, *PSEN2*) regulate APP protein metabolism by increasing production of amyloid products, including A $\beta$ 42
- Autosomal dominant, nearly 100% penetrant genetic syndrome

## THERAPEUTIC HYPOTHESIS

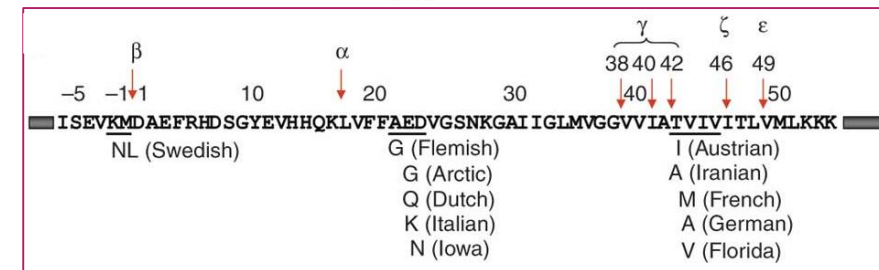
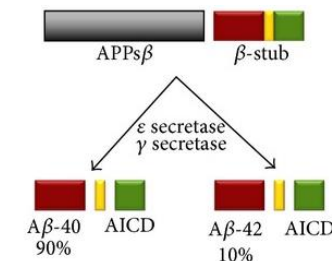
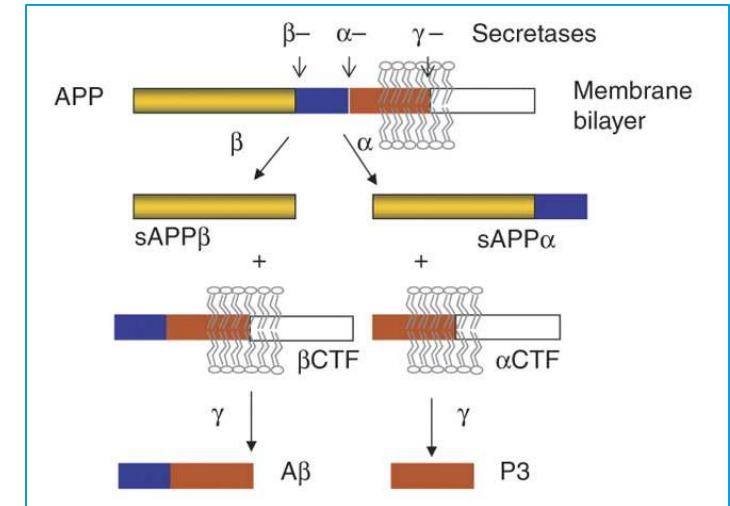
- A $\beta$ 42 is made in neurons and aggregates in the intracellular and extracellular brain parenchyma
- RNAi-mediated knockdown of *APP* transcript in neurons will lower production of A $\beta$ 42, halting aggregation and plaque formation

## OPPORTUNITY

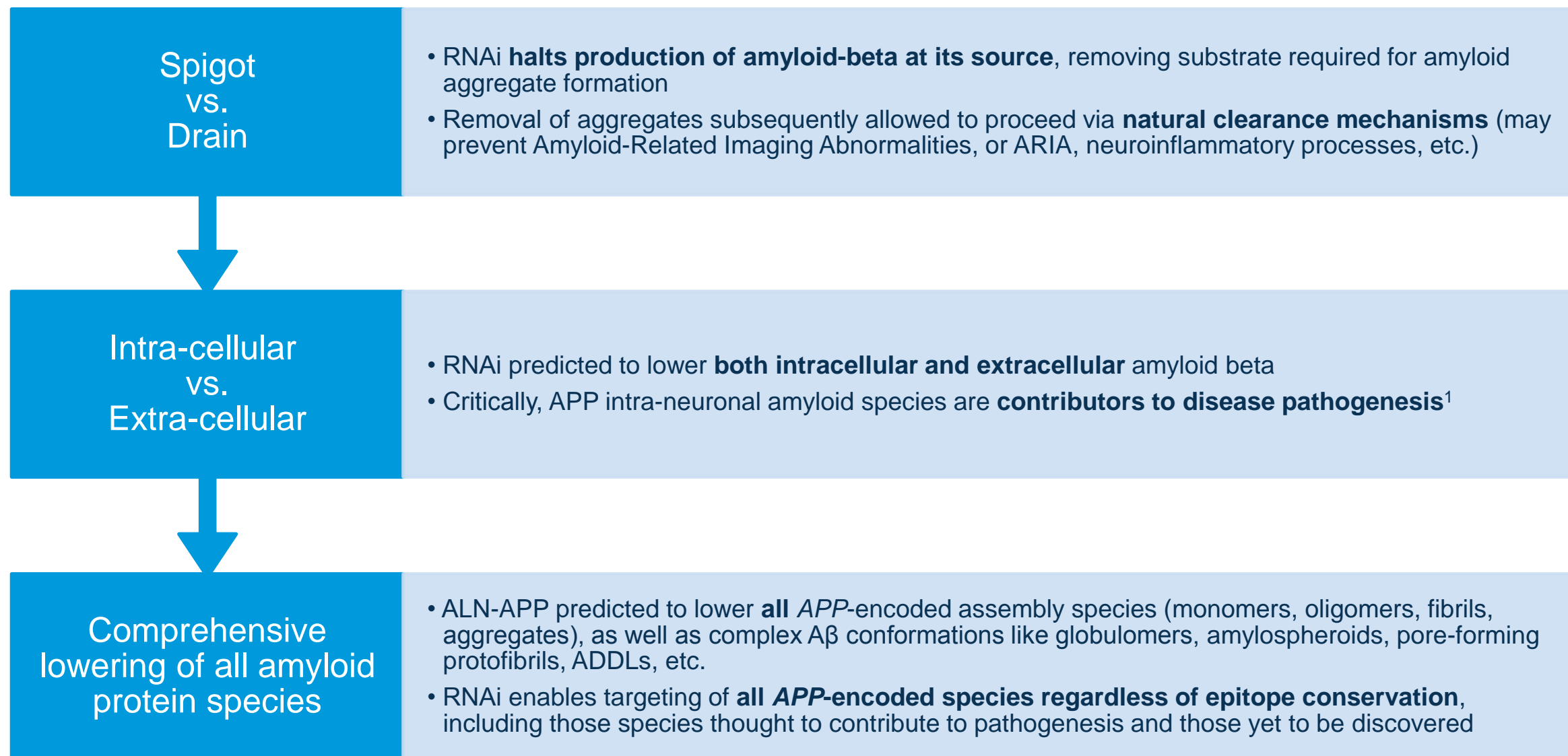
- Application of Anylam's CNS platform to reduce parenchymal *APP*-derived amyloid in ADAD with no existing disease-modifying treatment
- Potential for expansion into sporadic Alzheimer's disease

# Amyloid Precursor Protein (APP)

- 87 kDa membrane-associated protein produced in many tissues, but with highest expression in nervous system
- Thought to be involved in neurite growth, axonogenesis, and plasticity, though normal role poorly understood
  - APP KO mice exhibit mild deficits in behavioral performance
- Processed by serial secretase cleavage to produce soluble APP (sAPP) and other cleavage products
  - Cleavage by  $\alpha$ -secretase produces sAPP $\alpha$ , and  $\alpha$  c-terminal fragment (CTF)
  - Cleavage by  $\beta$ -secretase leads to production of sAPP $\beta$ ,  $\beta$ CTF, and, after further processing by  $\gamma$ -secretase, aggregation-prone  $\beta$ -amyloid peptides
- Autosomal dominant mutations in APP produce brain disease
  - Most pathogenic mutations in APP lead to early onset familial Alzheimer's Disease
    - Mutations in presenilin-1 and 2, components of the  $\gamma$ -secretase, also cause early onset familial Alzheimer's Disease
  - Certain APP mutations, such as Dutch mutation, lead to cerebral amyloid angiopathy, which also occurs frequently in conjunction with Alzheimer's Disease



# Potential Mechanistic Advantages of Silencing APP





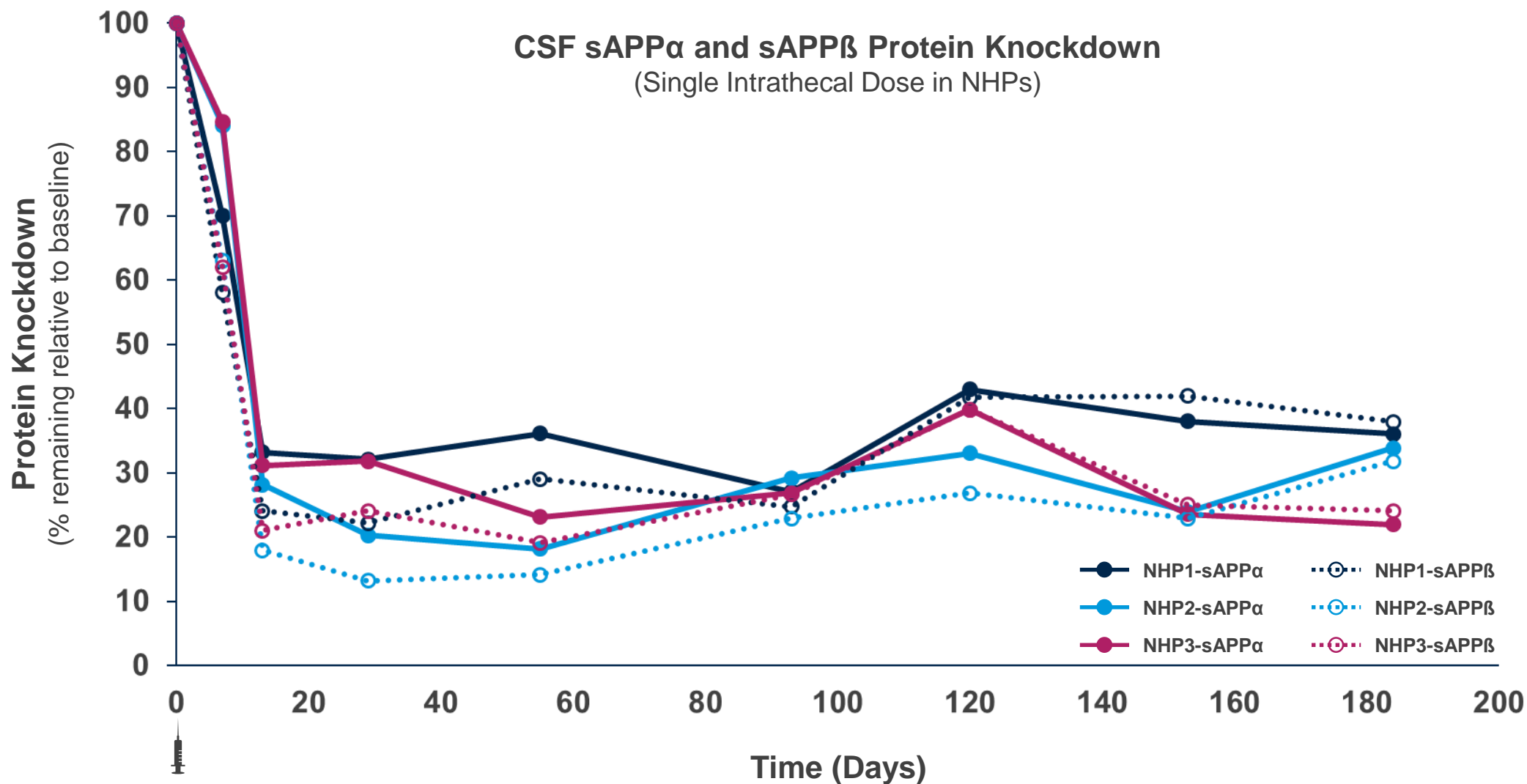
# RNAi Therapeutics Have Potential for Best-in-Class Mechanism Targeting APP

- Many monoclonal antibodies against  $\beta$ -amyloid peptides have been tested in clinical trials for AD. While several have cleared extracellular plaques, impact on disease is uncertain and likely modest.
- Unique aspects of RNAi as compared to monoclonal antibodies include:
  - Better pharmacokinetic and pharmacodynamic profile
  - Potential for greater durability, enabling less frequent dosing
  - Ability to target intracellular amyloid, to better define possible benefit of reducing both extracellular and intracellular deposits
  - No risk of antibody accumulation around clearance sites such as vasculature
  - Potentially less risk of ARIA, an amyloid antibody-associated adverse effect



# Highly Durable Amyloid Precursor Protein (APP) Knockdown in NHP

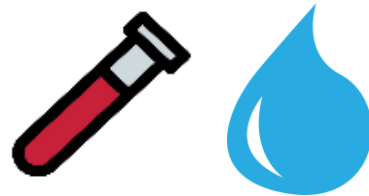
Single Intrathecal Dose of ALN-APP Supports Bi-Annual or Less Frequent Regimen



# ALN-APP Phase 1 Overview



Intrathecal  
Dose



Plasma and CSF  
biomarkers



Neuro  
Imaging



Clinical  
Measures

- Single Ascending Dose (SAD) trial in patients with symptomatic ADAD
- Primary endpoint: Safety and tolerability of ALN-APP
- Other potential endpoints: APP protein knockdown in plasma and cerebrospinal fluid, imaging, etc.
- All patients who complete study will be eligible to roll over into open-label extension (OLE) trial
- Highly motivated population pre-enrolled in Natural History study
- Population offers appropriate risk/benefit for safety, tolerability, and dose-finding

IND submission anticipated **mid-2021**

Phase 1 trial start anticipated **late 2021**

A woman with short dark hair, wearing a dark quilted jacket over a blue shirt, stands outdoors holding a dark cup. She is looking off to the side with a slight smile. The background consists of dense green foliage, including several tall, conical evergreen shrubs.

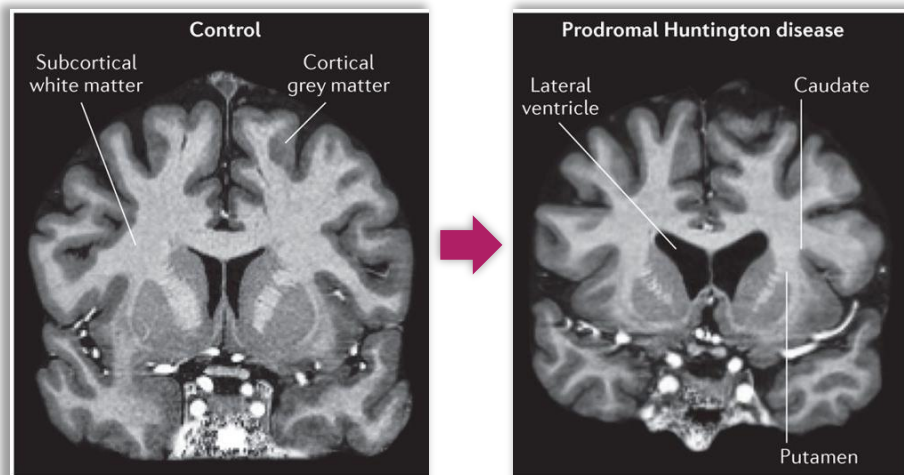
## Huntington (HTT) Program



# HTT Targeting for Early Manifest Huntington's Disease

## HTT

Patients present with progressive motor, cognitive and psychiatric decline



## BURDEN

- Affecting ~30,000 in U.S. with disease duration of 15-20 years

## TARGET IDENTIFICATION

- Autosomal dominant, gain-of-function genetic disease
- 100% age-related penetrance
- Trinucleotide repeat expansion in exon 1 of the Huntingtin gene (*HTT*)

## THERAPEUTIC HYPOTHESIS

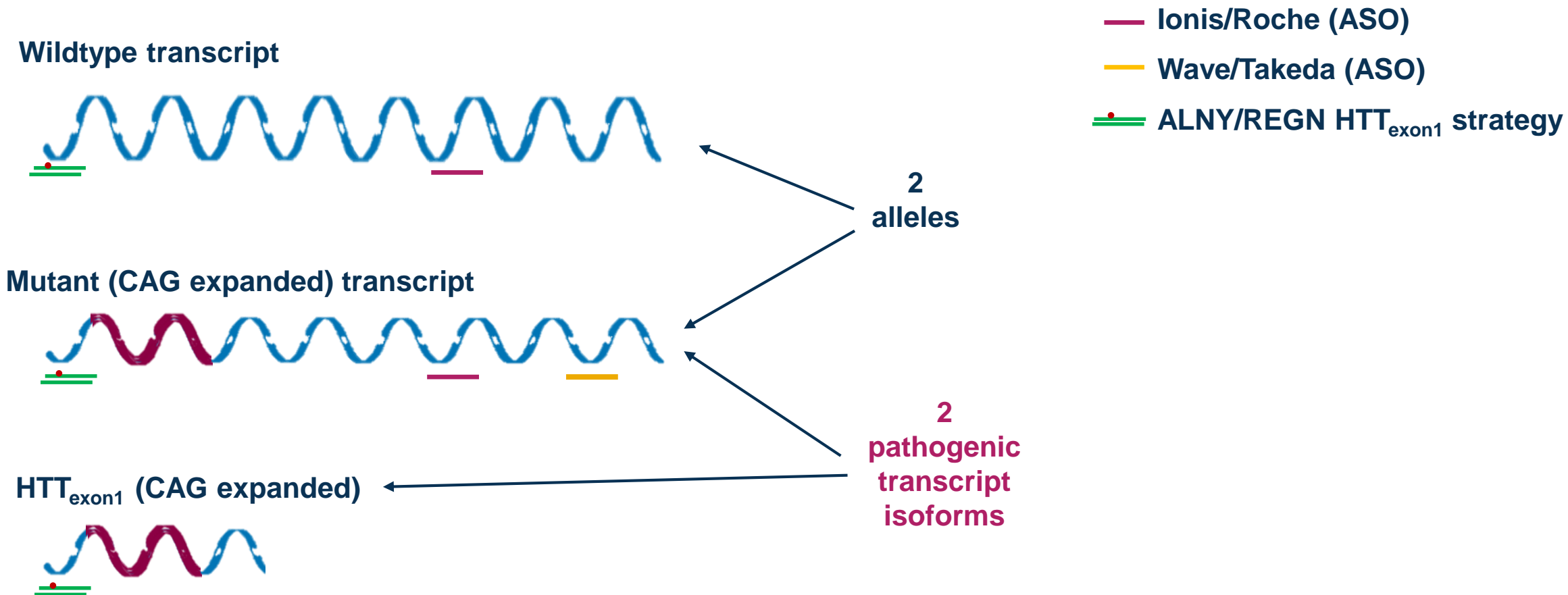
- RNAi-mediated knockdown of *HTT* transcript in neurons will reduce both RNA-induced and protein-induced neuronal toxicity, halting disease progression

## OPPORTUNITY

- Application of Alnylam's CNS platform to develop a therapeutic for a devastating progressive neurodegenerative condition
- Potential differentiation over competition via *HTT* exon 1 targeting strategy directed at pathogenic isoform that contributes to disease progression

# ALNY/REGN Primary Strategy to Target HTT

Targeting *HTT*<sub>exon1</sub> Potentially Offers Differentiated Strategy from Competitors



# HTT Program Summary and Next Steps

## Potential for best-in-class strategy with 3 key differentiating features

1. Exon 1 targeting
  - CAG-repeat length expands somatically throughout life leading to increased HTT<sub>exon1</sub> transcript expression
  - Hypothesis: HTT<sub>exon1</sub> transcript has outsized contribution to RNA-induced toxicity and seeding of nuclear aggregates
2. Superior delivery to striatum
  - CNS-targeting ligand enables enhanced deep brain biodistribution, including knockdown in caudate/putamen
3. Improved potency, duration and safety profile
  - Catalytic mechanism of RISC-mediated RNAi in neurons
  - Anticipate IT dosing q6 months with best-in-class safety profile

## Compelling opportunity in progressive disease with high unmet need

- ~30,000 patients in U.S. with disease duration of 15-20 years

## Next steps

- Development Candidate (DC) selection and IND-enabling work ongoing

# CNS Pipeline Strategy

Expanding Pipeline of Potentially Transformative Medicines in Neurological Diseases



**Genetically validated,  
CNS-expressed  
target gene**



**POC in  
Phase 1**



**Definable path to  
approval and  
patient access**

## CNS objectives include:

1. Advance 1<sup>st</sup> DC through 2020 with goal of 1<sup>st</sup> IND filing in mid-2021
2. First human proof of concept for RNAi platform in CNS expected from ALN-APP program
3. Continue to advance 1-2 CNS candidates per year, including IND filings and clinical trial starts



# Agenda

## Welcome

- Joshua Brodsky – Director, Investor Relations & Corporate Communications

## Introduction

- Vasant Jadhav, Ph.D. – Vice President, Research

## NASH Overview and ALN-HSD Development Program

- Josh Friedman, M.D., Ph.D. – Senior Director, Clinical Research

## RNAi Therapeutics for CNS Diseases

- Tanya Fischer, M.D., Ph.D. – Vice President, Clinical Development

## Q&A Session

## Upcoming RNAi Roundtables

### Lumasiran, in Development for the Treatment of Primary Hyperoxaluria Type 1

- Monday, August 10, 2:00 pm ET


### Patisiran and Vutrisiran, in Development for the Treatment of ATTR Amyloidosis

- Date TBD

### Givosiran, for the Treatment of Acute Hepatic Porphyria

- Monday, September 14

Additional details for upcoming RNAi Roundtables will be provided on the Capella section of the Company's website, [www.alnylam.com/capella](http://www.alnylam.com/capella)



To those who say “impossible, impractical,  
unrealistic,” we say:

**CHALLENGE ACCEPTED**