Investigating the Efficacy of Cinpanemab for Early Parkinson's disease: A Clinical Trial

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Key points

- Introduction, prevalence, etiology of Parkinson's disease
- No cure for Parkinson's disease yet. It is managed symptomatically.
- Study aimed to evaluate the efficacy and safety of the drug, Cinpanemab, in individuals with early-stage Parkinson's disease

This trial was aimed to investigate the efficacy of Cinpanemab, a monoclonal antibody directed at α-synuclein, in participants with early-stage Parkinson's disease. The trial included previously untreated participants who were randomized to receive either Cinpanemab or placebo for 52 weeks, with a dose-blinded extension period up to 72 weeks. The primary outcome measures were changes in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts 1 to 3, while secondary outcome measures included changes in non-motor function, activities of daily living, quality of life, and imaging biomarkers. The trial showed that Cinpanemab, at the doses studied, did not lead to differences in clinical measures of disease progression or changes in DaT-SPECT imaging as compared with placebo over the 52-week period. The trial's findings suggest that targeting extracellular α-synuclein with an N-terminal-directed antibody as monotherapy may be insufficient to slow the progression of Parkinson's disease.

Parkinson's disease is a neurodegenerative disorder that affects millions of people worldwide, with increasing prevalence as the population ages. It is a

disorder that primarily affects the motor system. It is characterized by the loss of dopaminergic neurons in the substantia nigra of the brain, resulting in a range of motor symptoms including tremors, rigidity, bradykinesia, and postural instability. Parkinson's disease is estimated to affect approximately 1% of the population over the age of 60, and its prevalence is expected to increase with the aging of the population.1 The exact cause of Parkinson's disease is not fully understood, but both genetic and environmental factors are thought to play a role in its etiology. Recent research has suggested that abnormalities in protein folding and degradation pathways, as well as chronic inflammation and oxidative stress, may contribute to the development of Parkinson's disease.2

Diagnosis of Parkinson's disease is primarily based on clinical symptoms and neurological examination. There are currently no definitive diagnostic tests for Parkinson's disease, although imaging techniques such as DaT-SPECT can be helpful in confirming the diagnosis.1

Although there is no cure for Parkinson's disease, a range of treatments are available that can help manage its symptoms. These include medications which increase dopamine levels in the brain, as well as physical therapy and deep brain stimulation.1

Overall, Parkinson's disease is a complex and debilitating condition that has significant impacts on both individuals and society. A better understanding of its etiology and the development of more effective treatments is urgently needed to address the growing burden of this disease.

Etiology

It's a disorder that affects dopaminergic neurons in the substantia nigra of the brain. Although the exact cause of Parkinson's disease is not yet fully understood, recent research suggests that it is likely influenced by both genetic and environmental factors. Abnormal protein folding and degradation pathways, chronic inflammation, and oxidative stress are among the factors that may contribute to the development of Parkinson's disease.3, 4

Alpha-synuclein is a protein found in the brain that regulates neurotransmitter release and is implicated in the pathogenesis of Parkinson's disease. Lewy bodies, insoluble protein deposits, form as a result of abnormal alpha-synuclein aggregation and are a hallmark of Parkinson's disease.3 Additionally, dysfunction of the ubiquitin-proteasome system, responsible for degrading misfolded proteins, may contribute to alpha-synuclein accumulation in Lewy bodies.4 fully understood, recent research has provided insights into the complex interplay of genetic and environmental factors that contribute to its development and progression. Abnormal protein aggregation, neuro-inflammation, and oxidative stress may also play a role in Parkinson's disease pathogenesis. Inflammation in the brain can damage neurons and promote Lewy body formation, while oxidative stress can damage neurons and contribute to the development of Parkinson's disease.3

Methods

The study aimed to evaluate the efficacy and safety of the drug, Cinpanemab, in individuals with early-stage Parkinson's disease. The trial enrolled participants between the ages of 40 and 80 who had been diagnosed with the disease within the past three years and had not received treatment for their symptoms. The trial had a multicenter, randomized, double-blind, placebo-controlled, phase 2 design and was conducted over a 52-week period, followed by a dose-blinded extension period of up to 112 weeks. Participants were enrolled in two stages, with the first stage including a lead-in group and the second stage including a larger group of participants. Both cohorts were assigned to receive varying doses of Cinpanemab or a placebo administered intravenously every 4 weeks. After 52 weeks, participants who had received placebo were given the option to receive Cinpanemab at a dose of 250 mg, 1250 mg, or 3500 mg. Throughout the double-blind and extension periods, both the investigators and the participants remained unaware of the trial-group assignments and the dose levels. The study was conducted in multiple countries, including Austria, Canada, France, Germany, Israel, Italy, Spain, the United Kingdom, and the United States. 5

Results

The clinical trial enrolled 357 participants, with 100 in the control group, 55 in the 250-mg Cinpanemab group, 102 in the 1250-mg group, and 100 in the 3500-mg group. The study was halted after an interim analysis at week 72 due to lack of efficacy. The change in the MDS-UPDRS score from baseline to week 52 was similar across all groups, with adjusted mean differences compared to the control group ranging from -0.3 to 0.5 points and all p-values > 0.05. At week 72, there was no significant difference in MDS-UPDRS scores between participants who received Cinpanemab for the entire 72 weeks and those who started at week 52. Adverse events were most commonly headaches, nasopharyngitis, and falls. DaT-SPECT imaging at week 52 also did not reveal any differences between the control group and any of the Cinpanemab groups.5

Discussion

In this study, participants with early-stage Parkinson's disease were treated with Cinpanemab, a monoclonal antibody directed at α-synuclein, and compared with a placebo group over 52 weeks. The trial showed that Cinpanemab did not lead to differences in the progression of motor function, non-motor function, activities of daily living, quality of life, or imaging biomarkers at 52 weeks. The lack of effect was also evident in the absence of a difference in the delayed-start analysis at 72 weeks. The most common adverse events reported in Cinpanemab-treated participants were mild to moderate in severity, and the incidence of infusion reactions was low. The timing of therapeutic intervention in degenerative neurologic diseases may be a factor in the failure agents targeted to a misfolded protein. Several methods of interference with the production or function of α-synuclein have been proposed, and the results of this trial suggest that targeting extracellular α-synuclein with an N-terminal–directed antibody as monotherapy may be insufficient to slow the progression of the disease.5

Conclusion

During a 52-week period, no significant differences were observed between Cinpanemab and placebo in their effects on clinical measures of disease progression and changes in DaT-SPECT imaging in participants with early Parkinson's disease.

References:

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