ASSESSMENT OF BEZISTERIM (NE3107) IN PATIENTS WITH EARLY PARKINSON'S DISEASE: A PHASE 2, PLACEBO-CONTROLLED, HYBRID DECENTRALIZED STUDY

Joseph Palumbo[1]; Clarence Ahlem[1]; Christopher L. Reading[1]; Jeffrey Zhang[2]; Mark Stacy[3]

1. BioVie Inc., Carson City, Nevada, USA; 2. Princeton Pharmatech, Princeton, New Jersey, USA; 3. Medical University of South Carolina, Charleston, South Carolina, USA.

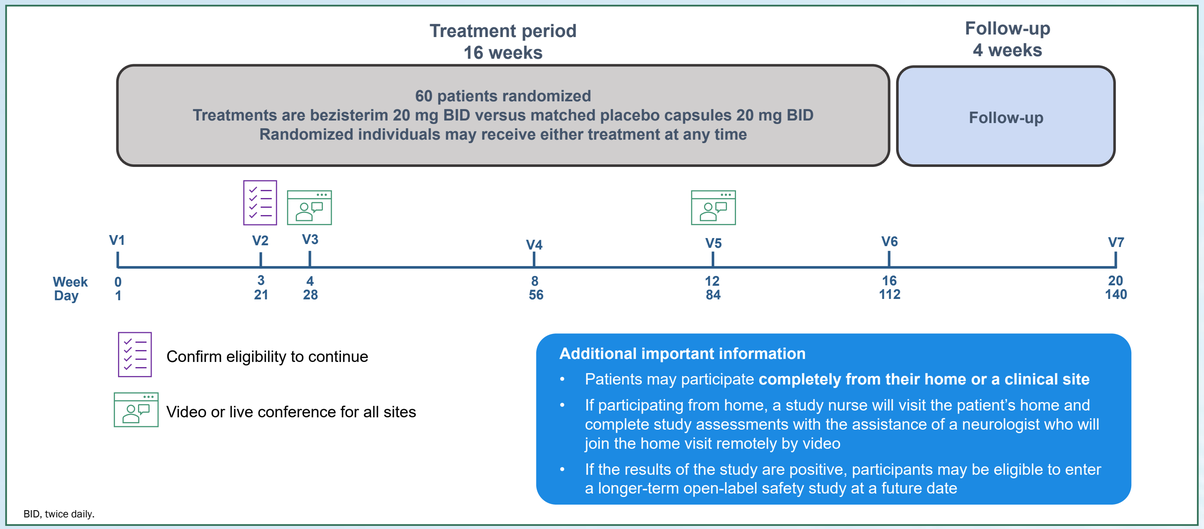
BACKGROUND

- Current symptomatic treatments for PD can alleviate symptoms with variable success over time, although motor worsening, fluctuations and dyskinesias, and functional disability inevitably accrue[1]
- Therapies that improve these disease features or act synergistically with existing treatments may be of substantial therapeutic significance
- Trimeric complexes of dopamine D2 receptor (D2R) with activated adenosine A2A receptor (A2AR) and metabotropic glutamate receptor type 5 (mGluR5) result in inhibition of D2R activity in the indirect pathway[2,3]
- Bezisterim decreases microglial activation,[4] which may in turn modulate A2AR-mGluR5 signaling, thereby enhancing D2R signaling and improving motor symptoms
- Pro-inflammatory cytokines, particularly tumor-necrosis factor alpha (TNF-α), may also have a role in sleep regulation and fatigue in patients with PD[5]
- Bezisterim is an oral, blood-brain-barrier–permeable molecule that binds extracellular signal-regulated kinase (ERK) and has anti-inflammatory and insulin-sensitizing activities via inhibition of inflammatory (but not homeostatic) ERK and nuclear factor kappa B (NF-κB) activation and TNF-α signaling[4]
- In a mouse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD, bezisterim as monotherapy demonstrated activity against parkinsonian motor symptoms and neurodegeneration[6]
- In a marmoset PD model, bezisterim demonstrated levodopa (L-dopa)-like promotoric activity and, in combination with L-dopa, was superior to either agent alone[7]
- In the same study, bezisterim dramatically decreased L-dopa–induced dyskinesia without decreasing the observed promotoric activity and significantly decreased the loss of tyrosine hydroxylase-positive neurons in the substantia nigra compared to placebo control; notably, bezisterim was superior to the positive control (amantadine) in all study measures
- In a phase 2a study in patients with PD (and reported elsewhere at this congress), bezisterim was associated with improvements in both motor and non-motor symptoms[8]
- To date, NE3107 has exhibited a benign safety profile in hundreds of clinical trial participants and extensive nonclinical safety evaluations
- In aggregate, these findings support further evaluation of the potential benefits of bezisterim in patients with PD

METHODS

- We plan to conduct SUNRISE-PD, a study of bezisterim in adult subjects with PD who are naïve to carbidopa/L-dopa treatment, in need of symptomatic therapy for motor symptoms, and are willing to defer currently approved pharmacologic treatment for the duration of this study (**Figure 1**)
- Centralized ratings of a modified Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III will be used to help reduce variability and increase sensitivity for detection of change excluding Rigidity and Postural Stability

Figure 1. Phase 2, hybrid, multicenter, decentralized, randomized, double-blind, placebo-controlled study



BID, twice daily.

OBJECTIVES

- Objectives and accompanying endpoints of the study are listed in **Table 1**

Table 1. Objectives and Endpoints

Objective	Endpoint
Primary	
Evaluate the efficacy of bezisterim in the treatment of motor symptoms of PD	Change in a modified MDS-UPDRS Part III score excluding rigidity and postural stability (centralized ratings)
Secondary	
Evaluate the impact of bezisterim on non-motor symptoms of PD and on overall symptoms of PD as assessed by the clinician	• Change in the MDS-UPDRS Part I and Part II scores • Subjects with any improvement as measured by the Clinical Global Impression-Improvement (CGI-I) • Subjects with any improvement as measured by Clinical Global Severity (CGI-S)
Exploratory	
Evaluate the efficacy of bezisterim in the treatment of motor symptoms of PD	Change in complete modified MDS-UPDRS Part III score
Assess the effects of bezisterim treatment on other aspects of PD	Change in MDS-UPDRS combined and sub-domain scores
Evaluate the effect of bezisterim on Patient Reported Outcomes (PROs)	• Change in Parkinson's Disease Questionnaire-39 (PDQ-39) • Change in Parkinson's Disease Sleep Scale (PDSS) score
Evaluate the effect of bezisterim on discontinuation events for worsening of PD	• Subjects discontinuing from the study due to worsening of PD • Time to discontinuation due to worsening of PD
Assess the effect of bezisterim on epigenetics associated with biological age and alpha synuclein gene methylation	Change in DNA methylation
Assess the effect of bezisterim on plasma biomarkers of inflammation and pharmacodynamics	Change in plasma biomarkers of inflammation and disease severity/progression
Assess the effect of bezisterim on circulating biomarkers and correlations between biomarkers and clinical endpoint changes	Change in pre-specified exploratory biomarkers and the correlation between biomarkers and clinical endpoints
Assess population pharmacokinetics (PPK) and exposure response (E-R) relationships for efficacy and safety of bezisterim	PK and E-R assessments for efficacy and safety where data permit
Safety	
Assess the safety and tolerability of bezisterim	Includes number/frequency of or changes in the following: • Treatment-emergent adverse events (TEAEs) • Vital signs • Electrocardiograms (ECGs) • Clinical laboratory values • Physical exam • Columbia-Suicide-Severity Rating Scale (C-SSRS)

Key inclusion criteria

- Age 45–80 years
- Diagnosis of idiopathic PD no more than 18 months prior to Screening and not more than 36 months since first motor symptoms
- Mild unilateral or bilateral involvement without impaired balance (Hoehn and Yahr stage <3)
- If on medications for glycemic control, medicines must be stable for at least 3 months prior to the study and remain stable during the study; glucagon-like peptide-1 (GLP-1) receptor agonists are not permitted

Key exclusion criteria

- Has taken or is taking L-dopa; a subject who has received an L-dopa challenge to diagnose their condition is NOT excluded if the L-dopa exposure was no greater than 42 total days and ended at least 3 months prior to Screening
- Has taken a dopamine receptor agonist other than L-dopa for the motor symptoms of Parkinson's; prior use of a monoamine oxidase B (MAO-B) inhibitor is permitted if discontinued 6 weeks prior to Screening
- A known or strongly suspected familial cause of PD

CONCLUSIONS

- Cumulative information from prior studies suggests that bezisterim's MOA has the potential to provide clinical benefit and modify fundamental inflammatory and epigenetic mechanisms associated with PD progression
- SUNRISE-PD is expected to provide important data on the benefits of bezisterim in patients with early PD, which would provide the foundation for a study of disease modifying activity

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DISCLOSURES

CLR, **CA**, and **JP** are employees of BioVie Inc. **JZ** and **MS** are consultants for BioVie Inc. **SHI** and **AEL** have served as advisors for BioVie Inc.