ABOUT PARKINSON’S DISEASE PSYCHOSIS (PDP)

Disease Overview

Parkinson’s disease is a chronic and progressive neurodegenerative disorder that affects about one million people in the United States and from four to six million people worldwide. It is the second most common neurological disorder after Alzheimer’s disease. Parkinson’s disease involves the death of neurons in a region of the brain that controls movement, creating a shortage of an important neurotransmitter known as dopamine, thereby rendering patients unable to direct or control their movements in a normal manner. Parkinson’s disease is characterized by well-known motor symptoms, including rest tremor, bradykinesia, rigidity, and disturbances of balance and posture, as well as by non-motor symptoms, including psychosis, depression, sleep disturbances, compulsive behaviors and dementia. Among these, the onset of psychosis is considered a particularly poor prognostic sign.

Parkinson’s disease psychosis, or PDP, is a debilitating disorder that develops in up to 60 percent of patients with Parkinson’s disease. The development of PDP substantially contributes to the burden of Parkinson’s disease and deeply affects the quality of life of Parkinson’s patients. PDP is associated with marked increases in caregiver stress and burden, is the single greatest precipitant of nursing home placement among patients with PD, and results in substantial morbidity and mortality.

PDP is characterized by the presence of hallucinations and delusions. Hallucinations are most common and are often visual but may also include somatic or other sensory phenomena. Initially, hallucinations may involve a sense of presence or passage, and insight is often retained, but as the condition progresses the hallucinations become more intransigent and delusions become more prominent. Delusions commonly involve suspicions of spousal infidelity or other paranoid themes and are often profoundly disturbing and debilitating. PDP therefore represents a major inflection point in the course of a patient’s disease, which is compounded by the lack of appropriate therapeutic options.

Current Standard of Care

Currently, there is no FDA-approved therapy for PDP. Traditionally, there are two approaches which may be applied in the treatment of the condition. First, physicians may attempt to reduce or withdraw dopaminergic therapy, the principal component for management of motor symptoms. However, this approach is generally not effective in alleviating PDP and often comes at the cost of significant worsening of motor function. Therefore, physicians frequently must resort to off-label use of antipsychotic medications and, in some cases, hospitalization. Due to their dopamine blocking properties, antipsychotics may counteract the anti-Parkinson’s therapy thereby worsening motor symptoms. Only clozapine, when given at low doses, has been shown to be effective without impairing motor function. Use of clozapine, however, is limited because
it may cause a potentially fatal blood disorder called agranulocytosis. Thus stringent blood monitoring is required. Low-dose clozapine has been approved in Europe, but not in the United States for treatment of PDP. Other antipsychotics, including seroquel, have been proven ineffective in blinded studies of PDP patients or have worsened motor function in these patients. These agents also are associated with a risk for other significant side effects in this elderly and fragile patient population. All current antipsychotics carry a black-box warning on their label for use in elderly patients with dementia-related psychosis because of increased mortality and morbidity. Nevertheless, because there is no alternative, antipsychotics continue to be widely used in the treatment of PDP, despite a high prevalence of dementia as a co-morbid condition in this patient group. Therefore, there is a large unmet medical need for new therapies that will treat PDP effectively without compromising motor control or incurring the risks of serious side effects.

NUPLAZID™ (pimavanserin), ACADIA’s proprietary small molecule that is a selective serotonin inverse agonist preferentially targeting 5-HT2A receptors, is in Phase III development for the treatment of PDP. Both scientific and clinical evidence support the rationale for use of 5-HT2A receptor inverse agonists, such as NUPLAZID, in the treatment of PDP. This receptor is strongly implicated in psychotic conditions and, specifically, in visual hallucinations in PDP; selective 5-HT2A inverse agonists are effective in an animal model of PDP; low doses of clozapine, which block 5-HT2A receptors but not dopamine D2 receptors, are effective in treating PDP; and PDP studies with NUPLAZID have provided encouraging results.

References