

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

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Presented at the 2024 International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders | March 5 - 9, 2024 | Lisbon, Portugal

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.

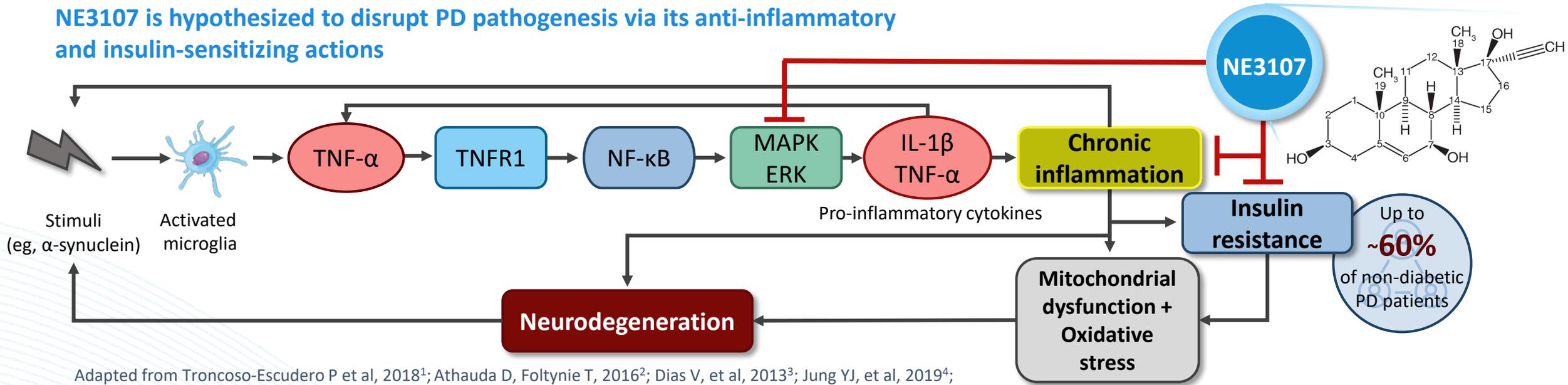
RLR and **RK** have received grants from BioVie Inc.

Acknowledgments

p-value communications provided editorial support. Funded by BioVie Inc.

Background

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



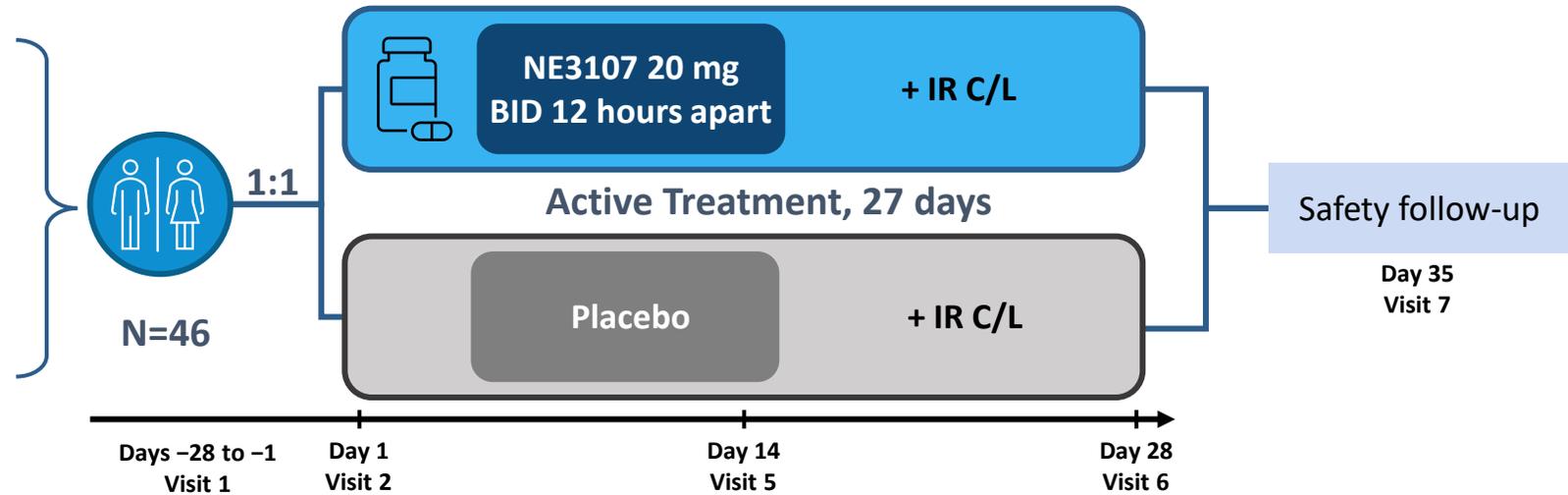
Adapted from Troncoso-Escudero P et al, 2018¹; Athauda D, Foltynie T, 2016²; Dias V, et al, 2013³; Jung YJ, et al, 2019⁴; Manzoor Z, Koh YS, 2012⁵; and Hogg E et al, 2018.⁶

- 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}
- NE3107 is an oral, blood-brain barrier-permeable molecule that binds ERK and has anti-inflammatory and insulin-sensitizing activities via inhibition of inflammation-stimulated ERK and NF- κ B activation and TNF- α signaling, without disrupting homeostasis⁹
- NE3107 has an excellent safety profile and was shown to improve insulin sensitivity and glucose metabolism and reduce CRP and HbA1c in obese and inflamed patients with impaired glucose tolerance or T2D⁹
- In a marmoset PD model, NE3107 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 levodopa¹⁰
- Pro-inflammatory cytokines, particularly TNF- α , may have a role in sleep regulation and fatigue in patients with PD¹¹

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 NE3107 on motor symptoms have previously been reported¹²
 - NE3107-levodopa combination treatment was associated with clinically meaningful and superior improvements (3+ points) on the motor examination part (Part III) of the MDS-UPDRS
- This presentation will report the effects of NE3107 on **non-motor symptoms of sleep and fatigue** as assessed by the Non-Motor Symptom Scale (NMSS)^{13,14}
 - Findings in a sub-set of the all-comers population, not required to have non-motor symptoms at baseline for inclusion in the study

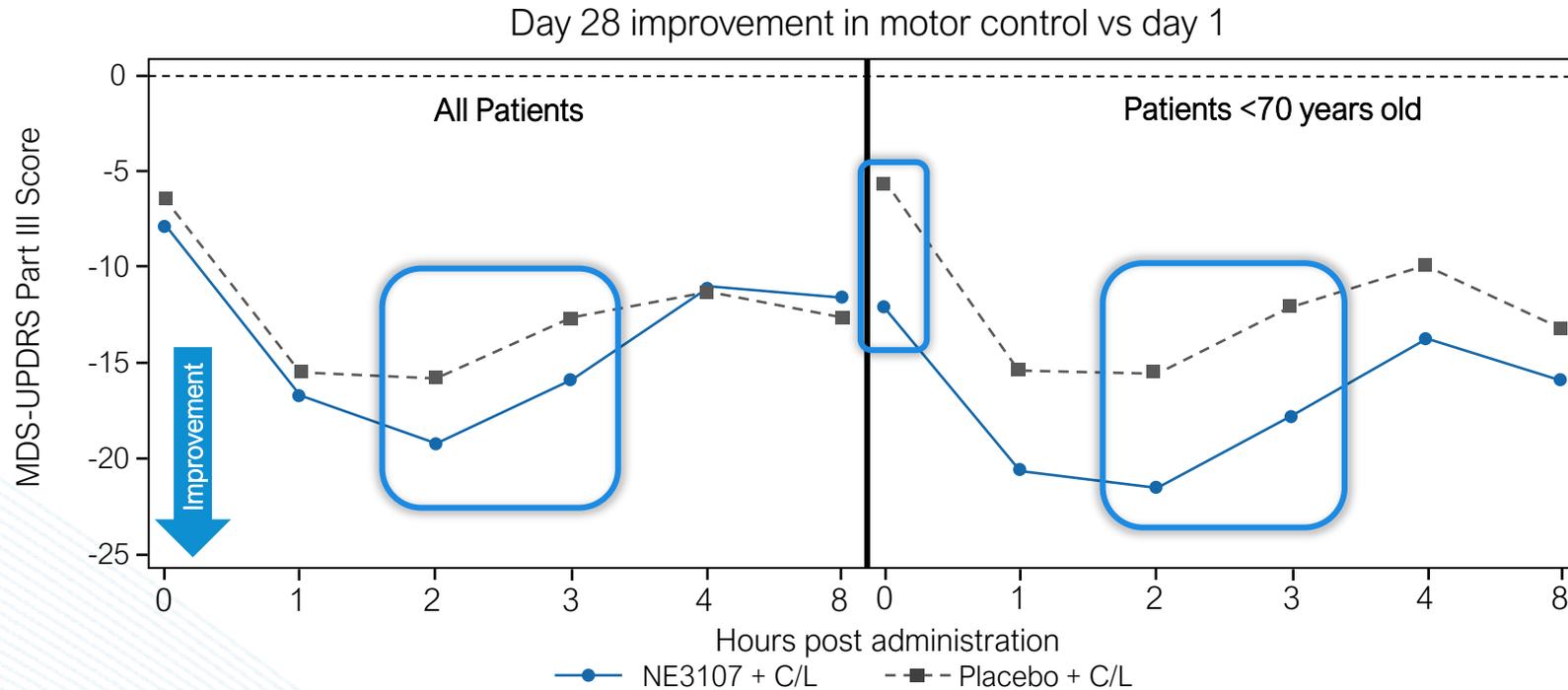
Baseline Characteristics

Characteristic	NE3107 + IR C/L (n=24)	Placebo + IR C/L (n=22)
Age, mean (y)	67.4	65.8
Gender, n (%)		
Female	10 (41.7)	8 (36.4)
Male	14 (58.3)	14 (63.6)
Weight, mean (kg)	80.1	80.8
BMI, mean	27.6	26.4
Time since diagnosis, mean (years)	7.6	7.2
Total daily levodopa, mean (mg)	548	691
Off-State MDS-UPDRS Scores, mean		
Part I	6.8	8.3
Part II	9.8	8.5
Part III	38.5	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; y, years.

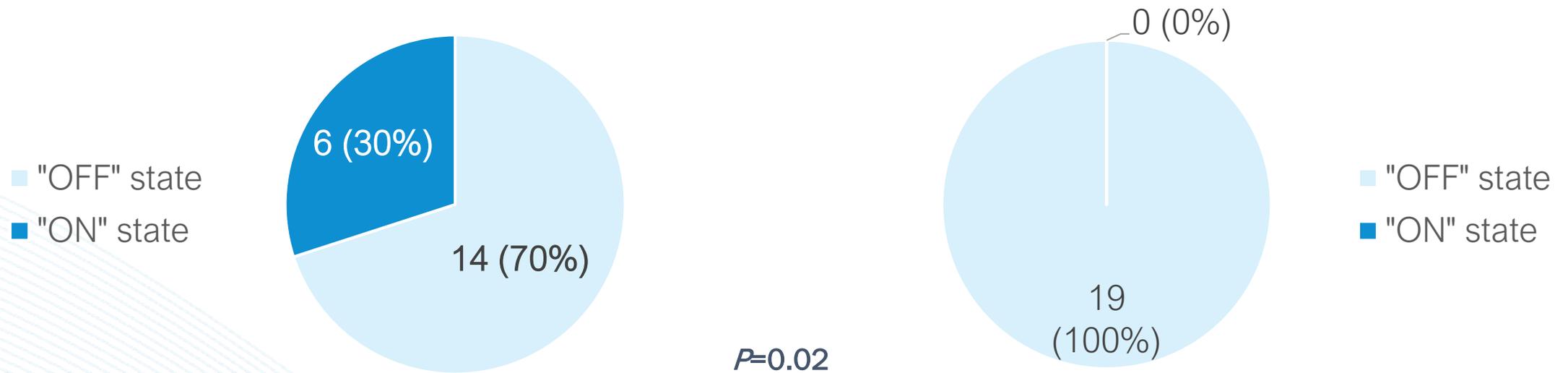
NE3107 treatment was associated with clinically meaningful and superior improvements (3+ points) on the motor examination part (Part III) of the MDS-UPDRS, with greatest improvement in patients <70 years old (~6+ points)



- Patients treated with NE3107 and C/L experienced greater improvements (3+ points) 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 NE3107 and C/L experienced improvements that are ~6 points better than those who received placebo and C/L
 - ~50% of the total patient population was <70 years old
 - NE3107-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 NE3107-levodopa combination treated patients who experienced an "OFF" state at baseline experienced a morning "ON" state prior to dosing on day 28

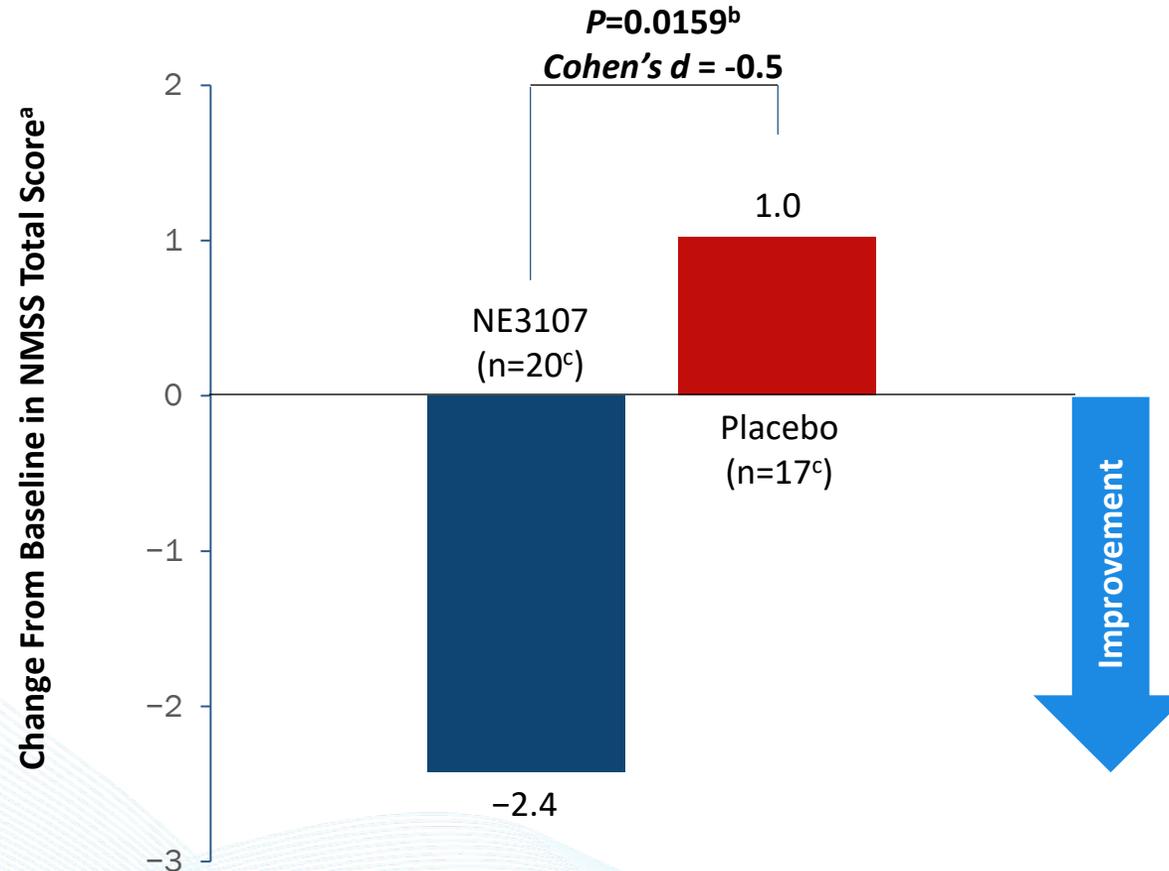
Post Hoc Efficacy Assessment



- 30% (6/20) of patients treated with NE3107, 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



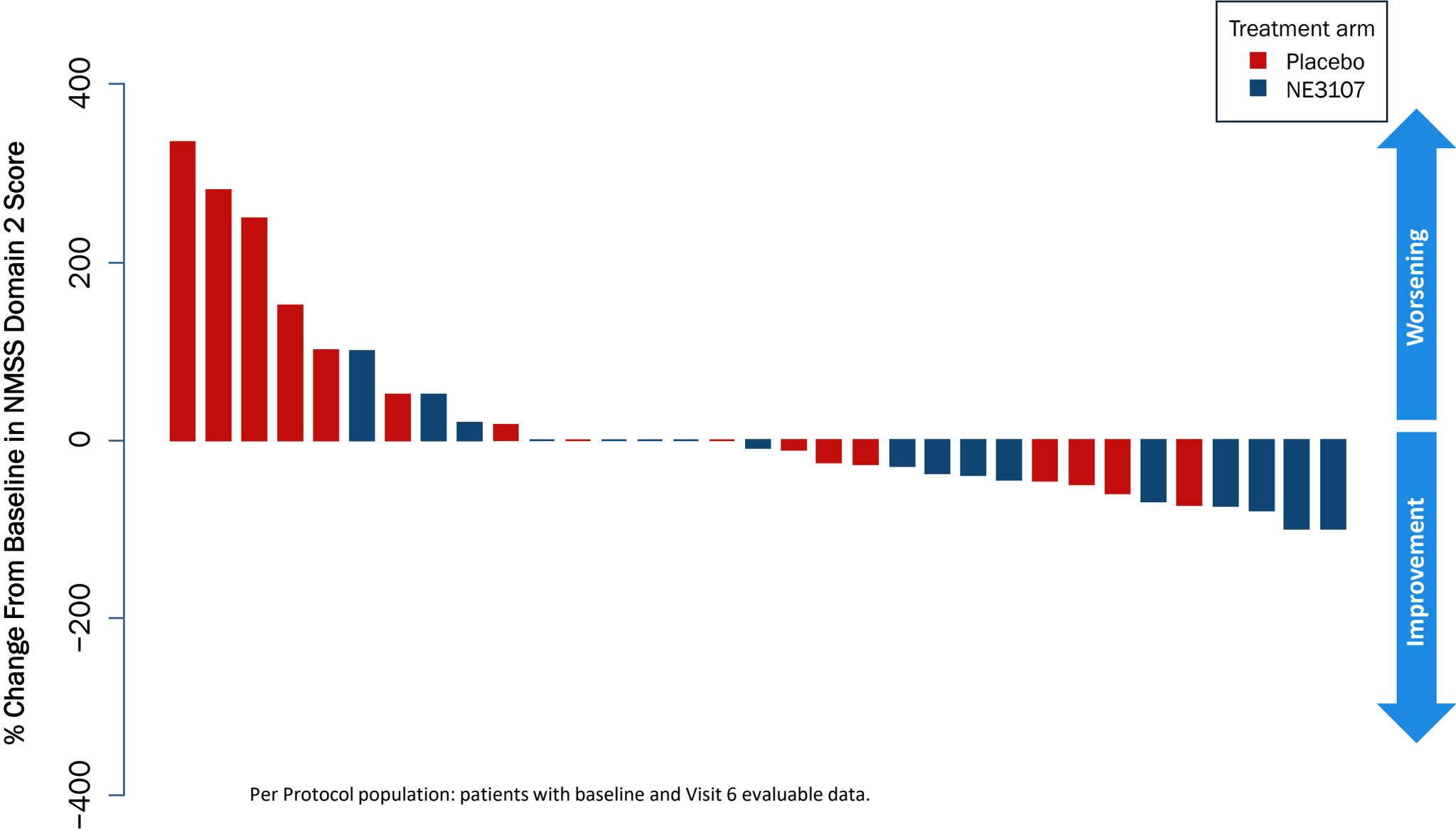
Sleep/fatigue domain improvements significantly correlated with motor score improvements, $r=0.51$; $P=0.0259$

^aLeast squares mean.

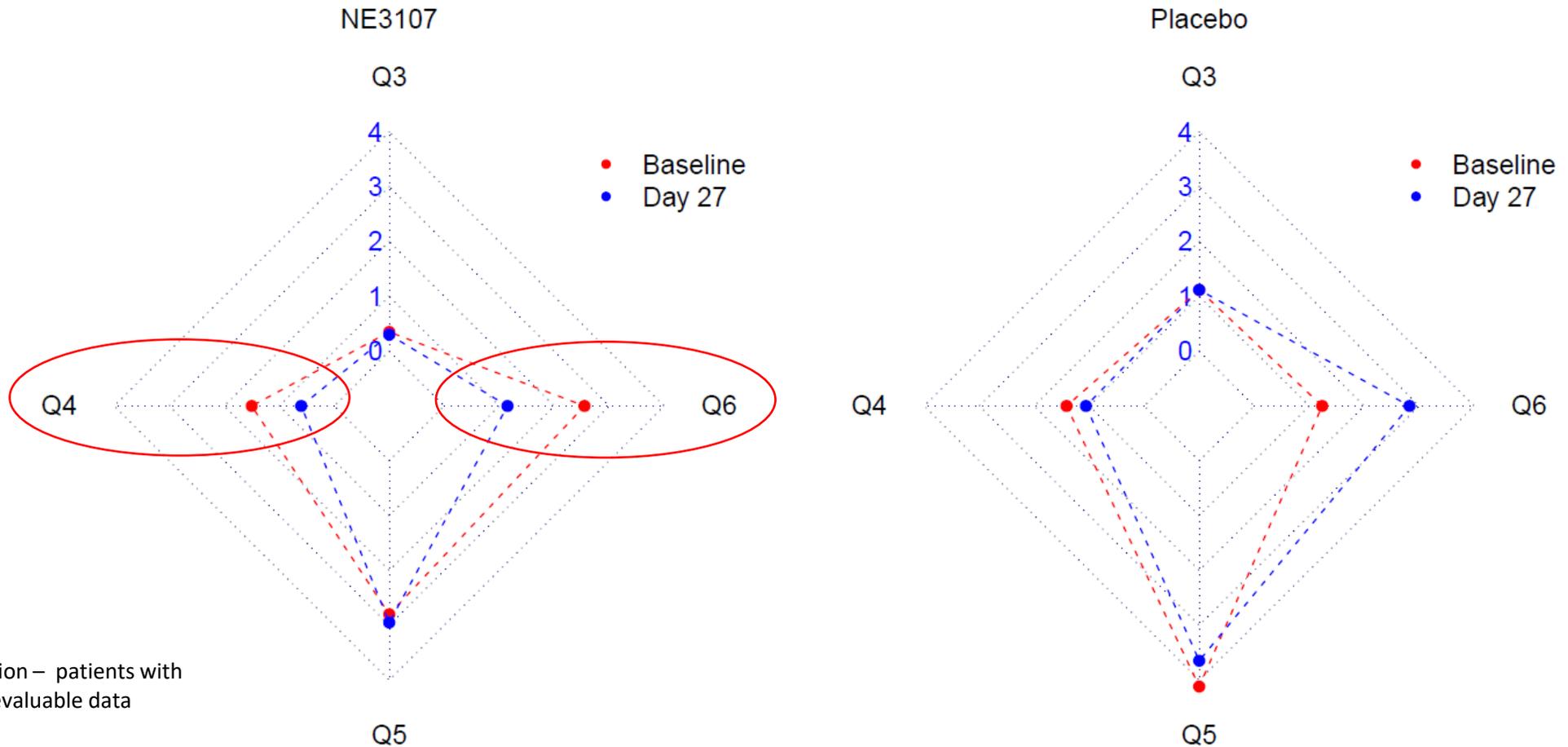
^b P values for between group change from baseline.

^cPer Protocol population: patients with baseline and Visit 6 evaluable data.

More Patients on NE3107 had Improvements in the NMSS Sleep/Fatigue Domain, While More Patients on Placebo Worsened



The Changed in the NMSS Sleep/Fatigue Domain Score Were Driven by Improvement in Fatigue/Lack of Energy (Q4) and Urge to Move Legs/Restlessness in Legs (Q6)



Per Protocol population – patients with baseline and Visit 6 evaluable data

Q3: Does the patient doze off or fall asleep unintentionally during daytime activities?

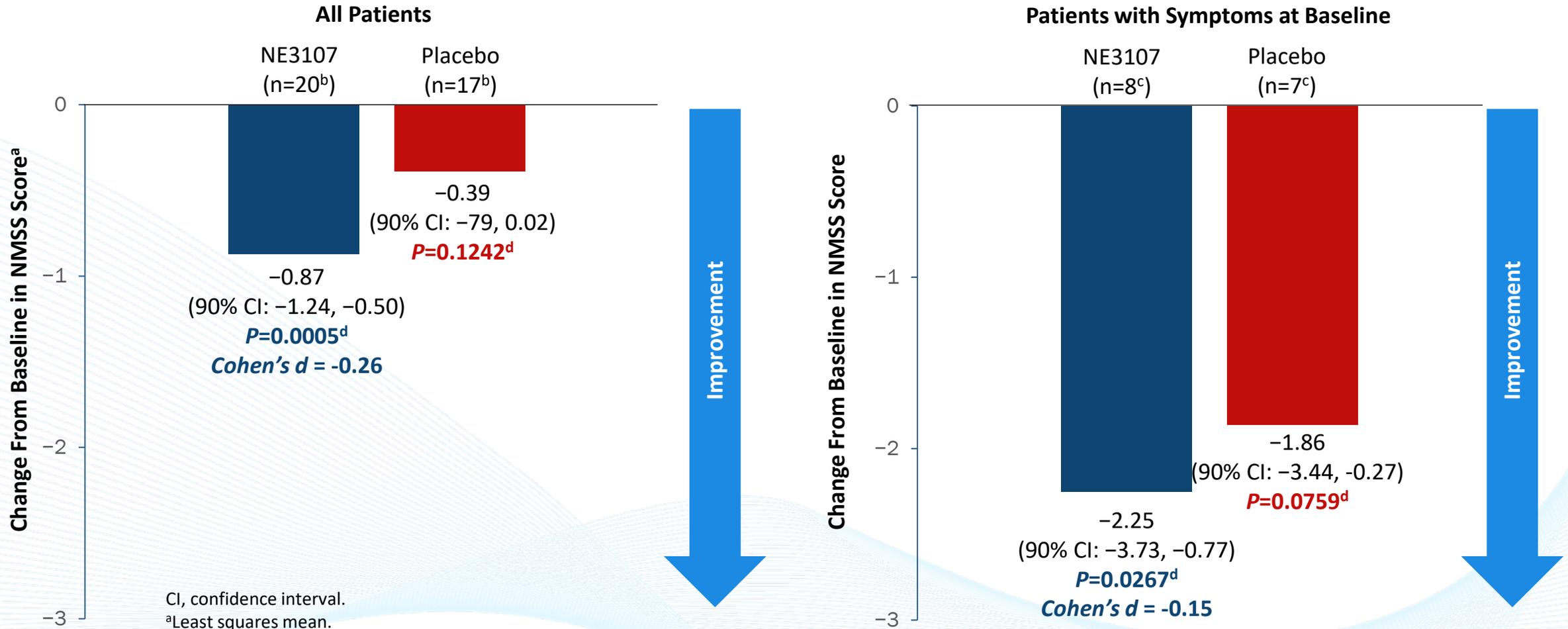
Q4: Does fatigue or lack of energy limit the patient's daytime activities?

Q5: Does the patient have difficulties falling or staying asleep?

Q6: Does the patient experience an urge to move the legs/restlessness in legs?

Significant Improvement From Baseline in Fatigue/Lack of Energy (Q4) Achieved With NE3107 but Not Placebo

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



CI, confidence interval.

^aLeast squares mean.

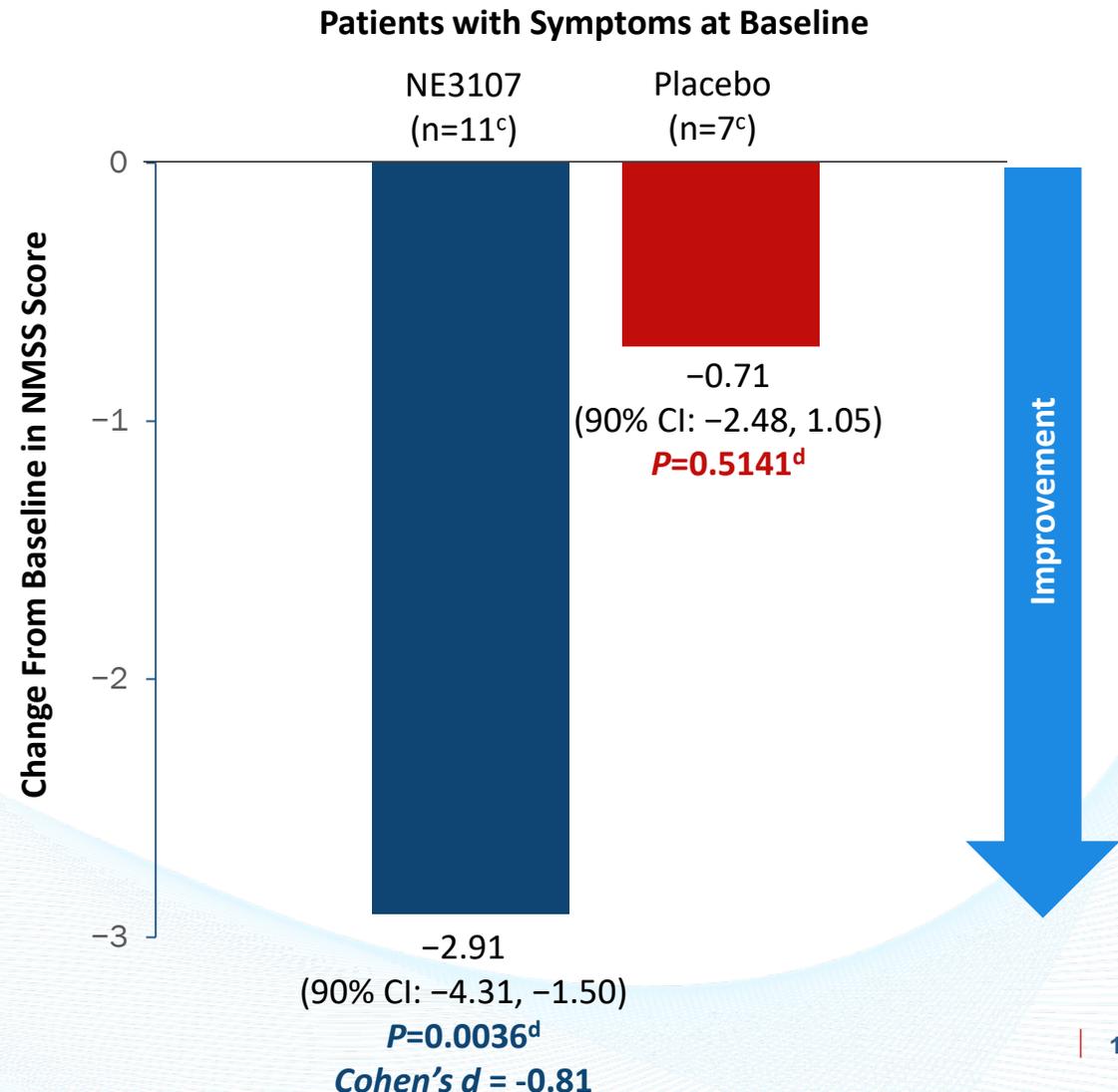
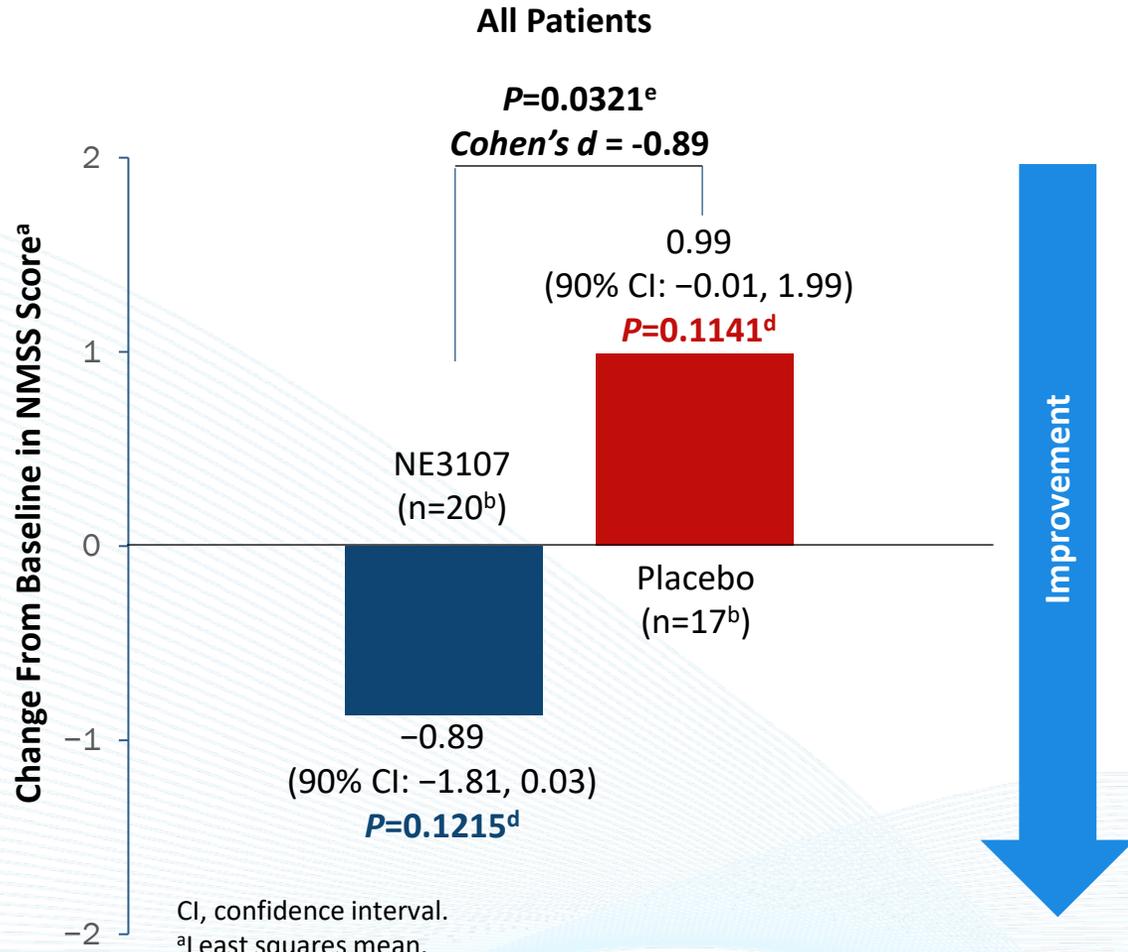
^bPer Protocol population: patients with baseline and Visit 6 evaluable data.

^cPer Protocol population: patients with baseline Q4 >0 and Visit 6 evaluable data

^dP values for within-group change from baseline.

Significant Improvement From Baseline in Urge to Move Legs/Restlessness in Legs (Q6) Achieved With NE3107 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.

^aLeast squares mean.

^bPer Protocol population: patients with baseline and Visit 6 evaluable data.

^cPer Protocol population: patients with baseline Q6 >0 and Visit 6 evaluable data

^dP values for within-group change from baseline.

^eP values for between group change from baseline.

Conclusions

- These data suggest that as adjunct therapy to levodopa, **NE3107 may hold promise in ameliorating specific non-motor symptoms of PD**, particularly in sleep/fatigue items of domain 2 of the NMSS assessment scale 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 extend previously reported improvement in motor symptoms with NE3107 and demonstrate potential **intrinsic and levodopa-enhancing activity** of NE3107 that is consistent with data from animal models and support further clinical investigation of NE3107 in late-phase trials

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