AZP2006 (Ezeprogind®): a Promising New Drug Candidate in the Battle Against Neurodegenerative Diseases

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Progressive Supranuclear Palsy (PSP) is a rare neurodegenerative disorder characterized by abnormal tau protein accumulation. This perspective article explores AZP2006 (INN: Ezeprogind), a novel small molecule targeting the Progranulin (PGRN) and Prosaposin (PSAP) axis to enhance lysosomal health in PSP treatment. AZP2006 stabilizes the PGRN-PSAP complex, improving lysosomal function and reducing tau pathology. Preclinical studies in tauopathy models demonstrated AZP2006's ability to decrease tau hyperphosphorylation, enhance neuronal survival, mitigate neuroinflammation and promote synaptogenesis. Clinical trials have shown AZP2006 to be well-tolerated in healthy volunteers and PSP patients. A Phase 2a study met its primary endpoints, as it provided valuable safety data and even encouraged further investigation of its efficacy in a larger clinical study. An upcoming Phase 2b/3 trial aims to assess long-term safety and efficacy in a larger PSP cohort. AZP2006's mechanism of action strongly suggests potential applications in other tauopathies, including Alzheimer's and Parkinson's diseases. By addressing lysosomal dysfunction and tau pathology, AZP2006 represents a promising disease-modifying approach for PSP and other neurodegenerative disorders.

Introduction

Neurodegenerative diseases represent one of the most significant medical challenges of the 21st century, driven largely by their increasing prevalence in aging populations. Progressive Supranuclear Palsy (PSP), a rare yet debilitating neurodegenerative disorder, falls under the broader category of tauopathies, which are characterized by the abnormal accumulation of hyperphosphorylated tau protein in neurons and glial cells. PSP affects on average 6.92 per 100,000 individuals globally, with a typical onset between ages 60 and 70, leading to severe motor, cognitive, and behavioral impairments.[1] Despite its impact, PSP remains without a disease-modifying treatment, creating an urgent need for therapeutic innovation.[2]

At the core of PSP's pathology is the dysfunction of tau protein, which aggregates into neurofibrillary tangles (NFTs) within neurons. This aggregation disrupts normal neuronal function, leading to widespread neurodegeneration, particularly in regions like the basal ganglia and brainstem.[3] Notably, the role of lysosomal dysfunction in tauopathies has gained increasing attention in recent years. Lysosomes, which are essential for the degradation and recycling of cellular waste, including tau, play a crucial role in maintaining neuronal homeostasis. However, when lysosomal function is compromised, the efficient clearance of misfolded tau proteins is reduced, further impairing cellular health and exacerbating neurodegeneration.[4,5]

Tau proteins can directly impair lysosomal function by disrupting the autophagy-lysosomal pathway, leading to lysosomal membrane permeabilization. This not only prevents the effective degradation of tau but also triggers lysosomal rupture, releasing harmful enzymes that further damage neurons.[6] Addressing lysosomal dysfunction, therefore, has emerged as a promising therapeutic approach for mitigating tau pathology and slowing disease progression in PSP and related tauopathies.[7]

Progranulin (PGRN), a neurotrophic factor critical for lysosomal function and modulating inflammation, has been identified as a key player in the pathogenesis of tauopathies. Reduced PGRN levels are associated with increased tau phosphorylation and neuroinflammation, making PGRN a promising therapeutic target for stabilizing lysosomal health and reducing tau pathology. [8–11] Additionally, Progranulin interacts with Prosaposin (PSAP), another lysosomal protein, to preserve lysosomal integrity and promote neuronal survival.[12]

AZP2006 (Figure 1), a small molecule currently under investigation for PSP, is designed to modulate PGRN levels by stabilizing the PGRN-PSAP complex. This stabilization slows the degradation of PGRN into its less active granulin peptides, thus maintaining its neuroprotective and anti-inflammatory properties.[13] By enhancing lysosomal function and reducing neuroinflammation, AZP2006 offers a novel therapeutic approach that directly targets the core pathological processes of PSP. Preclinical studies have demonstrated the drug's potential in reducing tau pathology, protecting neurons, and improving cognitive and motor function in models of tauopathy.[13]

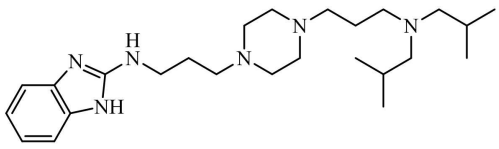

Figure 1. Structure of AZP2006.

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This perspective explores the potential of AZP2006 as a disease-modifying therapy for PSP. By examining its mechanism of action, preclinical findings, and early clinical data, we aim to evaluate the broader implications of AZP2006 for neurodegenerative research and its capacity to reshape the treatment landscape for tauopathies.

Mechanism of Action: Targeting Lysosomal Health and PSAP and PGRN

AZP2006 offers a novel therapeutic strategy for treating tauopathies, including PSP, by targeting PGRN and PSAP axis to enhance lysosomal health. PGRN is a neurotrophic factor essential for lysosomal function, neuronal survival, and modulation of neuroinflammation.[14] Deficiency in PGRN is strongly linked to accelerated tau deposition and hyperphosphorylation, both of which are hallmark features of neurodegenerative disorders like PSP and Alzheimer's disease.[11] Furthermore, PGRN binds to PSAP, a key protein responsible for ensuring proper lysosomal function and degradation of cellular waste.[12]

It is hypothesized that AZP2006 stabilizes the PGRN-PSAP complex, enabling its lysosomal targeting through a "piggyback" mechanism (Figure 2).. In addition to stabilizing the PGRN-PSAP complex, other therapeutic strategies targeting progranulin have been explored, such as Sortilin (SORT1) inhibition. Latozinemab (AL001), a monoclonal antibody developed by Alector, blocks the interaction between progranulin and Sortilin, leading to increased extracellular progranulin levels. While this approach enhances systemic progranulin availability, it differs from AZP2006's mechanism, which focuses on lysosomal targeting of PGRN through stabilization of the PGRN-PSAP complex. By facilitating PGRN delivery to lysosomes, AZP2006 directly addresses lysosomal dysfunction, a central feature of PSP pathology. These complementary strategies underscore the therapeutic potential of modulating progranulin in neurodegenerative diseases through distinct mechanisms. This placement ensures that the comparison between the two approaches is directly relevant to the mechanism of action of AZP2006.

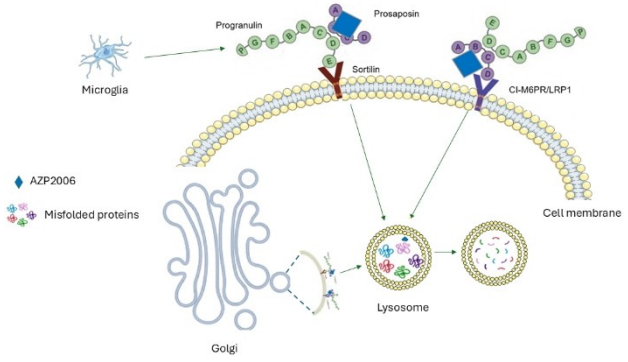

Figure 2. Proposed Mechanism of Action: AZP2006 enhances the trafficking of the progranulin-prosaposin (PGRN-PSAP) complex via two distinct pathways, promoting lysosomal homeostasis and the degradation of misfolded proteins. At the extracellular level, AZP2006 facilitates the binding of PGRN-PSAP to cell surface receptors such as Sortilin and CI–M6PR/LRP1, promoting its endocytosis and subsequent delivery to lysosomes. Intracellularly, AZP2006 also supports the transfer of the PGRN-PSAP complex through the Golgi-endosome-lysosome pathway, improving its lysosomal targeting. These mechanisms contribute to enhanced lysosomal function and the degradation of pathological misfolded proteins, including amyloid, phosphorylated Tau (P-Tau), and alpha-synuclein, thereby supporting neuroprotection.

Lysosomal targeting occurs via distinct receptor pathways: PSAP is directed through M6PR/LRP1, while PGRN is guided by sortilin.[15] By preserving full-length PGRN and enhancing its delivery to lysosomes, AZP2006 enhances lysosomal function, facilitating the removal of misfolded proteins, including tau, which can aggregate and cause neuronal damage. This process reduces tau hyperphosphorylation and neuroinflammatory activity, both of which are detrimental to neuronal health and exacerbate disease progression.[13]

Nonclinical Insights: Learning from Animal Models

The therapeutic potential of AZP2006 extends beyond PSAP-PGRN stabilization. Preclinical studies have demonstrated that AZP2006 reduces tau phosphorylation in models such as P301S and THY-Tau22 transgenic mice, which closely mimic the pathological features of tauopathies.[13] These studies further showed that AZP2006 significantly mitigates neuroinflammation by modulating microglial activity, which is key to neuroinflammatory responses in tauopathies.[12] By preventing both motor impairments and cognitive deficits in preclinical models, AZP2006 shows promise as a disease-modifying therapy for PSP and related neurodegenerative diseases.

The development of AZP2006 as a treatment for Progressive Supranuclear Palsy (PSP) has been supported by extensive preclinical studies in various animal models. These studies have provided critical insights into the drug's neuroprotective and disease-modifying potential.

In these models, AZP2006 significantly reduced tau hyperphosphorylation, a hallmark of PSP and other tauopathies, which is responsible for neurofibrillary tangle (NFT) formation and subsequent neuronal death (unpublished data). The drug was also shown to enhance neuronal survival, synaptogenesis, and neurite outgrowth, particularly in regions heavily affected by tau deposition, such as the basal ganglia and brainstem. These effects are believed to be mediated by AZP2006's ability to optimize Progranulin (PGRN) levels and lysosome targeting, thereby stabilizing the PGRN-Prosaposin (PSAP) complex and promoting lysosomal health.[13]

Moreover, AZP2006 has demonstrated neuroprotective effects beyond tau reduction. In the SAMP-8 mouse model of accelerated senescence, AZP2006 not only prevented memory deficits but also reversed existing cognitive impairments when administered chronically. In this model, the drug was shown to reduce markers of neuroinflammation, including microglial activation, as well as decrease oxidative stress, further supporting its potential as a disease-modifying therapy.[13]

The compound also showed efficacy in models of motor deficits, such as the α-syn-PFF-induced neurotoxicity model in aged mice (manuscript in preparation). AZP2006 significantly improved motor function in these lesioned animals, offering further evidence of its neuroprotective properties and broader applications such as Parkinson's disease. AZP2006's therapeutic effects are rooted in its ability to restore lysosomal function, which is central to the degradation of misfolded proteins and the modulation of neuroinflammation. Lysosomal dysfunction is a hallmark of neurodegenerative diseases, contributing to the accumulation of toxic aggregates such as tau, α-synuclein, and amyloid-beta, as well as exacerbating neuroinflammation. By stabilizing the PGRN-PSAP complex, AZP2006 enhances lysosomal activity, improving the clearance of misfolded proteins and attenuating inflammatory responses. Although AZP2006 does not specifically target α-synuclein phosphorylation or amyloid-beta plaques, its anti-inflammatory and lysosomal-stabilizing effects are likely to indirectly mitigate the pathological accumulation and modifications of these proteins.

In conclusion, the development of AZP2006 as a treatment for Progressive Supranuclear Palsy has been supported by extensive preclinical studies in various animal models. These studies have provided critical insights into the drug's neuroprotective and disease-modifying potential.

Clinical Development: The Journey So Far

The clinical development of AZP2006 as a treatment for Progressive Supranuclear Palsy (PSP) has progressed through several important stages, beginning with its early safety and tolerability assessments in human subjects. Phase 1 clinical trials investigated the safety profile of AZP2006 in healthy volunteers, assessing single and multiple ascending doses (SAD and MAD, respectively).The multiple ascending dose study was halted before the optional 180 mg dose due to high plasma levels of the main metabolite, AZP2045, which is a dealkylated form of AZP2006. The metabolite was observed in humans, rats, and dogs but is pharmacologically inactive and does not exhibit toxicity in animal models. These trials demonstrated that AZP2006 was well-tolerated, with no serious adverse events reported, paving the way for further clinical evaluation.[16]

A Phase 2a study followed, focusing on patients diagnosed with PSP. This randomized, double-blind, placebo-controlled trial aimed to evaluate the safety, tolerability, and pharmacokinetics of AZP2006 over a 12-week treatment period. In this study, AZP2006 was administered in two doses (60 mg once daily and 80 mg for 10 days followed by 50 mg once daily) to PSP patients aged 40–80 years. The results confirmed the pharmacokinetic profile observed in earlier studies, with AZP2006 showing rapid absorption and multiphasic elimination, while achieving higher concentrations in blood than in plasma.

Importantly, the trial showed that AZP2006 was well-tolerated in PSP patients experienced no significant safety concerns during the study. While improvements were observed in certain clinical endpoints, the primary efficacy endpoint, the PSP Rating Scale (PSPRS), did not reach statistical significance between the treatment and placebo groups. Nonetheless, the drug demonstrated a strong safety profile, and the initial signs of improvement are promising for further investigation. efficacy findings encouraged further investigation into its potential as a disease-modifying therapy.[17]

Looking forward, a Phase 2b/3 clinical trial is planned to assess the long-term safety and efficacy of AZP2006 in a larger cohort of PSP patients. This trial is aiming at building upon the findings of the Phase 2a study, focusing on the drug's impact on disease progression over a longer treatment period. The promising results from earlier clinical studies, combined with the extensive preclinical data supporting AZP2006's neuroprotective and anti-tau effects, suggest that this upcoming trial will be critical in determining AZP2006's potential as a therapeutic for PSP. This clinical trial in larger PSP patients' population will be a multicenter, randomized, double-blind, parallel-group, placebo-controlled adaptive trial with an open-label extension for another 12-month treatment. It will aim to evaluate the safety and efficacy of AZP2006 in PSP patients after 12-month treatment and will enroll 126 adults with onset of PSP symptoms within five years.

Two interim analyses are planned: the first at 30% completion (i.e. when 30% of the patient population reaches the end of treatment at 12-month) to assess safety and futility, and the second at 50% completion to evaluate safety, futility, and determine if a sample-size increase is needed. The trial may take place in France, Germany, Luxembourg, and Belgium, with the possibility of expanding to accelerate recruitment if necessary.

Implications for Broader Neurodegenerative Research

The therapeutic potential of AZP2006 extends beyond Progressive Supranuclear Palsy (PSP) and offers promising implications for other neurodegenerative diseases characterized by tau pathology and neuroinflammation, such as Alzheimer's and Parkinson's diseases. Tau hyperphosphorylation and the formation of neurofibrillary tangles (NFTs) are central features of these disorders, contributing to neuronal dysfunction and degeneration.[18] The ability of AZP2006 to target these processes through PGRN modulation opens new avenues for treating a range of tauopathies.

Alzheimer's disease, for instance, is characterized by both amyloid-beta (Aβ) plaques and tau tangles. While Aβ-targeting therapies have dominated the field, the failure to achieve significant clinical benefits has driven increased interest in tau-based treatments.[19] AZP2006's ability to reduce tau phosphorylation and promote neuronal survival by stabilizing the PGRN-PSAP complex presents a novel approach that could be effective in tau-driven pathologies like Alzheimer's.[13] Additionally, PGRN's role in regulating lysosomal function and inflammation may help mitigate neuroinflammatory processes that exacerbate disease progression in Alzheimer's and other neurodegenerative diseases.[14]

Parkinson's disease (PD), which shares common neurodegenerative mechanisms with PSP, could also benefit from therapies that target neuroinflammation and lysosomal dysfunction. In both diseases, microglial activation and chronic inflammation play a significant role in neuronal degeneration [17]. AZP2006's demonstrated ability to reduce neuroinflammation by optimizing PGRN levels and inhibiting microglial activation offers hope for broader applications in PD, where neuroinflammatory responses contribute to disease progression.[8]

In addition to the direct effects on tau and neuroinflammation, the lysosomal health benefits provided by AZP2006 could address the underlying cellular dysfunction observed in several neurodegenerative disorders.[8,20,21] Lysosomal dysfunction is a hallmark of many neurodegenerative diseases, including frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), where PGRN mutations are known to contribute to disease pathogenesis.[14] By stabilizing PGRN, AZP2006 has the potential to improve lysosomal function and reduce the toxic accumulation of misfolded proteins, offering broader neuroprotective effects.

Summary and Outlook

AZP2006 represents a promising new approach for the treatment of Progressive Supranuclear Palsy and potentially other tauopathies. Its unique mechanism of action, centered on the stabilization of the PGRN-PSAP complex, offers a multifaceted intervention by enhancing lysosomal function, reducing tau hyperphosphorylation, and attenuating neuroinflammation.[12,14] Preclinical studies have demonstrated that AZP2006 can significantly improve neuronal survival, reduce oxidative stress, and alleviate both cognitive and motor deficits in various animal models of tauopathy. These findings are particularly encouraging for neurodegenerative diseases like Alzheimer's and Parkinson's, where similar pathological processes play a critical role. [11,18,22]

While initial clinical trials in PSP patients have confirmed AZP2006's safety and tolerability, the next critical steps will be to confirm its efficacy in slowing down or stabilizing disease progression. The drug's potential to address tau pathology and lysosomal dysfunction, both common features across a range of neurodegenerative disorders, positions AZP2006 as a strong candidate not just for PSP but for tauopathies more broadly.[6,11,19,23]

The future of AZP2006 research lies in its upcoming Phase 2b/3 clinical trials, which will be critical to assess its long-term safety and therapeutic efficacy in a larger population of PSP patients. This trial will aim to confirm the neuroprotective benefits observed in preclinical models and provide further data on its ability to slow down disease progression.

From a regulatory perspective, AZP2006 faces several challenges, including meeting the stringent efficacy and safety requirements necessary for approval in a highly competitive neurodegenerative disease market. However, its designation as an orphan drug in Europe and the U.S. provides a strategic advantage for accelerated regulatory review and market exclusivity.

The broader application of AZP2006 in tauopathies such as Alzheimer's and Parkinson's diseases also warrants further exploration. Given the similarities in tau pathology and neuroinflammatory mechanisms across these conditions, future clinical trials may investigate AZP2006's utility in a broader range of neurodegenerative diseases.[24] Success in PSP could pave the way for its use in treating other tau-driven conditions, positioning AZP2006 as a versatile therapeutic in the neurodegenerative disease landscape.

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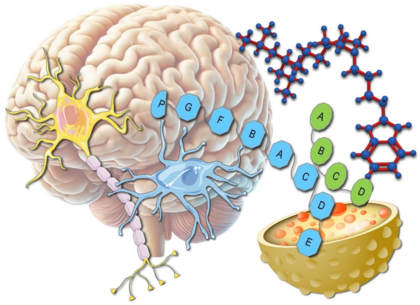
PERSPECTIVE

This article explores AZP2006 (Ezeprogind®), a novel drug targeting the progranulin (PGRN)-prosaposin (PSAP) complex to enhance lysosomal function in neurodegenerative diseases, particularly Progressive Supranuclear Palsy (PSP). Preclinical studies demonstrate its efficacy in reducing tau hyperphosphorylation, enhancing neuronal survival, and mitigating neuroinflammation. Clinical trials confirm AZP2006's safety, suggesting therapeutic potential in PSP and broader tauopathies, including Alzheimer's and Parkinson's diseases.



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