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### **Human proof of concept of ABCA1 agonist CS6253 treatment**

*This Phase 1 clinical trial will evaluate the safety and tolerability of a novel compound aimed at APOE and the brain's lipid transport system. This trial will also explore related biological markers.*

#### **Background**

The apolipoprotein E (APOE) gene makes ApoE protein, known to help carry fats, including cholesterol, in the brain and throughout the body. There are several APOE gene variations, including APOE-e2, APOE-e3 and APOE-e4. Possessing the APOE-e4 variation is thought to increase risk of developing Alzheimer's disease in some populations'. However, it remains unclear how variations of the APOE gene may be associated with dementia risk.

Studies have found that ApoE protein accepts cholesterol and other fats from cells, a process called lipidation. Lipidation is how the ApoE protein can transport fats throughout the brain. This process of ApoE lipidation is important in cholesterol transport and requires a protein on the surface of certain brain cells called ABCA1 which works to add lipids to the ApoE protein. ABCA1 activity has been shown to reduce beta-amyloid accumulation and abnormal tau (two hallmark brain changes in Alzheimer's). Interestingly ApoE-e4 has been shown to have reduced interaction with ABCA1 and reduced lipidation. A compound which increases activation of ABCA1 called CS6253, has been shown to improve the interaction between ApoE-e4 and ABCA1 and reduce Alzheimer's-related brain changes. In earlier studies in different animal model systems, CS6253 was shown to activate or 'turn-on' ABCA1, increase ApoE lipidation and increase clearance of beta-amyloid out of the brain. These findings have led the ARTERY research team to investigate how APOE variations impact lipidation and if increasing ABCA1 activity could reduce Alzheimer's-related brain changes in humans.

### **Research Plan**

Building on their past research findings, Dr. Jan Johansson and the ARTERY team will test the compound CS6253 for its safety and tolerability in cognitively unimpaired individuals aged 50 and older. They will also evaluate the impact of CS6253 on build-up of beta-amyloid in their participants.

Dr. Johansson's team will recruit 56-72 cognitively normal individuals; approximately half carrying APOE-e4 and the other half carrying other variations of APOE (APOE-e2 or APOE-e3) to evaluate the safety and tolerability of the treatment. As an exploratory measure, the team will compare effects on biological markers (biomarkers) of Alzheimer's disease in plasma and cerebrospinal fluid including measurement of beta-amyloid levels and lipid transportation in individuals with different APOE gene-variations.

### **Impact**

The study will primarily evaluate the safety and tolerability of CS6253. The exploratory measures of this study may further clarify our understanding of how the APOE-e4 risk factor is linked to dementia risk and affected by CS6253 treatment. If successful, this study could give rise to larger clinical trials, potentially in individuals with Alzheimer's carrying APOE-e4, to assess CS6253's ability to prevent or reduce Alzheimer's-related brain changes.

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