Mivelsiran (ALN-APP)

An Investigational RNAi Therapeutic in Development for the Treatment Of Alzheimer's Disease (AD) and Cerebral Amyloid Angiopathy (CAA)

Overview

- Mivelsiran is an investigational, intrathecally administered RNAi therapeutic targeting amyloid precursor protein (APP) in development for the treatment of Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA).
- APP is a genetically validated target for both AD and CAA. Genetic mutations that increase production of APP or alter its cleavage cause AD, CAA, or both.[1]
- Mivelsiran is designed to decrease APP mRNA in the central nervous system (CNS) and thereby may reduce synthesis of APP protein and all downstream intracellular and extracellular APP-derived cleavage products, including amyloid beta (Aβ).[2]
- The therapeutic hypothesis is that mivelsiran may enable the reduction of all Aβ isoforms as well as all other APP-derived peptides by targeting APP at the mRNA level. Because RNAi occurs upstream of APP protein production, the effect may alter amyloid levels both intracellularly and extracellularly, which may enable mivelsiran to address the drivers of the disease.[3]
- The interim Phase 1 results from the mivelsiran development program represent the first-human translation of an RNAi therapeutic targeting CNS diseases. The clinical candidate was designed using Alnylam's proprietary C16-siRNA conjugate technology, which enables enhanced delivery to cells in the CNS.

Phase 1 Clinical Development

- **About the Phase 1 Study of Mivelsiran in Patients with Early-Onset Alzheimer's Disease (EOAD)** (NCT05231785)[4]
  - Ongoing multi-center trial designed to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic effects of intrathecally administered mivelsiran in patients with EOAD.
  - The primary objective is to evaluate the safety and tolerability of mivelsiran; the secondary objective is to evaluate the pharmacology of mivelsiran.
  - The study is being conducted in two parts: a single ascending dose phase and a multiple dose phase. The single ascending dose (Part A) is randomized, double-blind, placebo-controlled and the multiple dose phase (Part B) is open label. The planned enrollment for this study is up to 60 patients.[4]

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Unmet Needs in AD and CAA

- AD is the most common neurodegenerative disease and the most common form of dementia, affecting over 30 million people worldwide.[5]
    - AD is characterized by progressive memory loss and cognitive decline. In AD, the accumulation of beta-amyloid plaques and neurofibrillary tangles leads to chronic inflammation in the brain which ultimately results in significant brain atrophy. Disease progression results in progressive loss of independence, increased caregiver burden, institutionalization, and premature death.[6]
    - EOAD refers to a subgroup of AD with symptom onset prior to the age of 65, representing approximately 4% to 6% of all AD. EOAD is the leading cause of dementia in younger individuals and is a significant cause of disability and early mortality.[7]
    - There are currently no approved RNAi therapeutics for AD.[8]
- CAA is the second most common cause of spontaneous intracranial hemorrhage (ICH), the most severe type of stroke.[9,10]
    - CAA is defined by progressive deposition of Aβ into the walls of small arteries, arterioles and capillaries in the brain, causing impaired vascular reactivity, focal tissue damage and increased risk for intracerebral hemorrhage.
    - CAA progresses over time: amyloid deposits spread and vascular damage becomes more severe. CAA has also been shown to be an independent contributor to cognitive impairment. More severe CAA pathology is associated with faster rate of cognitive decline.
    - There are currently no approved RNAi therapeutics for CAA.

For more information about ALN-APP, please contact media@alnylam.com or visit alnylam.com.

The safety and efficacy of ALN-APP have not been evaluated by the U.S. Food and Drug Administration, European Medicines Agency, or any other health authority.

The ALN-APP program is being developed in collaboration with Regeneron Pharmaceuticals.

Current information as of May 2024.

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1 Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, et al. Nat Rev Neurol. 2020;16(1):30–42.
2 K Brown et al. Discovery and nonclinical development of ALN-APP, an investigational RNAi therapeutic. Presented at AD/PD April 2023.
3 Brown KM, Nair JK, Janas MM, et al. Nature Biotechnology. 2022;40:1500-1508.
4 A Study to Evaluate the Safety and Tolerability of ALN-APP in Patients With EOAD. Available from: https://clinicaltrials.gov/ct2/show/NCT05231785. Accessed June 2023.
5 Haque RU, Levey AI, et al. Proc Natl Acad Sci U S A. 2019;116(52):26224-9.
6 2020 Alzheimer's disease facts and figures. Alzheimer's Dement. 16:391-460.
7 Mendez MF. Neurol Clin. 2017;35(2):263–281.
8 Cummings J. Mol Neurodegener. 2021;16(1):2.
9 Vilela P, Wiesmann M. Diseases of the Brain, Head and Neck, Spine 2020–2023: Diagnostic Imaging. Cham (CH): Springer; 2020. Chapter 5.
10 Woo D, Comeau M, Venema S, et al. JAMA Netw Open. 2022;5(3):e221103.

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