The Future of PD Treatment - Buntanetap Tartrate and Prasinezumab: How these Novel Treatments Affect the Practice

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Abstract
Parkinson's Disease is among the most common neurodegenerative diseases in the contemporary world. Recent years have witnessed increasing intensification of development of therapies for the disease. Particularly notable are the therapies based on targeting the α-synuclein neurotoxic protein. The present study aims to provide a snapshot of the status quo of developing two such therapies, namely buntanetap tartrate and prasinezumab. The study adopts the literature review research methodology. Topics discussed in the study include the following: overview of Parkinson's Disease; types of therapies for Parkinson's Disease; status quo of therapy development for Parkinson's Disease; research on buntanetap tartrate as a treatment to Parkinson's Disease; research on prasinezumab as a therapy for Parkinson's Disease; potential effectiveness of buntanetap and prasinezumab as treatments for Parkinson's Disease; criticism and doubts surrounding the use of buntanetap and prasinezumab as therapies for Parkinson's Disease. Discussions in this study show that buntanetap and prasinezumab are being actively tested in order to confirm their effectiveness in halting the progression of Parkinson's Disease. However, trial studies conducted for testing the therapies thus far have presented inconclusive findings. Therefore, further research is needed for arriving at better understanding of the extent to which buntanetap and prasinezumab are potential therapies for controlling Parkinson's Disease.

Keywords: Parkinson's Disease, buntanetap, prasinezumab, α-synuclein, neurodegenerative diseases.

Introduction:

Neurodegenerative diseases are medical conditions that cause constant declining in patients' physical and cognitive abilities, resulting in lower levels of quality of life and declining autonomy. These diseases are a subset of neurological orders, which are currently found in 15% of the world's population, with expectations of prevalence doubling within the next two decades due to the increasing aging of populations in the contemporary world (Cheslow et al., 2024).

Parkinson's Disease is recognized by the World Health Organization (WHO) as the fastest increasing neurological disorder. A report published by the WHO in 2022 highlights that the number of Parkinson's Disease patients globally has almost doubled over the last quarter of a century. The report calls for new urgent initiatives to address the various needs of Parkinson's Disease patients in order to improve their quality of life and overall functioning and prevent the incidence of the disability (McFarthing et al., 2023).

New therapies are being developed for treating Parkinson's Disease. Some of them are, at the time of writing article, undergoing testing for use as disease-modifying therapies. One of such therapies is buntanetap, which is a compound that inhibits the aggregation of neurotoxicα-synucleinby by binding their Messenger RNA (mRNA) (Curtis et al., 2023, 6).

Another emerging potential new therapy for Parkinson's Disease is prasinezumab, which is a monoclonal antibody that, similar to buntanetap, targets the neurotoxic protein α-synuclein. In a Phase I of testing, the antibody was found to be tolerable and safe. Phase II trials are still being undertaken at the time of writing this article (Murakami et al., 2023).

This article aims to discuss the new developments in Parkinson's Disease therapies. The article focuses specifically on buntanetap and prasinezumab, which are gaining increasing attention due to their promising, potential impacts on the outcomes of interventions for managing Parkinson's Disease. However, due to the novelty of these therapies, using them in therapeutic applications for addressing the needs of Parkinson's Disease patients remains a subject of skepticism. The ongoing relevant research and trials may arrive at new, more conclusive findings on the impact that buntanetap and prasinezumab can have on responding to the needs of Parkinson's Disease patients.

Overview of Parkinson's Disease:

Parkinson's Disease is a progressive neurodegenerative disorder associated with various symptoms of motor impairment. These symptoms progressively worsen over time. The real causes of pathogenesis of Parkinson's Disease remain unknown, but there is general consensus on the belief that the incidence and progression of the disease are associated with a combination of both environmental and genetic factors (Curtis et al., 2023).

One of the main factors associated with the pathogenesis of Parkinson's Disease is the aggregation of a neurotoxic protein known as α-synuclein (Pagano et al., 2022).

In terms of the sources of pathogenesis, there are two forms of Parkinson's disease (Ball et al., 2019):

1. Familial Parkinson's Disease: this form is inherited genetically, and that can occur in either a recessive or autosomal manner. This form is estimated to account for 10-15% of all incidences of Parkinson's Disease.
2. Sporadic Parkinson's Disease: this form develops as an outcome of interaction between genetic and environmental factors. It is estimated to account for 85-90% of all incidences of Parkinson's Disease.

Types of Therapies for Parkinson's Disease:

- **Disease-Modifying Therapies:**

These therapies halt or slow the progression of neuronal cell death caused by the disease. In other words, these therapies are implemented for the purpose of preventing the occurrence of further damage to neuronal cells as a result of the disease (Chattree, 2024).

- **Symptomatic Therapies:**

These therapies aim to restore or improve patients' functioning. For example, such therapies may focus on improving patients' overall cognitive or motor functioning (Chattree, 2024).

Status Quo of Therapy Development for Parkinson's Disease:

The most significant unachieved goal in treating Parkinson's disease is the development of a disease-modifying therapy that can effectively prevent or slow the progression of the disease (Wüllner et al., 2023).

Despite the significant efforts aiming at developing treatments for Parkinson's Disease, there is still no known treatment that can influence the underlying biology resulting in the pathogenesis of the disease. The most powerful treatments available are designed to merely control symptoms of the dieses, not to affect the progression of the disease (Pagano et al., 2022).

Several companies are developing treatments for Parkinson's Disease that target α-synuclein. According to GlobalData, a total of 12 products are being developed and tested in the United States and Europe, with focus on α-synuclein as the molecular target (Laws, 2023).

Targeting α-synuclein is a prominent approach adopted in developing therapies for Parkinson's Disease. Table 1 below provides a brief explanation of the approach's hypotheses, main goal, and strategies.

Table 1. A brief explanation of the concept of targeting α-synuclein (Chattree, 2024).

Hypotheses	• Several triggers result in the misfolding of accumulations of the α-synuclein neurotoxic protein. • Due to misfolding, the α-synuclein accumulations spread across the brain resulting in neuronal cell dysfunction and death. These changes represent the distinctive feature characterizing the onset of Parkinson's Disease.
Goal	• The prevention of the misfolding and spreading of α-synuclein accumulations.
Strategies	• Passive provision of antibodies to target α-synuclein formations. • Solutions for enabling the body to generate antibodies that target α-synuclein formations, such as vaccines. • Use of small molecules that interfere with the activity of α-synuclein. • Creation of proteins that can break the complex misfoldings of α-synuclein.

Research on Buntanetap Tartrate as a Therapy for Parkinson's Disease:

Buntanetap is a newly discovered promising treatment of Parkinson's Disease. In essence, it is a small molecule characterized by oral bioavailability. It was originally discovered by the National Institutes of Ageing in the United States (Fang et al., 2023).

Buntanetap is being developed and tested by Annovis Bio, Inc., which is a company headquartered in Berwyn, PA, United States. The company is interested in developing therapies for neurodegenerative diseases, such as Parkinson's Disease and Alzheimer's Disease. It is arguably the only corporation in the world seeking to develop therapies for treating such diseases. The company focuses in therapy development on inhibiting the aggregation of neurotoxic proteins in the brain in order to restore and promote synaptic and axonal activity. The company views the improvement of brain functioning as a solution for treating the symptoms of Alzheimer's Disease (e.g., dementia and memory loss) and Parkinson's Disease (e.g., impaired brain and motor functioning) (BioSpace, 2023).

Buntanetap is being tested for indirect targeting of α-synuclein aggregation, which is believed to be a potentially effective approach for treating Parkinson's Disease. The antibody targets Lewy bodies, focusing specifically on iron response elements (IREs) of mRNAs encoding proteins. Early tests of the antibody showed promising results, as the antibody was found to be effective in lowering α-synuclein aggregation as well as in improving the overall cognitive functioning in patients with Parkinson's Disease (Khanna & Jones, 2023).

The value of buntanetap as a potential treatment for Parkinson's disease stems from its effectiveness in the reduction of production of theα-synuclein protein by brain cells. The brain of a patient with Parkinson's Disease accumulates build ups of this protein. Misfolded accumulations of this protein have toxic effects on brain cells. The findings of Phase II trials for testing buntanetap were published in 2022. According to the findings, buntanetap is safe for Parkinson's Disease patients and may help in improving their quality of life and mitigating their motor issues (Chattree, 2023).

The period of time for Phase III of testing the buntanetap is six month, which is considered a relatively lengthy for testing a disease-modifying therapy – a treatment that is used for slowing or delaying the progression of a disease by addressing the biological processes underlying the disease (McFarthing et al., 2023).

According to GlobalData, if the results of Phase III of testing prove the effectiveness of buntanetap, it could become the first therapy capable of targeting α-synuclein, thereby potentially leading to major transformations in how care is provided to Parkinson's Disease patients. The Institute for Cell Engineering at John Hopkins has expressed similar hope and optimism regarding the potential impact success in Phase III trials. Dr. Ted Dawson, director of the institute, believes that antibodies capable of targetingα-synuclein could be the solution for slowing the pace of progression of symptoms of Parkinson's Disease. However, Dawson emphasizes the need to wait for the final results of trials in order to determine whether buntanetap will be truly effective for treating patients with Parkinson's disease. (Beaney, 2023)

According to forecasts by analytics, Annovis Bio is expected to launch buntanetap in the United States and five European countries, namely the United Kingdom, Spain, Italy, Germany, and France. Expected launch dates are Q4 of 2026 (United States) and Q4 of 2028 (Europe) (Laws, 2023).

As of the time of writing this paper (May 2024), the current status of testing buntanetap is as outlined in Figure 1 below.

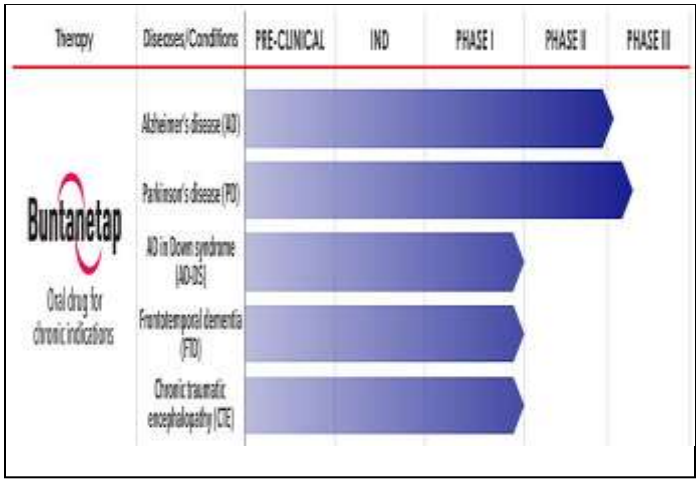

Figure 1. The current status of testing buntanetap, as of May 2024 (Annovis Bio, 2024).

According to Annovis Bio, the results of testing buntanetap in the main phases of studies are as outlined in Table 2.

Table 2. Results of testing buntanetap in the main phases of studies (Annovis Bio, 2024).

Phase	Results
Preclinical Studies	Improvement in axonal transport among both Alzheimer's Disease and Parkinson's Disease patients. This is attributable to the antibody's effectiveness in inhibiting the aggregation of neurotoxic proteins, such as α-synuclein, tau/phospho-tau, and APP/Aβ, which are damaging to nerve cells.
IND	Transitioning from preclinical to clinical studies.
Phase I	The antibody was tested in three studies. Results showed that it is well-tolerated by patients.
Phase II	The antibody was tested in two studies. Results showed that it is well-tolerated by patients. It was also found to be efficacious in both Parkinson's Disease and Alzheimer's Disease patients. Improvements in functioning were found to be statistically significant, as measured using the WAIS Coding Scale and ADAS-Cog11 (for assessing Alzheimer's Disease patients) and the MDS-UPDRS (for assessing Parkinson's Disease patients). In the light of these results, Annovis Bio emphasizes a conclusion that buntanetap is the only therapy to result in improvement in motor functioning in Parkinson's Disease patients and cognitive functioning in Alzheimer's Disease patients.
Phase III	Pending.

Phase III launched in August 2022. The patients included were patients in the early stage of Parkinson's Disease. They were assigned to one of two different treatment interventions, which are placebo treatment and administration of buntanetap. Patients who received the buntanetap therapy were given doses of either 20 or 10 mg (Lobo, 2023). Although the Phase III study itself is already completed, the phase is still ongoing. Findings were originally planned to be reported in January 2024, but the research team decided to postpone this step due to a perceived need to undertake more cleaning of data in order to ensure presenting reliable and accurate results (Chattree, 2024).

The study of Fang et al. (2023) is pioneer in testing the effectiveness of buntanetap. It is cited by Annovis Bio for highlighting the antibody's effects on patients. It tested the effectiveness of buntanetap on a sample of patients in the early stages of Parkinson's Disease in the United States. The sample included 54 patients who were classified into several treatment conditions: receiving varying doses (80mg, 40mg, 20mg, 10mg, 5mg) and placebo treatment. Patients' mobility was assessed using MDS-UPDRS (Part III of the instrument and the total score).

Part III of the instrument is widely used as a standard for assessing the impact of therapies on mobility in Parkinson's Disease patients. Figure (2) below illustrates the differences between sample members' mobility scores, by treatment condition.

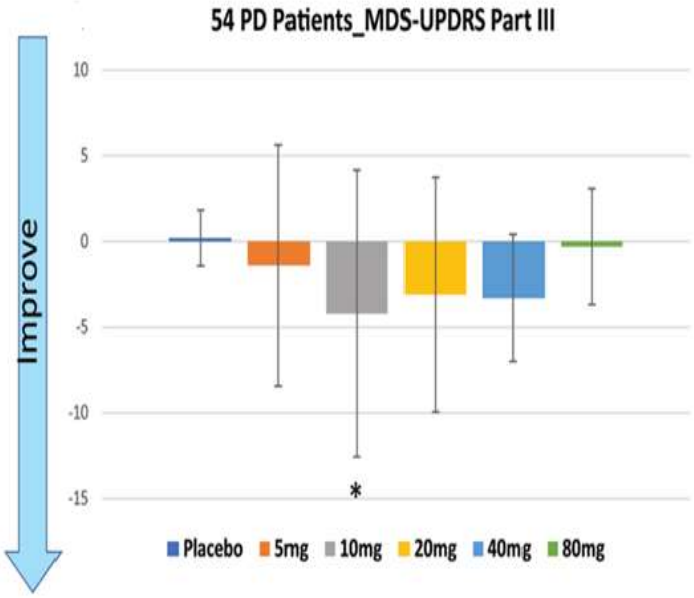

Figure 2. Mobility scores of sample members in the study of Fang et al. (2023), as measured using Part III of MDS-UPDRS.

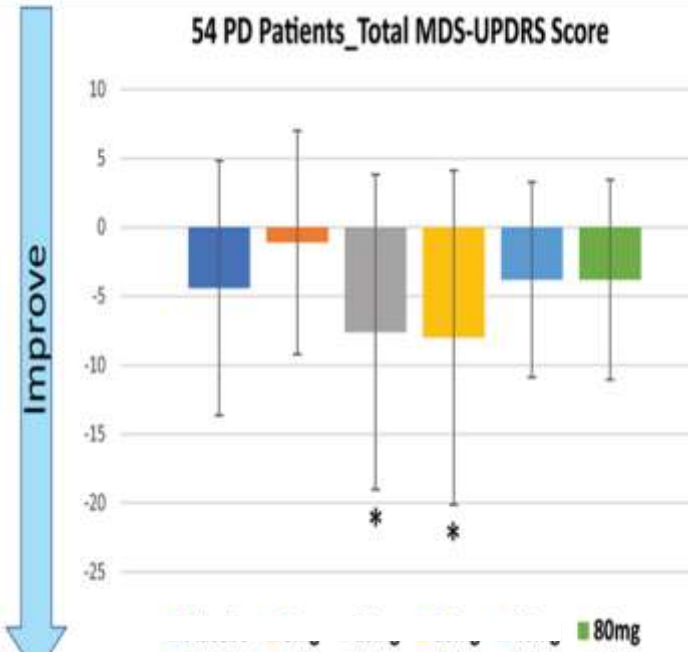

Figure 3. Mobility scores of **sample members in the study of Fang et al. (2023), as measured usin**g the total score of MDS-UPDRS.

Figure 3 below illustrates the differences between sample members' mobility scores, by treatment condition, based on the total score of MDS-UPDRS.

The study of Fang et al. (2023) also used the WAIS Coding Test for assessing motor functioning in sample members. Results of the assessment are illustrated in Figure 4.

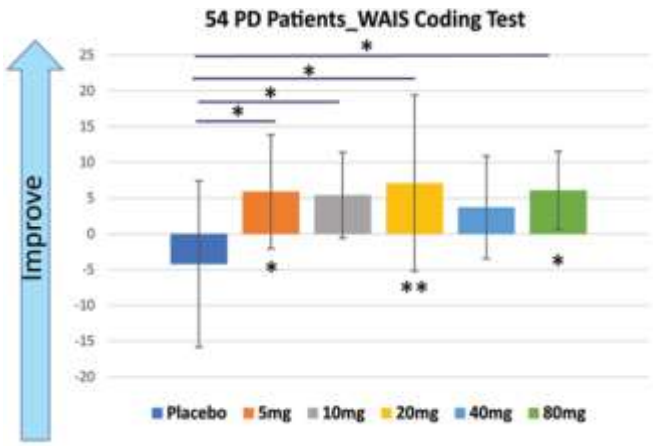

Figure 4. Motor functioning of the sample of the study of Fang et al. (2023), as measured using the WAIS Coding Test.

Through of the findings illustrated in Figures 1-4, the study of Fang et al. (2023) concluded that the most effective therapeutic intervention for Parkinson's Disease is having a dose of 10mg or 20mg of buntanetap**.**

Research on Prasinezumab as a Therapy for Parkinson's Disease:

A promising new therapy being tested for treating Parkinson's Disease is Prasinezumab. It is being developed through a collaboration between Prothena and Roche (Harrison & Lai, 2024). Prasinezumab is considered the main competitor to Buntanetap. The product is still undergoing trials, titled Padova and Pasadena. Prothena and Roche hope to launch the therapy in the United States by Q4 of 2029 (Laws, 2023).

Prasinezumab is a monoclonal antibody with strong anti-α-synuclein effects that is gaining increased prominence as a treatment for Parkinson's Disease. The therapy is effective for targeting both soluble and insoluble forms of α-synuclein accumulations. It can mitigate the neurotoxic effects of α-synuclein and improve cognitive and motor functioning in patients. It can be administered intravenously with a high level of safety. The therapy is currently being tested in a Phase II as a potential treatment for Parkinson's Disease patients (Degirmenci et al., 2023).

Prasinezumab is designed to target aggregations of α-synuclein. It protects neurons from the neurotoxic protein through interception by binding it at the C-terminus. The mechanism by which the therapy takes effect is illustrated in Figure 5 below.

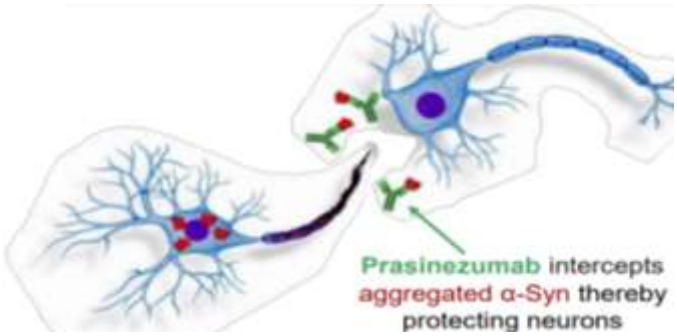

Figure 5. The mechanism by which prasinezumab takes effect (Pagano et al., 2022).

Prasinezumab is undergoing tests for determining its effectiveness as a treatment for Parkinson's Disease. The findings of the phases of testing the therapy are summarized in Table 3.

Table 3. The main findings obtained in the phases of testing prasinezumab (Manoutcharian & Gevorkian, 2024).

Phase	Main Findings
Phase I	The antibody was administered three times with four-week intervals. Findings include the following: 1. The antibody was found to be tolerable and safe. 2. The use of the antibody helped in reducing the levels of free serum α-synuclein. 3. The antibody is capable of concentrating in the cerebrospinal fluid; thus, the antibody is capable of crossing the blood-brain barrier and binding extracellular α-synuclein produced in the brain.
Phase II	This phase was conducted as a part of the Pasadena study. The phase involved conducting a "multicenter, randomized, double-blind, and placebo-controlled trial". Participants in the trial were patients with early stages of Parkinson's Disease in Europe and the United States. Patients received monthly intravenous doses of prasinezumab over a total period of 52 months. Findings of the trials show no significant difference between administering prasinezumab and the placebo treatment in the patterns of progression of Parkinson's Disease. From among participating patients, a group will be selected to participate in Part II of the trial, which is planned to be conducted over 52 months.
Phase III	This phase is planned to include patients who participated in Part II of Phase II. The phase is planned to last for 260 weeks, ending by September 2026.

The Phase II trial is the latest for which results were published. It was part of the Pasadena study that examined the effects of prasinezumab on Parkinson's Disease patients. Pagano et al. (2022) reported findings from the Pasadena study.

It examined the effects of different treatment conditions. The conditions tested in the study included Placebo treatment (control), pooled prasinezumab (prespecific analysis), administering a 1500mg dose of prasinezumab, and administering a 4500mg dose of prasinezumab.

The analysis provides several comparisons between these conditions. The main comparison is regarding the main endpoint; the main endpoint was not met, but prasinezumab still demonstrated more effectiveness in addressing the motor symptoms of Parkinson's Disease compared to the control condition. Figure 6 illustrates a comparison between the total scores of the main conditions under study (sum of Parts of I, II, and III of MDS-UPDRS).

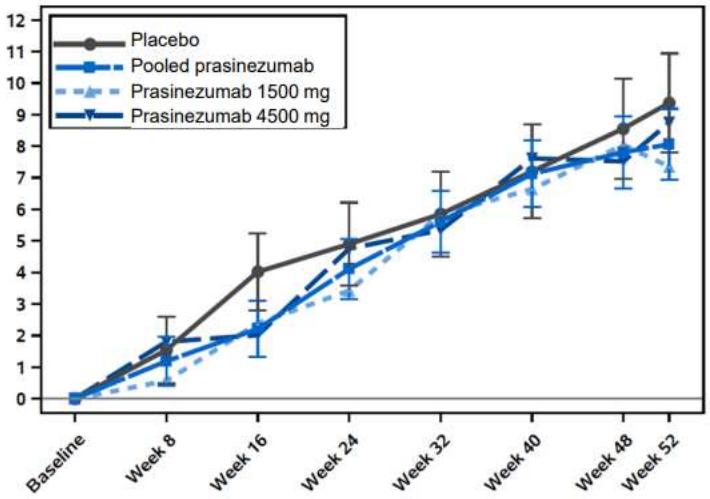

Figure 6. Total scores (sum of Parts of I, II, and III of MDS-UPDRS) for the main conditions examined in the Pasadena study (Pagano et al., 2022).

Prasinezumab-based therapies were found to be more effective than the placebo treatment in reducing clinical decline in patients over the 52-week period of the trial.

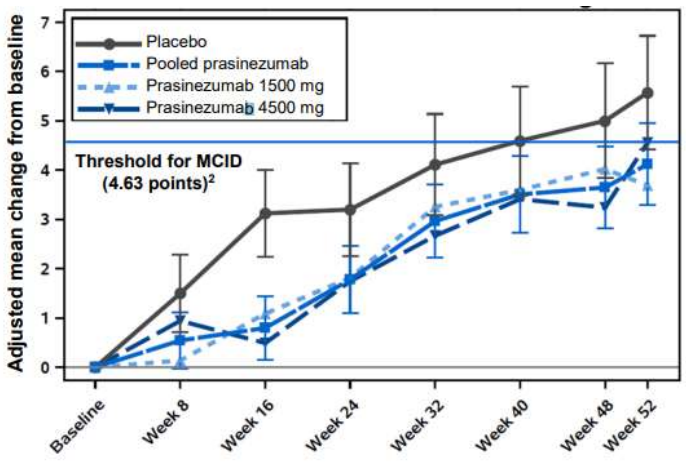

Figure 7. Comparison between the main conditions in the Pasadena study in terms of clinical decline scores (Pagano et al., 2022)

MDS-UPDRS Part III bradykinesia scores also show that prasinezumab is superior to the placebo treatment in the reduction of clinical decline over the period of conducting the trial. A comparison between the scores of the main conditions under study is illustrated in Figure 8.

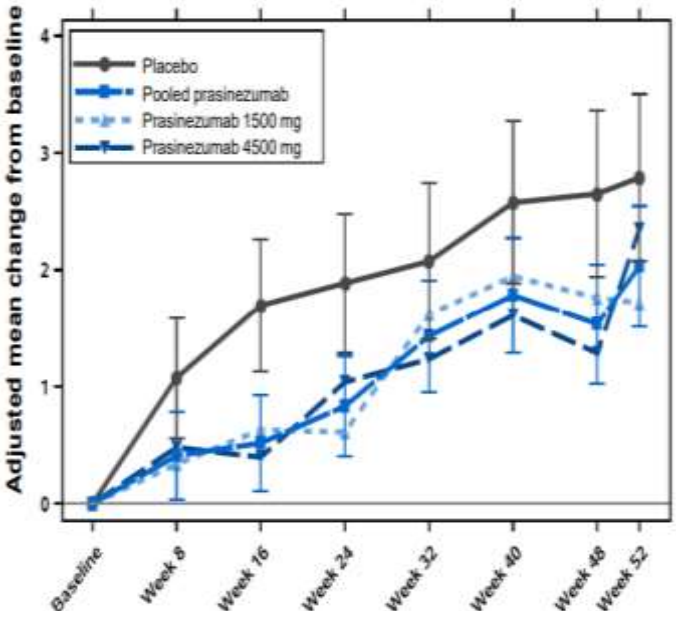

Figure 8. Comparison between MDS-UPDRS Part III bradykinesia scores of the conditions under investigation in the Pasadena study (Pagano et al., 2022).

Potential Effectiveness of Buntanetap and Prasinezumab as Treatments for Parkinson's Disease:

- **Buntanetap:**

Despite the similarity between buntanetap and prasinezumab in terms of certainty of effectiveness in managing symptoms of Parkinson's Disease, the former is expected to establish superiority over the latter in the markets. This is attributable to two main factors (Laws, 2023):

Compared to prasinezumab, buntanetap is a more promising treatment for the symptoms of Parkinson's Disease, as the latter's effect mechanism focuses on inhibiting the translation of neurotoxic proteins. Buntanetap has also been found to produce superior effects in addressing motor impairment and reducing the aggregations of α-synuclein in the cerebrospinal fluid (Cheslow et al., 2024).

- **Prasinezumab:**

Tests have shown that Prasinezumab is efficacious in addressing the needs of Parkinson's Disease patients. The main effects of the antibody include the following (Pagano et al., 2022):

1. Reduction of accumulations of intracellular α-synuclein as well as protection of neurons.
2. Blocking the transmission of α-synuclein between cells.
3. Reduction of gliosis and protection of synapses.
4. Mitigation of cognitive and motor impairments.
1. Buntanetap is expected to enter the markets significantly earlier than prasinezumab.
2. Although buntanetap tartrate is administered daily while prasinezumab is administered monthly, the former is administered orally, while the latter is administered intravenously.

Although prasinezumab can target aggregations of α-synuclein, it was found to be of limited effectiveness in reducing these aggregations in the cerebrospinal fluid or plasma. Moreover, the antibody cannot slow the pace of progression of motor symptoms associated with Parkinson's Disease (Cheslow et al., 2024).

Criticism and Doubts Surrounding the Use of Buntanetap and Prasinezumab as Therapies for Parkinson's Disease:

The promise of buntanetap in treating Parkinson's disease is now questionable. In late April 2024, Annovis Bio revealed the results of Phase 2/3 of testing the effectiveness of buntanetap in treating Alzheimer's Disease, which is similar in many aspects to Parkinson's Disease. Overall, results show that patients witnessed significant improvement in cognitive functioning. However, details of reported results imply that the test was largely a failure, thereby creating doubt regarding the feasibility of using the antibody for treating Parkinson's Disease. The study used the Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change scale (ADCS-CGIC) for evaluating the effects of using the antibody. Changes measured using this scale were minimal and did not amount to statistical significance. Moreover, this data collection instrument is highly subjective in nature, resulting in obtaining somewhat exaggerated responses, due to a strong placebo effect, especially from patients in advanced stages of the disease and their caregivers, who are normally more likely to have high hopes for the effectiveness of new therapies (Armstrong, 2024).

Key opinion leaders in the pharmaceutical industry express doubts and concerns over whether buntanetap and prasinezumab can be really effective in treating the symptoms of Parkinson's Disease. At the time of writing this paper, results of trials conducted thus far have shown inconclusive findings, resulting in uncertainty over whether targeting extracellular α-synuclein can be effective in slowing the progression of Parkinson's Disease and improving patients' overall motor functioning (Laws, 2023).

The study of Kalia (2022) suggest that trials for testing therapies for Parkinson's Disease that are based on targeting α-synuclein have several limitations. These limitations create doubts around the extent to which such therapies can become of value to the management of Parkinson's Disease. The study highlights the issues listed below concerning the trials:

1. Findings from Phase I studies do not clearly show whether antibodies enter in sufficient volumes into the brain. This issue is especially noticeable with antibodies administered intravenously, such as prasinezumab, as they cannot penetrate intact cell membranes.
2. Findings from Phase I and Phase II studies do not clearly confirm whether antibodies bind to α-synuclein formations in the brain. This raises doubts on the effectiveness of therapies based on targeting α-synuclein. The toxicity of α-synuclein is caused by its intracellular damaging effects; however, due to its inability to penetrate cell membranes, prasinezumab cannot reach the α-synuclein inside neuronal cells. Instead, prasinezumab is likely to affect α-synuclein only in extracellular spaces.

3. The proof of effectiveness of antibodies in breaking accumulations of α-synuclein is significantly insufficient. In Phase II studies, makers needed to test the effectiveness were lacking.
4. It remains unclear whether the time allocated for measuring the impact of antibodies in Phase II trials was sufficient. Parkinson's Disease progresses in a slow pace, and thus conducting studies over longer periods of time is needed to gain a clearer understanding of the effects of using the antibodies on the progression of Parkinson's Disease.

The potential of buntanetap and prasinezumab, or any other product for treating Parkinson's Disease, remains highly hypothetical, as there are no validated biomarkers or endpoints that can be used as adequately reliable measures for quantifying the effects of anti-Parkinson's disease therapies. Moreover, no imaging technology exists for monitoring changes in the patterns of accumulation of α-synuclein. Therefore, success in developing therapies for Parkinson's Disease necessitates new advancements in assessing aggregations of α-synuclein as reliable biomarkers for measurement (Laws, 2023).

Companies that are currently developing therapies for treating Parkinson's Disease should pay careful attention to the significant importance and value of investing in research and development (R&D) for validating α-synuclein aggregations as biomarkers quantifying the effects of disease-modifying therapies, such as buntanetap and prasinezumab. Proving the effectiveness of such therapies can start a revolution in the development of therapies for treating Parkinson's Disease (Laws, 2023).

Conclusion:

The present article has provided a discussion of the status quo and expected future developments in testing buntanetap tartrate and prasinezumab. Discussions show that these two therapies are still undergoing rigorous testing, with the aim of officially launching them in selected markets, namely the United States and a number of Europe countries, within the few coming years.

At the time of writing this article, studies conducted thus far have shown inconclusive results regarding the effectiveness of buntanetap and prasinezumab in addressing one of the main factors leading to the pathogenesis of Parkinson's Disease, namely the accumulation of the neurotoxic α-synuclein protein responsible for neuronal cell death, which is a distinctive feature characterizing the disease.

The inconclusiveness of the findings obtained by trial studies has led to emerging skepticism on the value of buntanetap and prasinezumab as potential therapies for Parkinson's Disease. However, given the fact that further studies are already planned to be conducted in the coming few years, it is expected to witness a shift in perceptions on the value of the two therapies. Thus, the question around which revolves the main topic of interest for the present study, which concerns whether buntanetap and prasinezumab may influence practices of treating Parkinson's Disease patients, remains unanswered.

It is hoped that further studies will lead to arriving at a clearer understanding of how valuable these two novel therapies can become to Parkinson's Disease interventions.

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