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

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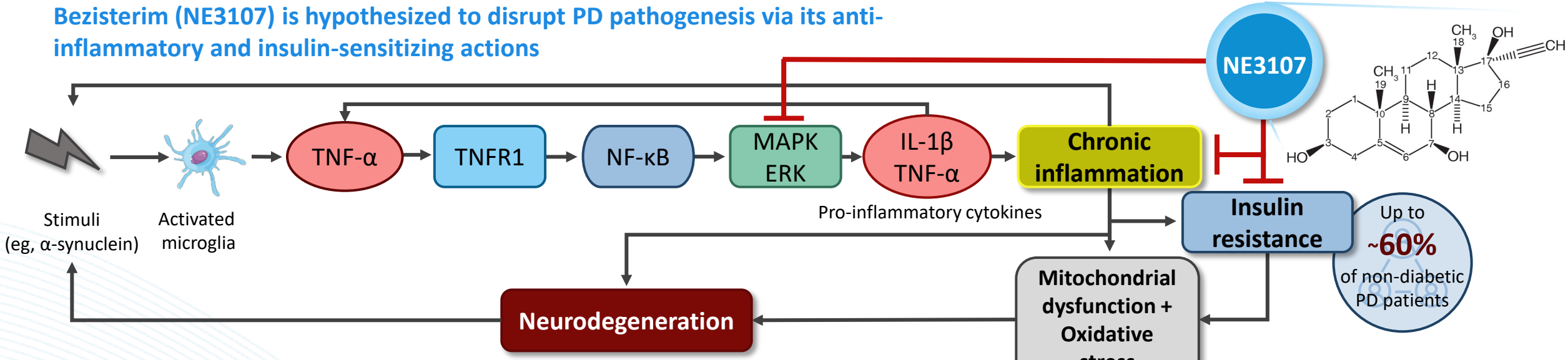
Background

Bezisterim (NE3107) is hypothesized to disrupt PD pathogenesis via its anti-inflammatory and insulin-sensitizing actions



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]

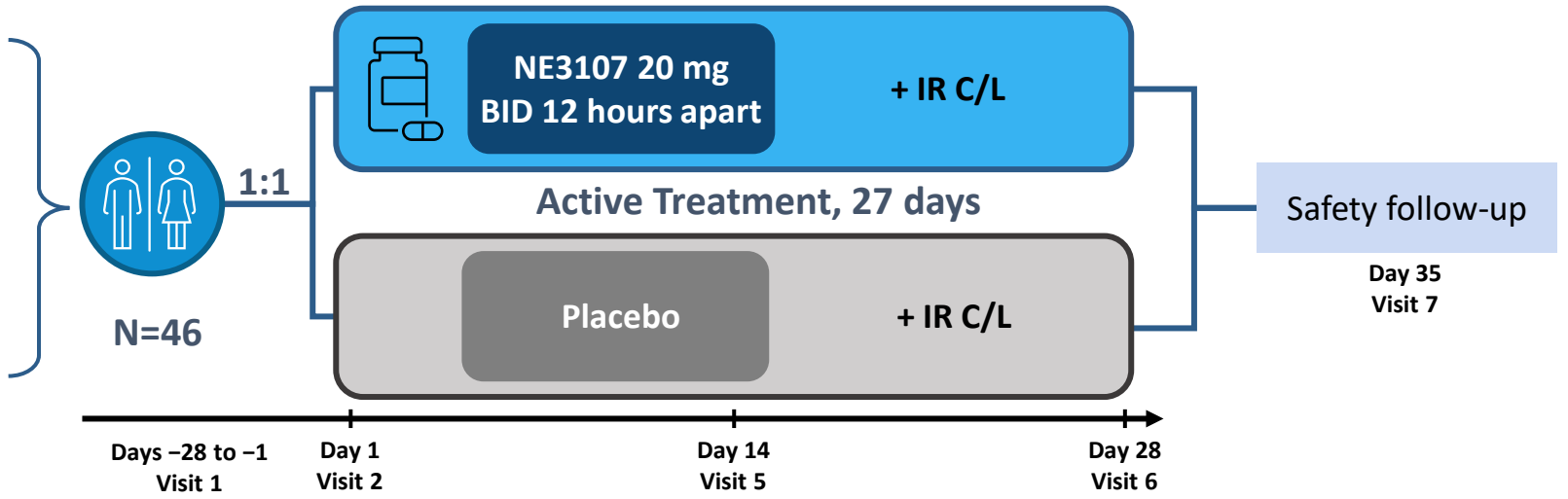
- Disrupting the feed-forward loop formed by neuroinflammation, insulin resistance, and oxidative stress may be an effective strategy to limit PD progression[1-4,7,8]
- Bezisterim is an oral, blood-brain barrier–permeable molecule that binds ERK and has anti-inflammatory and insulin-sensitizing activities via inhibition of inflammatory (but not homeostatic) ERK and NF-κB activation and TNF-α signaling[9]
- Bezisterim has an excellent safety profile and was shown to improve insulin sensitivity and glucose metabolism and to reduce CRP and HbA1c, in obese and inflamed patients with impaired glucose tolerance or T2D[9]
- 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[10]
- Pro-inflammatory cytokines, particularly TNF-α, may have a role in sleep regulation and fatigue in patients with PD[11]

CRP, C-reactive protein; ERK, extracellular signal-regulated kinase; HbA1c, hemoglobin A1C; IL, interleukin; MAPK, mitogen-activated protein kinases; NF-κB, nuclear factor kappa B; PD, Parkinson's disease; T2D, type 2 diabetes; TNF-α, tumor necrosis factor-α; TNFR, TNF-α receptor.

Study Design: Phase 2, Double-Blind, Placebo-Controlled, 28-Day Duration

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



- Safety, tolerability, and exploratory efficacy of bezisterim on motor symptoms have previously been reported[12]
  - Bezisterim -levodopa combination treatment was associated with clinically meaningful and superior improvements on the motor examination part (Part III) of the MDS-UPDRS
- This presentation will also report the effects of bezisterim on **non-motor symptoms of sleep and fatigue** as assessed by the Non-Motor Symptom Scale (NMSS)[13,14]
  - Findings in a subset of the all-comers population, ie, patients were not required to have non-motor symptoms at baseline for inclusion in the study

BID, twice per day; IR C/L, immediate-release carbidopa/levodopa; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

Bezisterim Treatment Was Associated With Superior Improvements Versus Placebo on the Motor Examination Part (Part III) of the MDS-UPDRS, With Greatest Improvement in Patients <70 Years old

All Patients

Time Point (hours post dose)	0	1	2	3	4	8
Bezisterim + Levodopa	−7.1	−15.8	−18.6	−15.6	−10.8	−11.4
Levodopa	−7.0	−16.3	−16.2	−12.8	−11.6	−12.9
Difference	−0.1	0.5	−2.4	−2.8	0.7	1.5

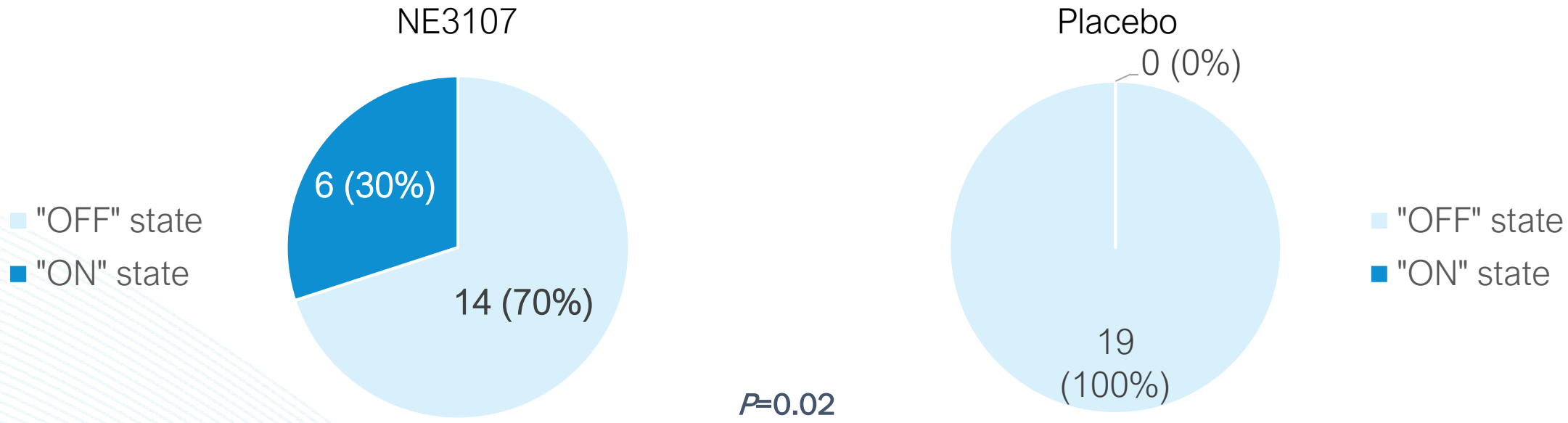
Patients <70 years old

Time Point (hours post dose)	0	1	2	3	4	8
Bezisterim + Levodopa	−10.2	−18.4	−20.2	−17.0	−12.9	−15.1
Levodopa	−6.6	−16.9	−16.3	−12.3	−10.4	−13.7
Difference	−3.6	−1.5	−3.9	−4.7	−2.5	−1.4

- Patients treated with bezisterim and C/L experienced greater improvements in their MDS-UPDRS Part III score than patients treated with placebo and C/L at the **2- and 3-hour marks**
- Patients **<70 years** old treated with bezisterim and C/L experienced improvements that were better than those who received placebo and C/L
  - **~50%** of the total patient population was <70 years old
  - Bezisterim-treated patients <70 years old had lower Part III scores prior to medication administration (t=0) compared to those treated with C/L alone

More Bezisterim-levodopa Combination Treated Patients who Experienced an “OFF” State at Baseline Experienced a Morning “ON” State Prior to Dosing on day 28

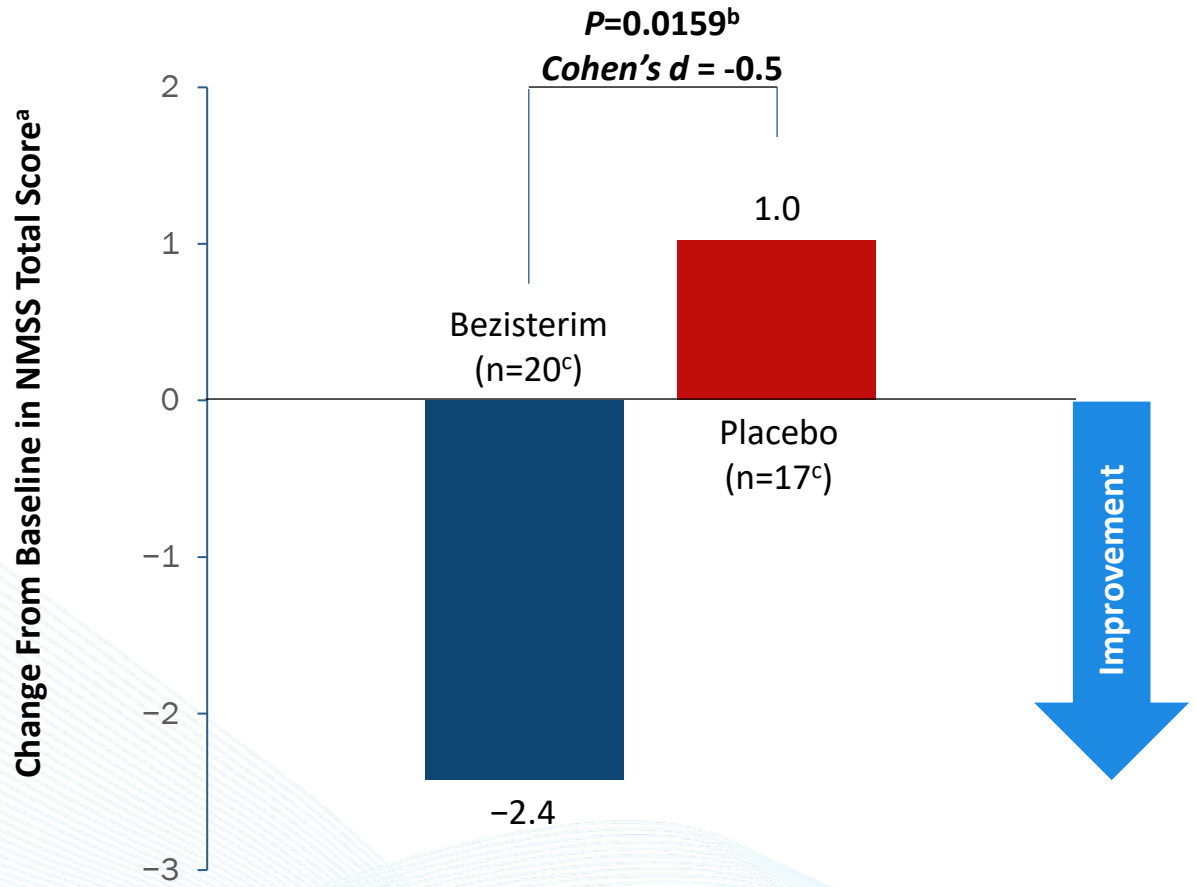
Post hoc efficacy assessment



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

Significant Improvement in the NMSS Sleep/Fatigue Domain Score

Improvements were correlated with Motor Score improvements

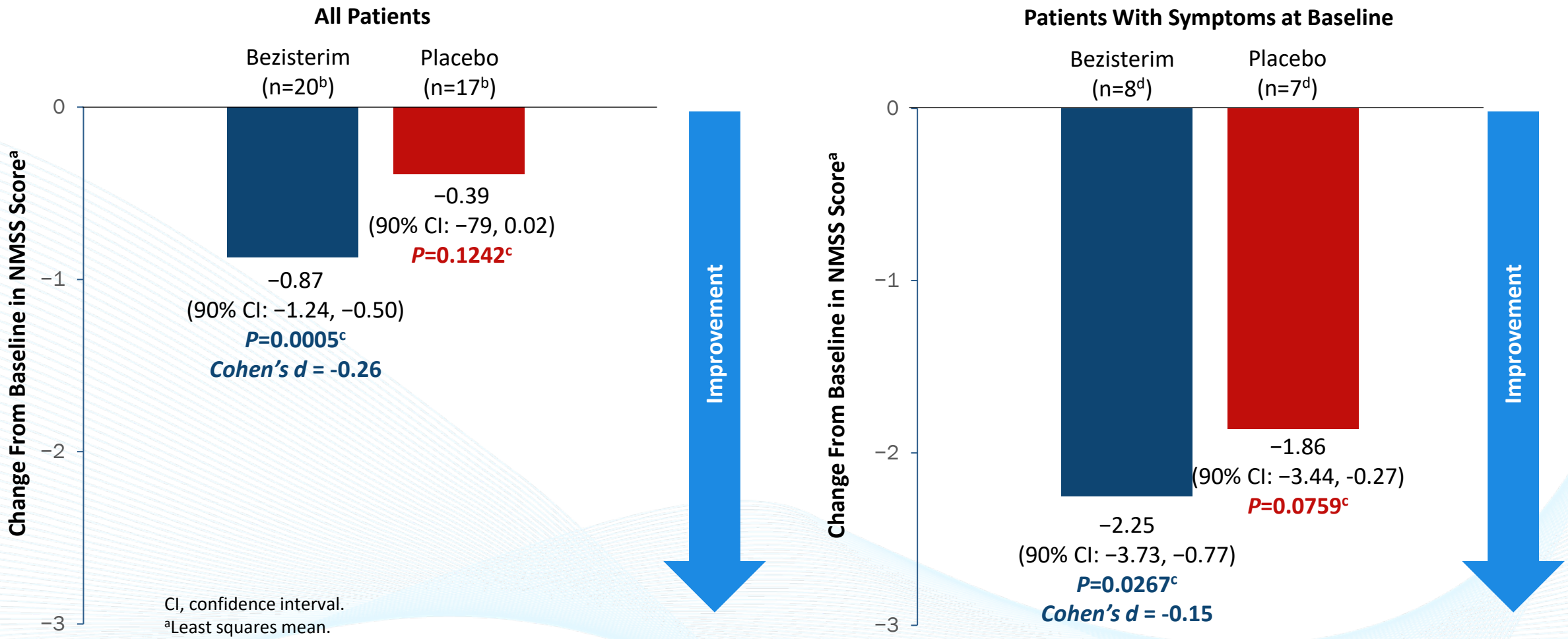


Sleep/fatigue domain improvements significantly correlated with motor score improvements, r=0.51; *P*=0.0259

[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.

Significant Improvement From Baseline in Fatigue/Lack of Energy (Q4) Achieved With Bezisterim but Not Placebo

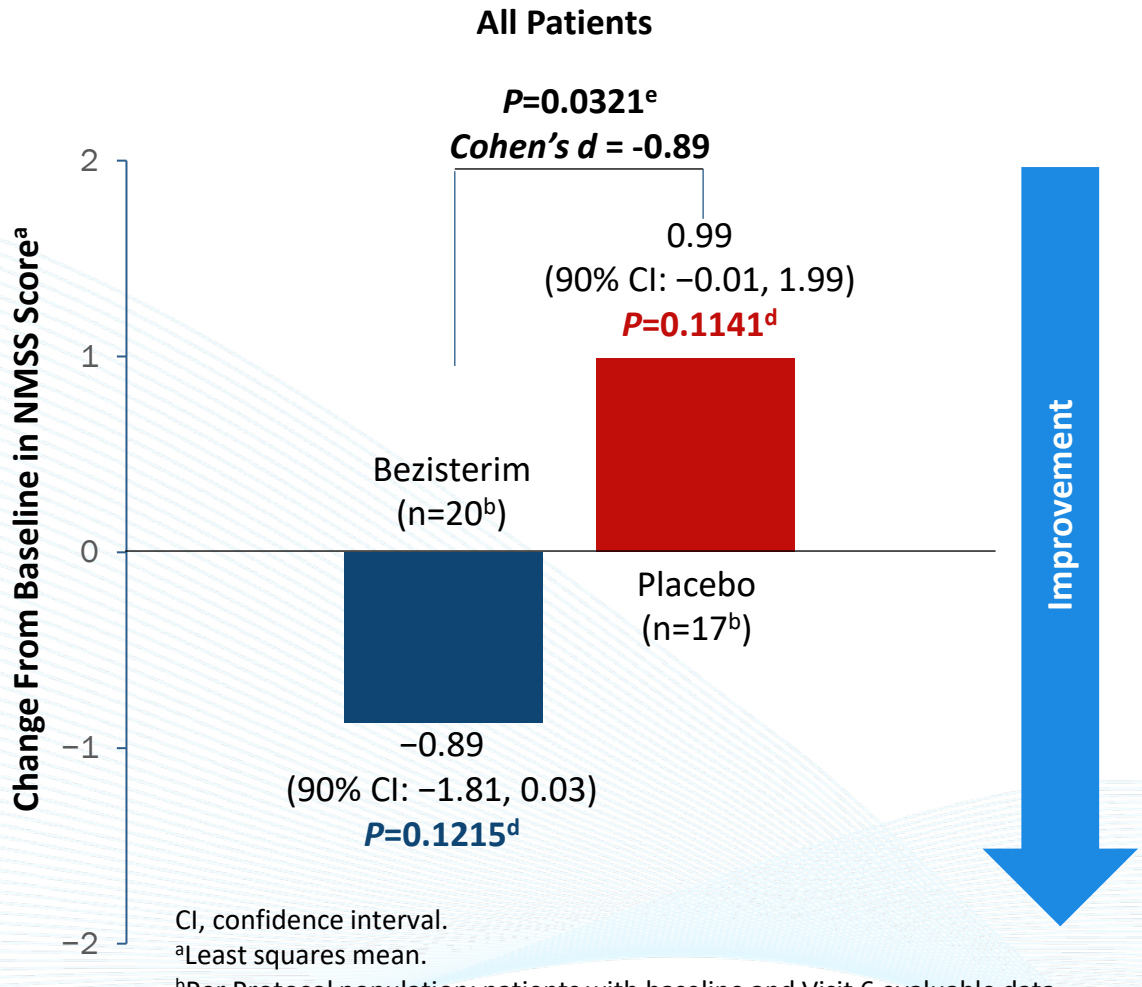
Does fatigue (tiredness) or lack of energy (not slowness) limit the patient's daytime activities?

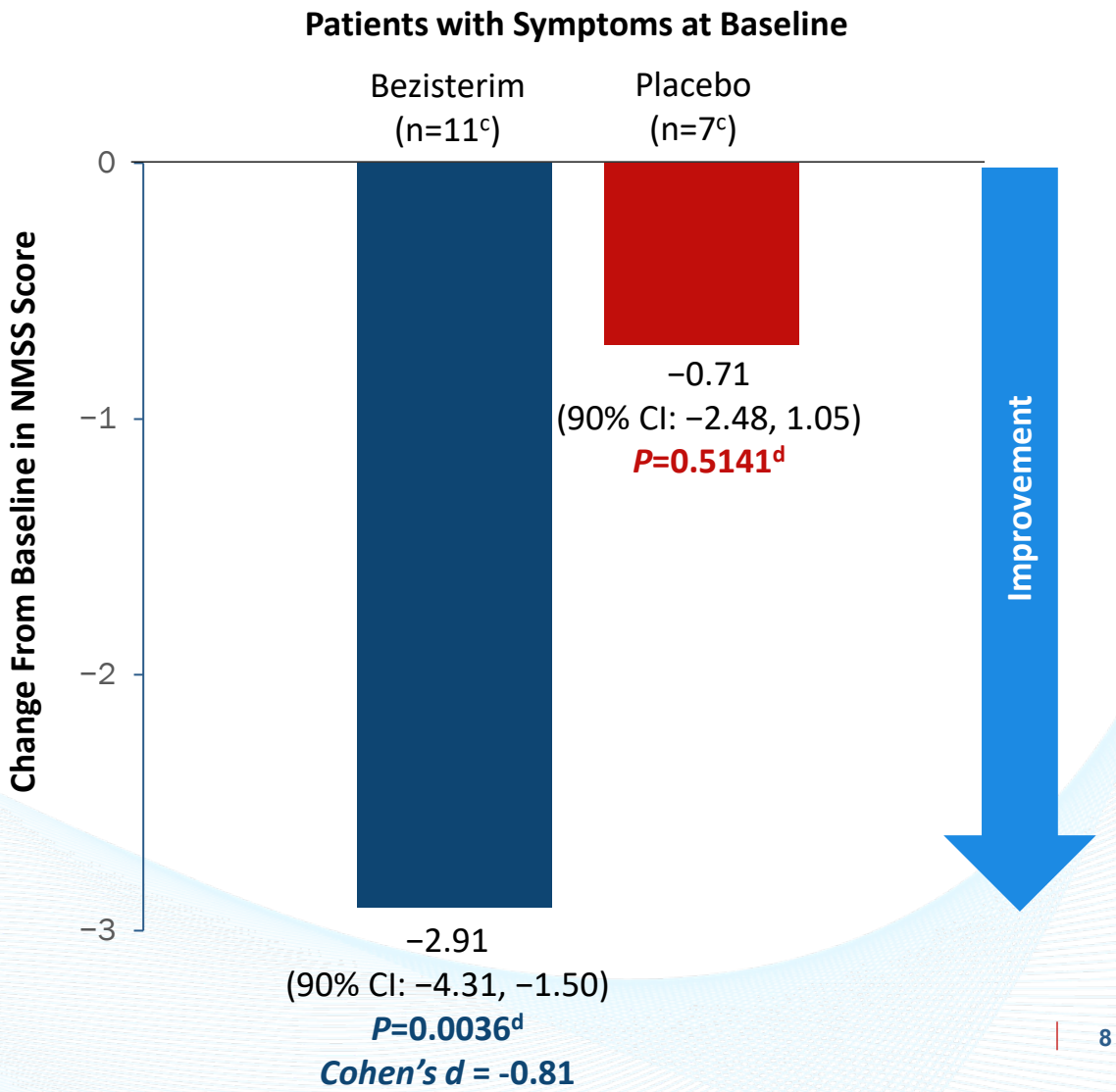


CI, confidence interval.
[a]Least squares mean.
[b]Per Protocol population: patients with baseline and Visit 6 evaluable data.
[c]*P* values for within-group change from baseline.
[d]Per Protocol population: patients with baseline Q4 >0 and Visit 6 evaluable data

Significant Improvement From Baseline in Urge to Move Legs/Restlessness in Legs (Q6) Achieved With Bezisterim but Not Placebo

Does the patient experience an urge to move the legs or restlessness in legs that improves with movement when he/she is sitting or lying down inactive?





CI, confidence interval.
[a]Least squares mean.
[b]Per Protocol population: patients with baseline and Visit 6 evaluable data.
[c]Per Protocol population: patients with baseline Q6 >0 and Visit 6 evaluable data
[d]*P* values for within-group change from baseline.
[e]*P* values for between group change from baseline.

Conclusions

- These data 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
- These findings warrant confirmation in patients who are significantly impacted by these non-motor symptoms
- These findings are accompanied by improvement in motor symptoms with bezisterim and demonstrate potential intrinsic, levodopa-enhancing activity of bezisterim that is consistent with data from animal models and support further clinical investigation of bezisterim in late-phase trials

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.

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Back up slides

Baseline Characteristics

Characteristic	NE3107 + IR C/L (n=24)	Placebo + IR C/L (n=22)
Age, mean (y)	67.4	65.8
Gender, n (%) Female Male	 10 (41.7) 14 (58.3)	 8 (36.4) 14 (63.6)
Weight, mean (kg)	80.1	80.8
BMI, mean (kg/m^2)	27.6	26.4
Time since diagnosis, mean (y)	7.6	7.2
Total daily levodopa, mean (mg)	548	691
OFF-State MDS-UPDRS Scores, mean Part I Part II Part III	 6.8 9.8 38.5	 8.3 8.5 37.8
ON time without dyskinesia within 4 h of morning dose, mean (h)	1.9	2.1
OFF time during 4 h following first morning dose of levodopa, mean (h)	2.1	1.7

Modified ITT population
BMI, body mass index.