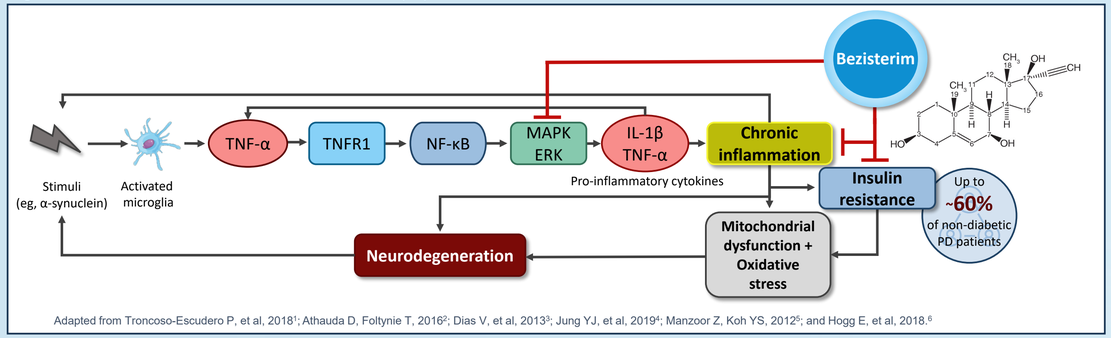
IMPROVEMENT OF MOTOR AND NON-MOTOR SYMPTOMS WITH BEZISTERIM (NE3107) ADJUNCTIVE TO CARBIDOPA/LEVODOPA IN PATIENTS WITH PARKINSON'S DISEASE: A PHASE 2A, PLACEBO-CONTROLLED STUDY

Joseph Palumbo[1], Christopher L. Reading[1], Clarence Ahlem[1], Jeffrey Zhang[2], Jason L. Aldred[3], Ramon L. Rodriguez[4], Edgardo J. Rivera-Rivera[5], Stuart H. Isaacson[6], Rajeev Kumar[7], Aaron L. Ellenbogen[8], Anthony E. Lang[9]

1. BioVie Inc., Carson City, Nevada, USA; 2. Princeton Pharmatech, Princeton, New Jersey, USA; 3. Selkirk Neurology & Inland Northwest Research, Spokane, Washington, USA; 4. Neurology One, Winter Park, Florida, USA; 5. Charter Research, Winter Park, Florida, USA; 6. Parkinson's Disease & Movement Disorders Center of Boca Raton, Boca Raton, Florida, USA; 7. Rocky Mountain Movement Disorders Center, Englewood, Colorado, USA; 8. Quest Research Institute, Farmington Hills, Michigan, USA; 9. Edmond J. Safra Program in Parkinson's Disease, University Health Network and the University of Toronto, Toronto, Ontario, Canada.

Figure 1. Potential role of bezisterim in Parkinson's disease (PD)



Adapted from Troncoso-Escudero P, et al, 2018[1]; Athauda D, Foltynie T, 2016[2]; Dias V, et al, 2013[3]; Jung YJ, et al, 2019[4]; Manzoor Z, Koh YS, 2012[5]; and Hogg E, et al, 2018.[6]

ERK, extracellular signal-regulated kinase; IL, interleukin; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; TNF, tumor necrosis factor.

BACKGROUND

- Disrupting the feed-forward loop formed by neuroinflammation, insulin resistance, and oxidative stress may be an effective strategy to limit PD progression (**Figure 1**)[1-4,7,8]
- 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 tumor necrosis factor-alpha (TNF-α) signaling[9]
- 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[10,11]
- Bezisterim decreases microglial activation,[9] which may in turn modulate A2AR-mGluR5 signaling, thereby enhancing D2R signaling and improving motor symptoms
- In a marmoset PD model, bezisterim was associated with improved mobility, enhanced levodopa activity, and decreased neuronal death in the substantia nigra; it also alleviated levodopa-induced dyskinesia, a side effect of long-term exposure to levodopa[12]
- Pro-inflammatory cytokines, particularly TNF-α, may also have a role in sleep regulation and fatigue in patients with PD[13]

OBJECTIVES

- To evaluate the effects of bezisterim treatment on motor and non-motor symptoms (NMS) in patients with carbidopa/levodopa (C/L)-treated PD experiencing motor fluctuations
- Here we report safety outcomes from the phase 2a, randomized trial (NM201)

METHODS

Study Design

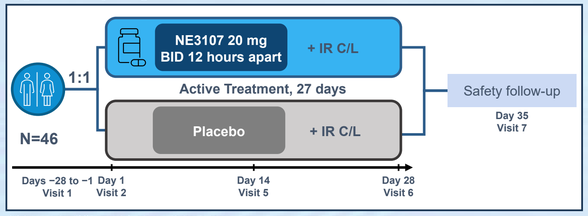
- This was a phase 2a, randomized, placebo-controlled, 28-day study of 46 C/L-treated patients with PD to evaluate the safety, efficacy, and pharmacokinetics of adjunctive bezisterim. (**Figure 2**)

Study Population

Key inclusion criteria

- 30-80 years old
- Diagnosis of PD
- Bradykinesia and motor response to levodopa
- History of motor fluctuations + early morning OFF episodes
- Receiving ≥300 mg of carbidopa/levodopa daily

Figure 2. Study design



BID, twice per day; IR C/L, immediate-release carbidopa/levodopa.

Assessments

- Changes in motor symptoms were evaluated using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III
- NMS of PD were evaluated using the Non-Motor Symptom Assessment Scale (NMSS) for PD[14,15]

RESULTS

Baseline characteristics and effects on motor symptoms

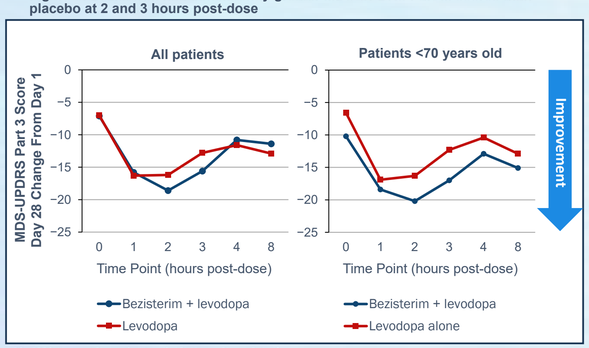
- Baseline characteristics are shown in **Table 1**
- As shown in **Figure 3**, bezisterim treatment was associated with superior improvements vs placebo on the motor examination part (Part III) of the MDS-UPDRS at the 2- and 3-hour marks
- We noted greatest improvement in patients <70 years old (50% of the total patient population)
  - Bezisterim-treated patients <70 years old had lower Part III scores prior to medication administration (t=0) compared to those treated with IR C/L alone

Table 1. Baseline characteristics

Characteristic	NE3107 + IR C/L (n=22)	Placebo + IR C/L (n=23)
Age, mean (y)	67.6	66
Gender, n (%) Female Male	 9 (41) 13 (59)	 8 (35) 15 (65)
Weight, mean (kg)	80.1	80.8
BMI, mean	28.2	27.9
Time since diagnosis, mean (y)	7.6	7.3
Total daily levodopa, mean (mg)	548	691
MDS-UPDRS Scores, mean Part I Part II Part III	 6.8 9.4 28.4	 7.5 8.2 25.8
ON time without dyskinesia within 4 h, mean (h)	1.95	1.93
OFF time within 4 h, mean (h)	2.1	1.7

BMI, body mass index; h, hour(s); IR C/L, immediate-release carbidopa/levodopa; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; y, year(s).

Figure 3. Bezisterim had consistently greater MDS-UPDRS Part III scores than placebo at 2 and 3 hours post-dose



MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale.

Post hoc assessment of motor symptom efficacy

- As shown in **Figure 4**, 30% (6/20) of patients treated with bezisterim, compared to none (0/19) of the placebo patients, who had a baseline of morning OFF experienced a morning ON state prior to receiving their morning medications on day 28 (*P*=0.02)

Figure 4. Patients with morning "ON" state prior to receiving day 28 dose

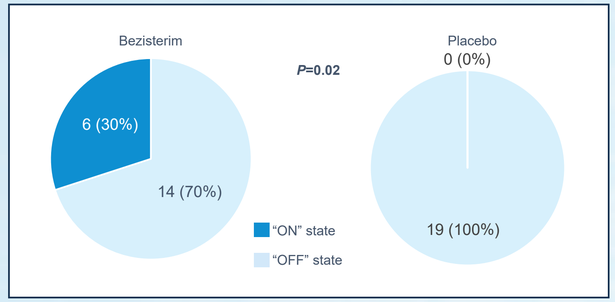
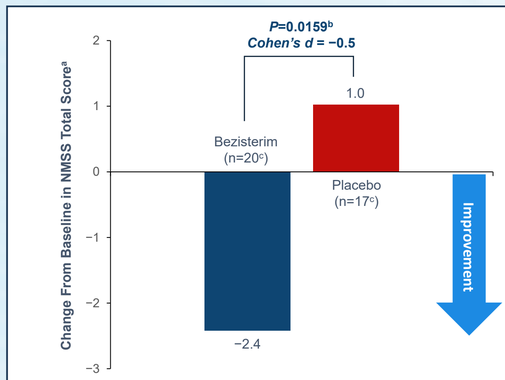


Figure 5. Significant improvement in NMSS sleep/fatigue domain score

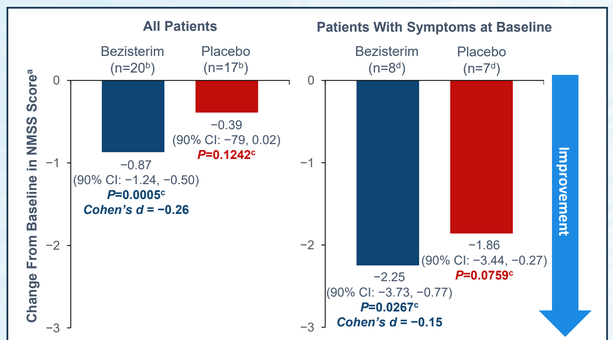


Sleep/fatigue domain improvements significantly correlated with motor score improvements, r=0.51; *P*=0.0259

[a]Least squares mean. [b]*P* values for between-group change from baseline.
[c]Per-protocol population: patients with baseline and Visit 6 evaluable data.

NMSS, Non-Motor Symptom Assessment Scale; *r*, Pearson correlation coefficient.

Figure 6. Significant improvement from baseline in fatigue/lack of energy achieved with bezisterim but not placebo



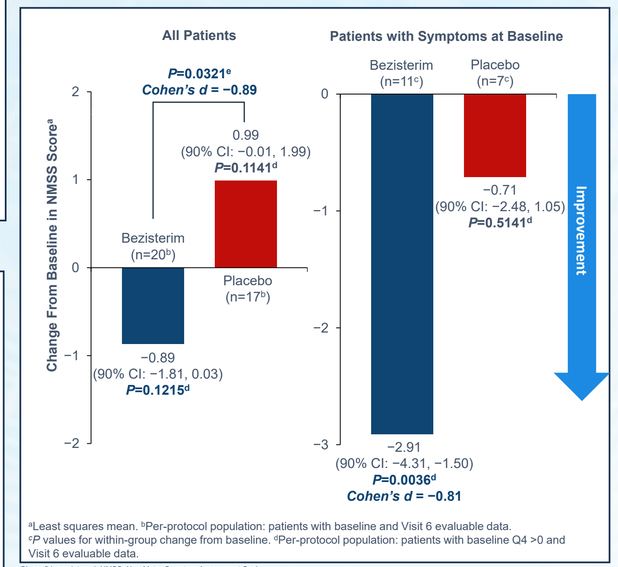
[a]Least squares mean. [b]Per-protocol population: patients with baseline and Visit 6 evaluable data.
[c]*P* values for within-group change from baseline. [d]Per-protocol population: patients with baseline Q4 >0 and Visit 6 evaluable data.

CI, confidence interval; NMSS, Non-Motor Symptom Assessment Scale.

NMS efficacy assessment

- Bezisterim was associated with significant improvement in the NMSS sleep/fatigue domain score compared with placebo (**Figure 5**)
- Bezisterim, but not placebo, was associated with significant improvements from baseline in fatigue symptoms in all patients and in patients with symptoms at baseline (**Figure 6**)
- Bezisterim, but not placebo, was associated with a significant improvement from baseline in the urge to move the legs in patients with symptoms at baseline (**Figure 7**)

Figure 7. Significant improvement in restless legs among patients with symptoms at baseline



[a]Least squares mean. [b]Per-protocol population: patients with baseline and Visit 6 evaluable data.
[c]*P* values for within-group change from baseline. [d]Per-protocol population: patients with baseline Q4 >0 and Visit 6 evaluable data.

CI, confidence interval. NMSS, Non-Motor Symptom Assessment Scale.

CONCLUSIONS

- **Our data show improvement in motor symptoms with bezisterim and demonstrate potential intrinsic, levodopa-enhancing activity of bezisterim that is consistent with data from animal models**
- **Our data also suggest that, as an adjunctive therapy to levodopa, bezisterim may hold promise in ameliorating specific non-motor symptoms of PD, particularly in sleep/fatigue items of domain 2 of the NMSS related to fatigue/lack of energy and restlessness of the legs**
- **This study supports the need for more comprehensive exploration of bezisterim's potential benefits in PD**

REFERENCES

1. Troncoso-Escudero P, Parra A, Nassif M, Vidal RL. Outside in: unraveling the role of neuroinflammation in the progression of Parkinson's disease. *Front Neurol*. 2018;9:860. doi: 10.3389/fneur.2018.00860
2. Athauda D, Foltynie T. Insulin resistance and Parkinson's disease: a new target for disease modification? *Prog Neurobiol*. 2016;145-146:98-120.
3. Dias V, Junn E, Mouradian MM. The role of oxidative stress in Parkinson's disease. *J Parkinsons Dis*. 2013;3(4):461-491.
4. Jung YJ, Tweedie D, Scerba MT, Greig NH. Neuroinflammation as a factor of neurodegenerative disease: thalidomide analogs as treatments. *Front Cell Dev Biol*. 2019;7:313. doi: 10.3389/fcell.2019.00313
5. Manzoor Z, Koh YS. Mitogen-activated protein kinases in inflammation. *J Bacteriol Virol*. 2012;42(3):189-195.
6. Hogg E, Athreya K, Basile C, Tan EE, Kaminski J, Tagliati M. High prevalence of undiagnosed insulin resistance in non-diabetic subjects with Parkinson's disease. *J Parkinsons Dis*. 2018;8(2):259-265.
7. Albeely AM, Ryan SD, Perreault ML. Pathogenic feed-forward mechanisms in Alzheimer's and Parkinson's disease converge on GSK-3. *Brain Plast*. 2018;4(2):151-167.
8. Peter I, Dubinsky M, Bressman S, et al. Anti-tumor necrosis factor therapy and incidence of Parkinson disease among patients with inflammatory bowel disease. *JAMA Neurol*. 2018;75(8):939-946.
9. Reading CL, Ahlem CN, Murphy MF. NM101 phase III study of NE3107 in Alzheimer's disease: rationale, design and therapeutic modulation of neuroinflammation and insulin resistance. *Neurodegener Dis Manag*. 2021;11(4):289-298.
10. Mori A, Chen J-F, Uchida S, et al. The pharmacological potential of adenosine A_{2A} receptor antagonists for treating Parkinson's disease. *Molecules*. 2022;27(7):2366. doi: 10.3390/molecules27072366
11. Romero-Fernandez W, Taura JJ, Crans RAJ, et al. The mglu5 receptor protomer-mediated dopamine D2 receptor trans-inhibition is dependent on the adenosine A2A receptor protomer: implications for Parkinson's disease. *Mol Neurobiol*. 2022;59(10):5955-5969.
12. Philippens IH, Baarends G, Batenburg F, Ahlem C. Anti-Parkinson and anti-L-Dopa induced dyskinesia efficacy of HE3286 in a MPTP non-human primate model [Poster 138.12/G44]. Presented at: Neuroscience 2013; November 9, 2013; San Diego, CA.
13. Wang H, Liu Y, Zhao J, Guo X, Hu M, Chen Y. Possible inflammatory mechanisms and predictors of Parkinson's disease patients with fatigue. *Clin Neurol Neurosurg*. 2021;208:106844. doi:10.1016/j.clineuro.2021.106844
14. Chaudhuri KR, Martinez-Martin P, Brown RG. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. *Mov Disord*. 2007;22:1901-1911.
15. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR; NMSS Validation Group. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease on behalf of the NMSS Validation Group. *Mov Disord*. 2011;26:399-406.

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DISCLOSURES

CLR, **CA**, and **JP** are employees of BioVie Inc. **NO** is formerly an employee of BioVie Inc. **JZ** is a consultant for BioVie Inc. **SHI** and **AEL** have served as advisors for BioVie Inc. **RLR** and **RK** have received grants from BioVie Inc.