ALN-APP Interim Phase 1 Results

April 26, 2023

Agenda

Welcome

- Christine Lindenboom
  Senior Vice President, Investor Relations & Corporate Communications

Overview

- Yvonne Greenstreet, MBChB, MBA
  Chief Executive Officer

ALN-APP Interim Phase 1 Results

- Pushkal Garg, M.D.
  Chief Medical Officer

Bringing RNAi Therapeutics to Neurologic Diseases

- Akshay Vaishnaw, M.D., Ph.D.
  President

Q&A Session

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This presentation discusses investigational RNAi therapeutics and is not intended to convey conclusions about efficacy or safety as to those investigational therapeutics. There is no guarantee that any investigational therapeutics will successfully complete clinical development or gain health authority approval.

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Yvonne Greenstreet, MBChB, MBA

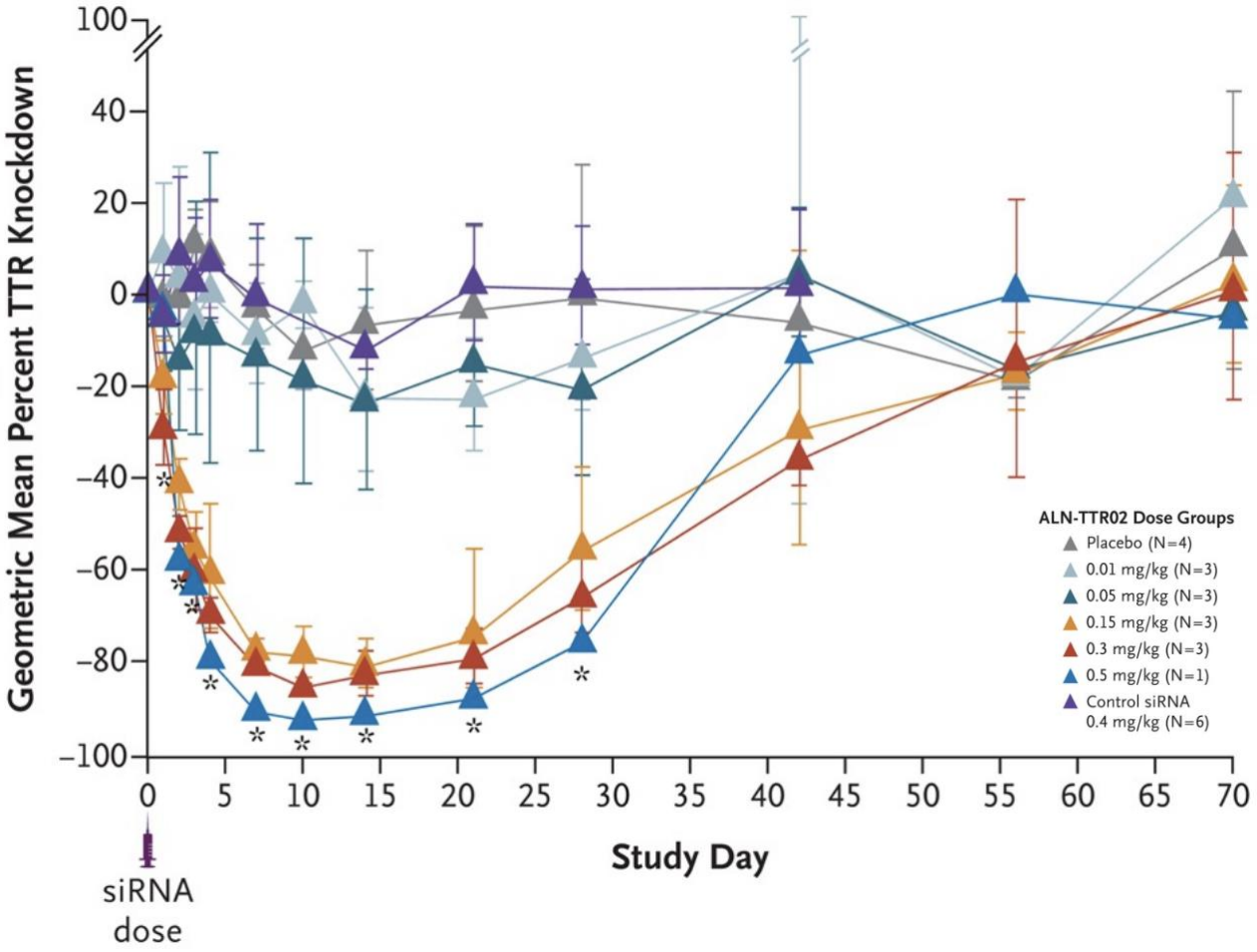
Chief Executive Officer

Overview

2012: Initial Clinical Evidence of Safe and Robust Target Knockdown in Liver

Led to Development of Broad Commercial and Investigational Product Portfolio

Efficacy of Patisiran in Healthy Volunteers*



Current Alnylam Liver-Targeting RNAi Therapeutics

Phase 3

Patisiran

Vutrisiran

Fitusiran

Cemdisiran

Phase 2

Zilebesiran

ALN-HBV02

ALN-HSD

Phase 1

ALN-TTRsc04

ALN-KHK

ALN-PNP

* Coelho et al., *N Engl J Med* 2013; 369:819-829

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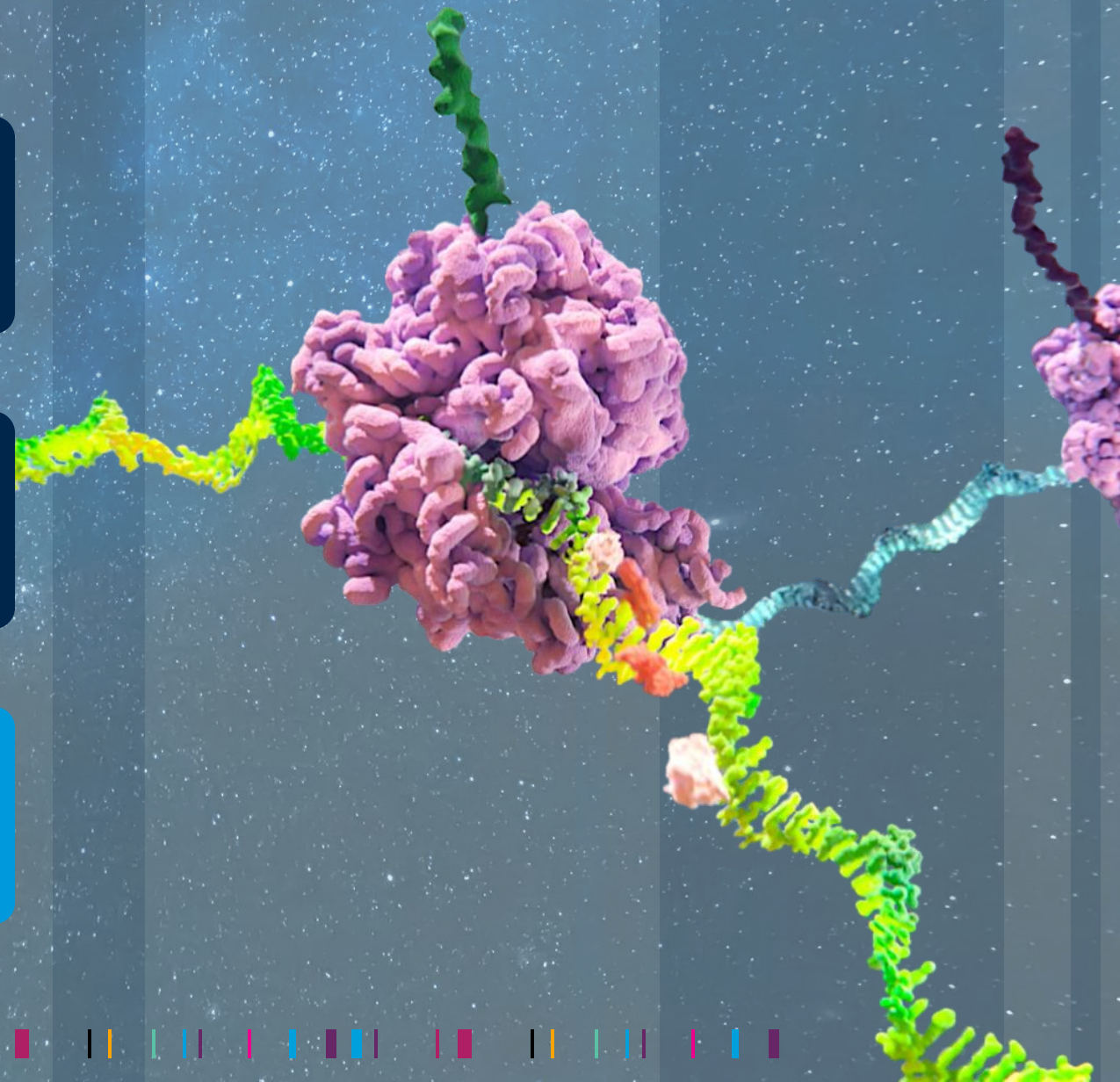
Multiple Drivers of Future Growth

TTR Franchise Leadership

Expansion Beyond Rare Diseases

Engine for Sustainable Innovation



Ambitious Five-Year Strategy to Drive Growth

Alnylam P5x25

Patients: Over 0.5 million on Alnylam RNAi therapeutics globally

Products: 6+ marketed products in rare and prevalent diseases

Pipeline: Over 20 clinical programs, with 10+ in late stages and 4+ INDs per year

Performance: ≥40% revenue CAGR through YE 2025

Profitability: Achieve sustainable non-GAAP profitability within period

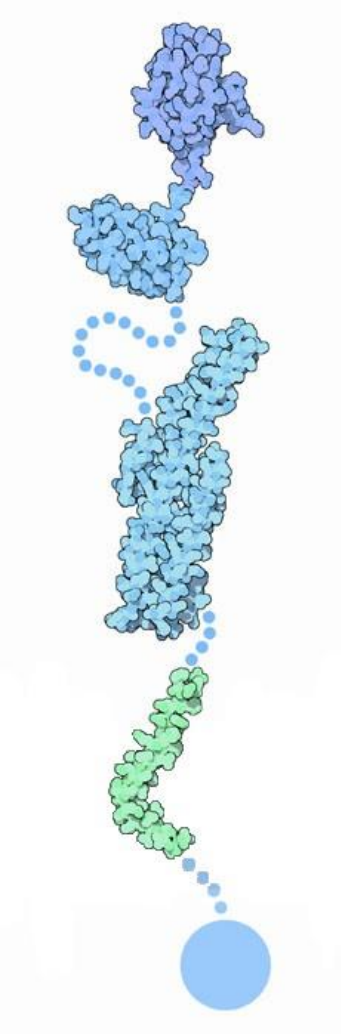
Pushkal Garg, M.D.

Chief Medical Officer

ALN-APP Interim Phase 1 Results

Amyloid Precursor Protein (APP)

Target for Alzheimer's Disease and Cerebral Amyloid Angiopathy



APP: One target, two distinct pathological processes

- ☑ Genetically validated target for AD and CAA
- ☑ Soluble biomarkers of target engagement (sAPPα and sAPPβ) in CSF
- ☑ Significant patient population with high unmet need in both diseases
  - AD: Over 5M people affected in U.S. (over 30M worldwide)
  - CAA: Second leading cause of intracerebral hemorrhage

Alzheimer's Disease (AD)

- APP mutations and duplications cause Early Onset AD
- Amyloid deposits in brain tissue, tau tangles in neurons, neurodegeneration

Cerebral Amyloid Angiopathy (CAA)

- APP mutations cause hereditary CAA
- Amyloid deposits in walls of vessels in CNS and results in cerebral hemorrhages and cognitive impairment

APP Protein Structure courtesy of David S. Goodsell and the RCSB Protein Data Bank

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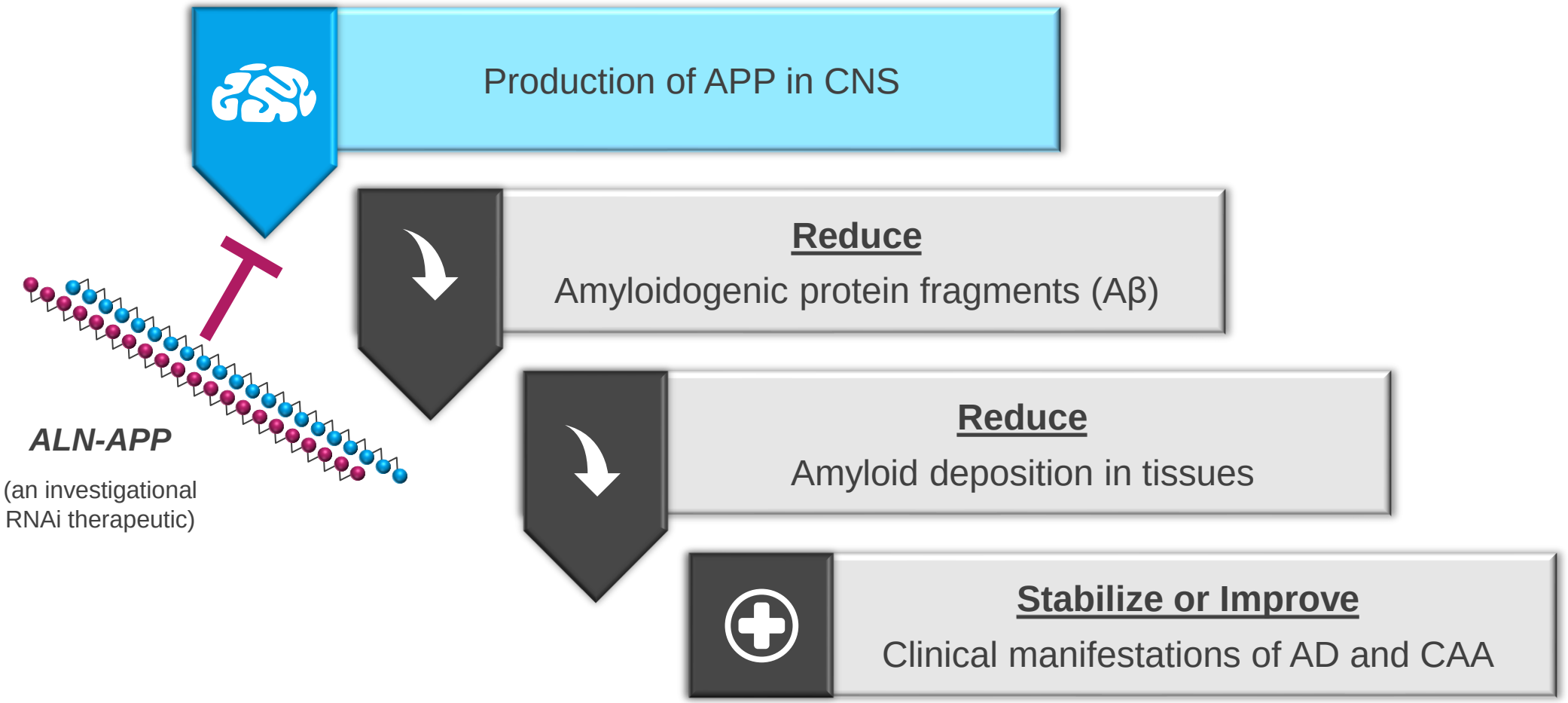
Building on Success of RNAi Therapeutics for Other Types of Amyloidosis

ALN-APP is Designed to Reduce APP Protein Production Upstream of Amyloidogenic Process

Therapeutic hypothesis



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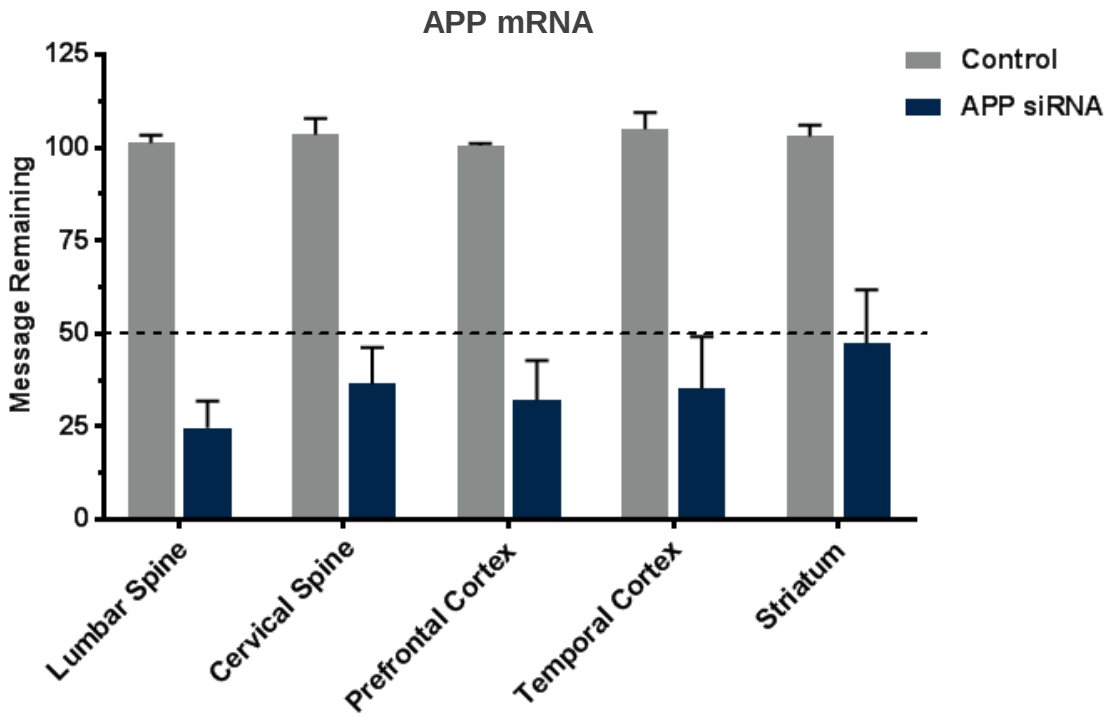
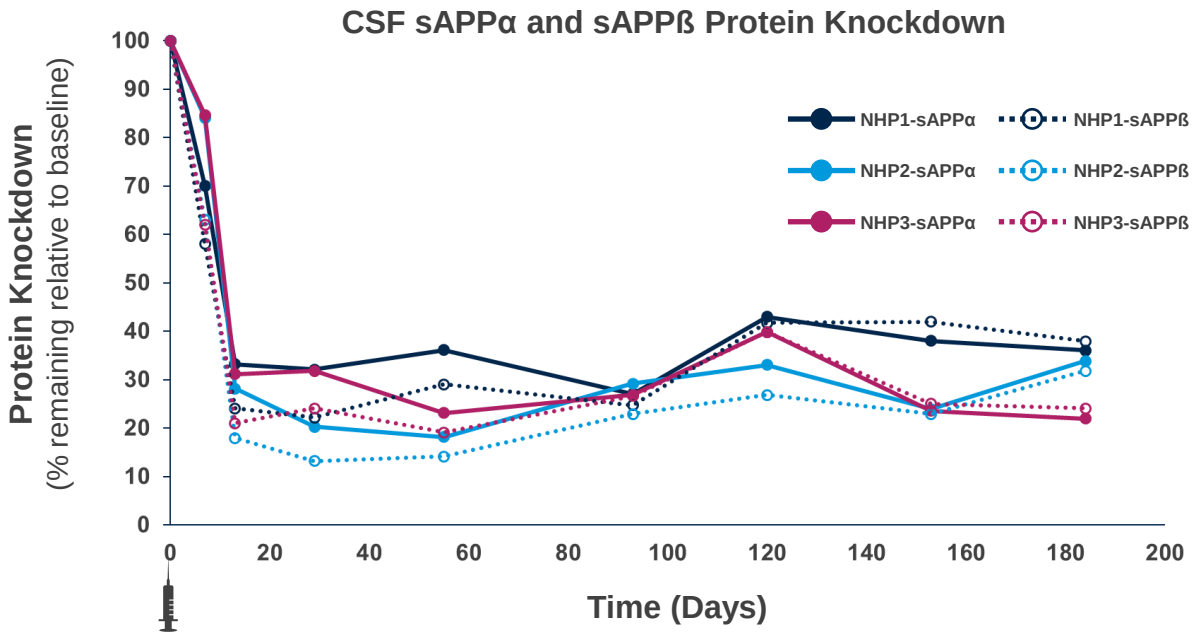
Preclinical Data Demonstrate Extensive, Potent, and Durable APP Reduction

Non-Human Primate Data of APP-targeting siRNAs

Single Intrathecal Dose of APP siRNA Distributes Throughout Spine and Brain



Single Intrathecal Dose of APP siRNA Supports Biannual or Less Frequent Regimen



Data on file

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ALN-APP Phase 1 Overview

Randomized, Double-Blind Study in Patients with Early-Onset Alzheimer's Disease (EOAD)

Part A: Single Ascending Dose
(Ongoing)

Part B: Multiple Dose
(expected to begin 2023)

- **Population**: Patients with Early Onset Alzheimer's Disease
- **Primary Objective**: Safety and tolerability of ALN-APP
- **Secondary Objective**: Pharmacology of ALN-APP
- **Exploratory Objective**: Impact of ALN-APP on disease
  - Fluid biomarkers for amyloid, tau, and neurodegeneration
  - Measures of synaptic health
  - Neuroimaging
  - Exploratory cognitive and functional clinical measures

Dose exploration continuing in Part A

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Interim Phase 1 Results

- Twenty patients with early-onset Alzheimer's disease enrolled in 3 single-dose cohorts in Part A of Phase 1 study

- Single doses of ALN-APP well tolerated to date
  - All adverse events (AEs) mild or moderate in severity
  - Available CSF data, including white blood cells and protein appeared similar to placebo
  - Early data for neurofilament light chain (NfL) also looked comparable to placebo

- ALN-APP treatment led to dose-dependent, rapid, and sustained reduction in soluble APPα and APPβ in CSF
  - Robust decline in biomarkers seen as early as Day 15
  - Maximum knockdown of 84% and 90% for sAPPα and sAPPβ, respectively
  - Median knockdown of both biomarkers of greater than 70% sustained for at least 3 months at highest dose

Next Steps

- Part A of Phase 1 study ongoing to further explore single doses and characterize durability in Canada, Netherlands, United Kingdom and United States

- Multiple dose regimens to be evaluated in Part B will be informed by learnings from Part A
  - To support initiation of Part B in U.S., additional pre-clinical data and interim Phase 1 clinical data will be shared with FDA to address findings from chronic toxicology studies and partial clinical hold
  - Part B has received regulatory approval to proceed in Canada, where majority of Part A patients have been enrolled

- Detailed interim results planned to be presented at upcoming scientific conference

Akshay Vaishnaw, M.D., Ph.D.

President

Bringing RNAi Therapeutics to Neurologic Diseases

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RNAi Therapeutics for CNS Diseases

No Current Therapies to Prevent Loss of, or Restore, Function in Neurologic Disease

Very high unmet need for new treatments for CNS Diseases

- Genetically defined neurologic 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
- Significant opportunity for RNAi therapeutics directed to disease-causing, CNS-expressed genes

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Positive Interim Phase 1 Results with ALN-APP

First Ever Clinical Results of RNAi Therapeutics in CNS Establish Human Translation of Platform

- ☑ Robust target engagement
- ☑ Durable
- ☑ Clinically relevant
- ☑ Encouraging safety profile

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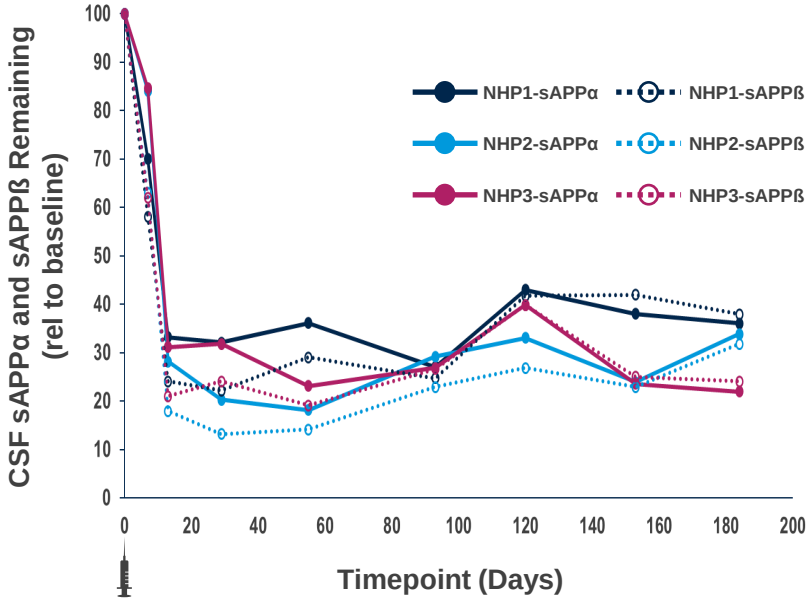
Modular and Reproducible Platform for Silencing CNS Disease Genes

Potent and Durable Knockdown After Single Intrathecal Injection in Non-Human Primates

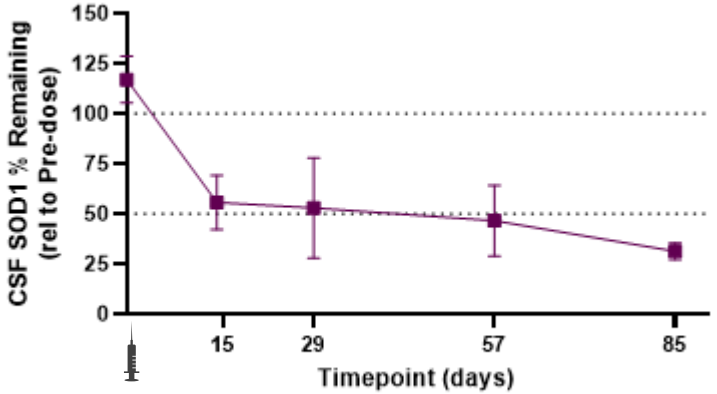
Clinical Stage

CSF sAPPα and sAPPß

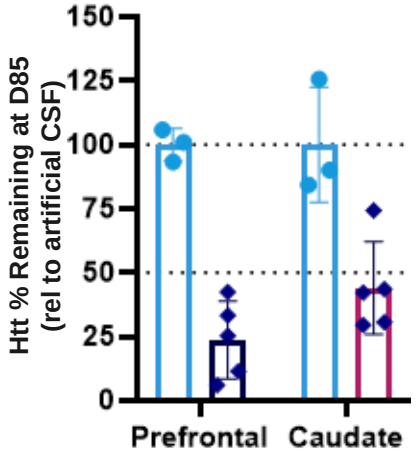


IND-Enabling Development

CSF SOD1

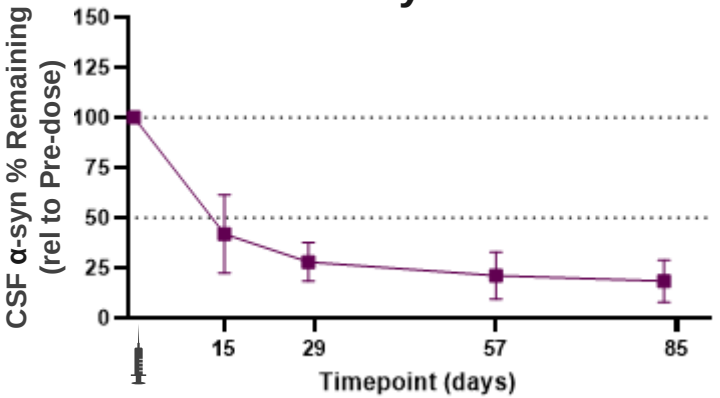


Huntingtin

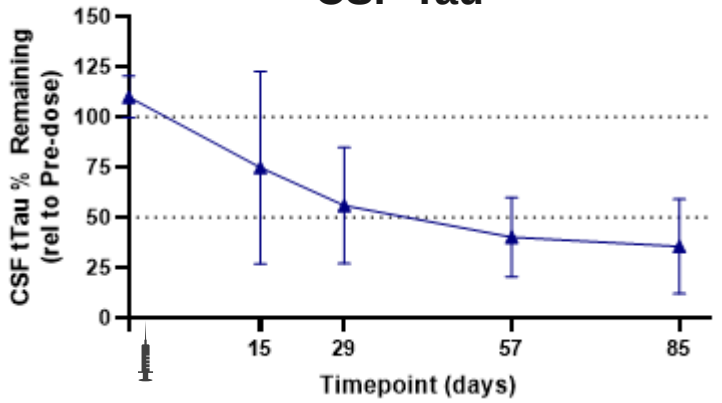


Next Wave of CNS Targets

CSF α-synuclein



CSF Tau



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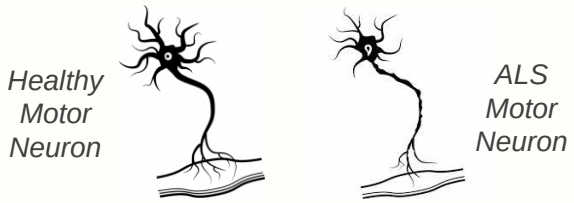
Leading RNAi Therapeutics to New Frontiers

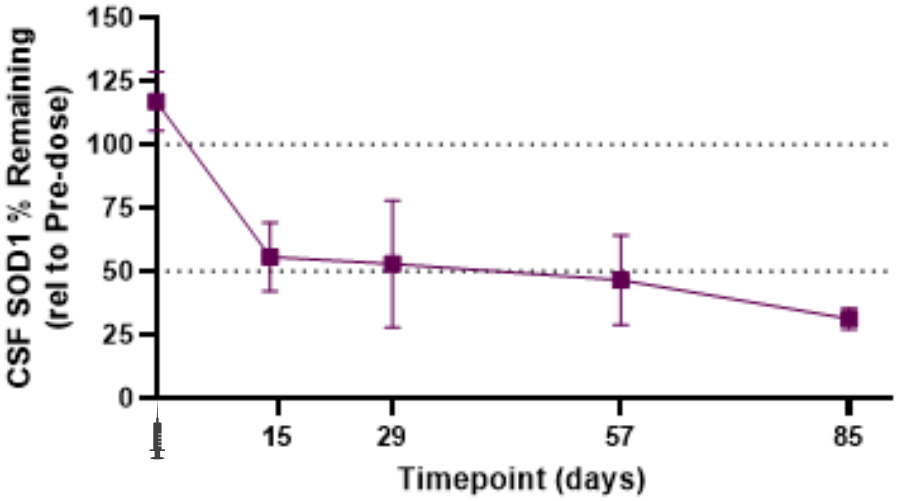
Potential to Open New Opportunities in CNS

ALN-SOD: SOD1-Specific ALS

Fatal progressive neurodegenerative disease characterized by motor neuron loss in the spinal cord and brain

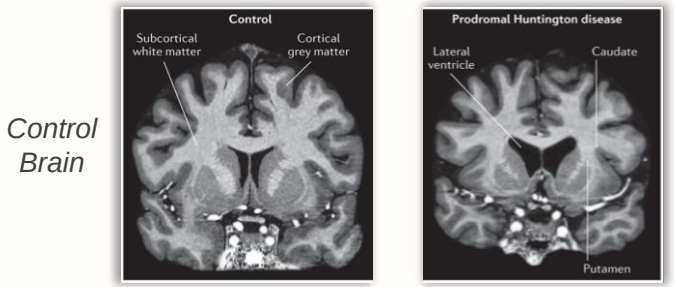


Program status:
Development Candidate selected
Advancing toward IND



ALN-HTT: Huntington's Disease

Fatal progressive neurodegenerative disease characterized by motor, cognitive, and psychiatric decline



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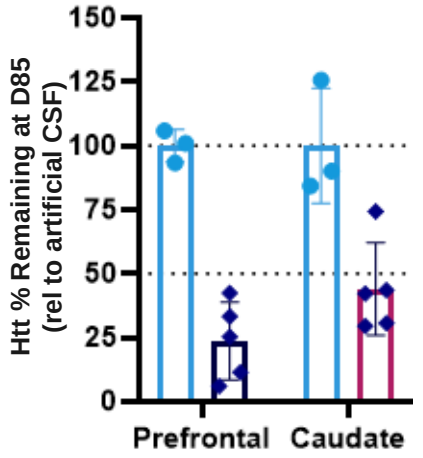

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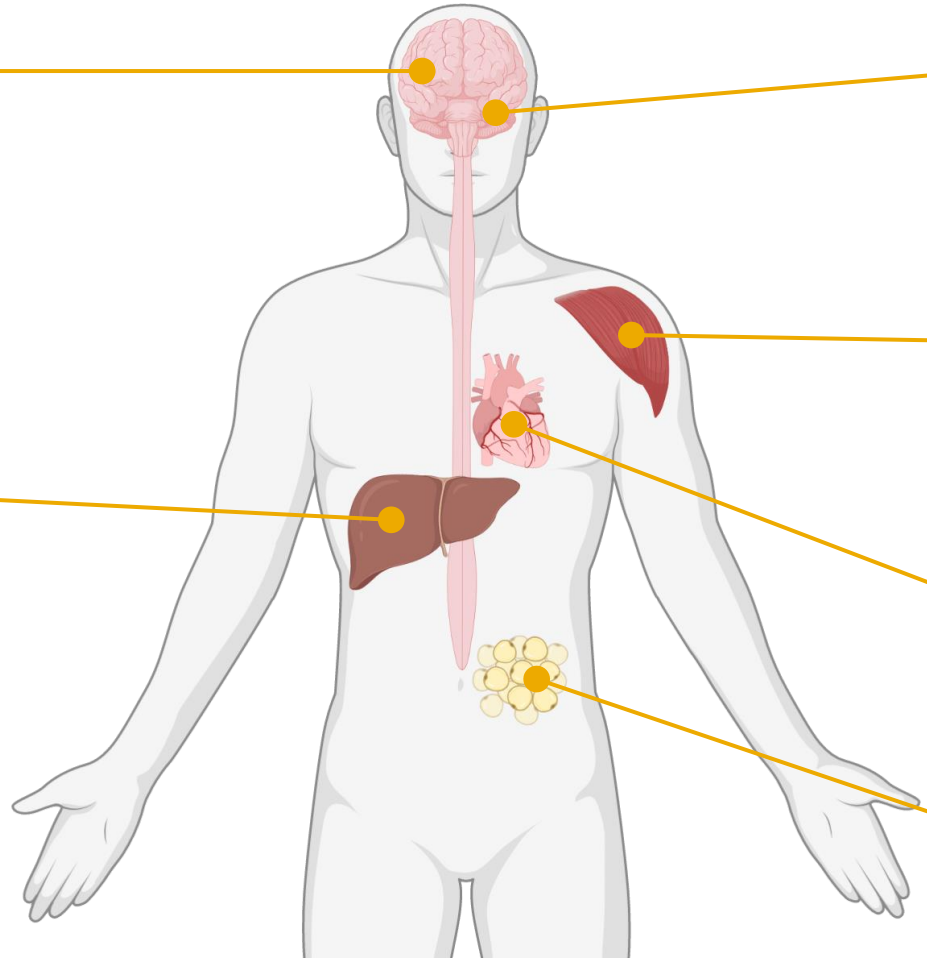
Target Opportunities for RNAi Therapeutics Across Range of Tissues

Many With Very High Unmet Need for New Treatments

CNS
- *Alzheimer's Disease*
- *Amyotrophic Lateral Sclerosis*
- *Frontotemporal Dementia*
- *Huntington's Disease*
- *Parkinson's Disease*
- *Spinocerebellar Ataxia*

LIVER
- *ATTR Amyloidosis*
- *Acute Hepatic Porphyria*
- *Primary Hyperoxaluria*
- *Hypercholesterolemia*
- *Hemophilia*
- *Hepatitis B Virus*
- *Hypertension*
- *NASH*
- *Cardiometabolic diseases*
- *Diabetes*



EYE
- *Glaucoma*
- *Age-related Macular Degeneration*
- *Stargardt Disease*

MUSCLE
- *Duchenne Muscular Dystrophy*
- *Facioscapulohumeral Muscular Dystrophy*
- *Metabolic Disease*

HEART
- *Heart Failure*
- *Atrial Fibrillation*

ADIPOSE
- *Metabolic Syndrome*
- *Obesity*
- *Lipodystrophy*

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ALN-APP Interim Phase 1 Results

Q&A Session

Thank You!

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