

Bezisterim (NE3107) in Early Parkinson’s Disease (SUNRISE-PD): Initial Results and Observations From a Phase 2 Hybrid Design Trial

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BACKGROUND

- Bezisterim (NE3107), an oral, anti-inflammatory agent, has demonstrated favorable safety and is being developed as a novel, broad-spectrum treatment for Parkinson’s disease (PD)¹⁻³
- A prior phase 2a study in patients with PD found bezisterim was associated with improvements in motor and non-motor symptoms²
- SUNRISE-PD (NCT06757010) was a signal-seeking trial exploring the effect of bezisterim on motor and non-motor symptoms in early PD, pre-specified markers of inflammation associated with disease progression, and safety⁴ (Table 1)
- Patients chose to participate fully from home or at a clinic site
- This presentation focuses on specific clinical endpoints, including the Movement Disorder Society- Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Parts I, II, and III, and a composite measure of efficacy
 - Future biomarker data will be addressed in future scientific reports

STUDY DESIGN and METHODS

- This trial included patients 45-80 years with a diagnosis or first motor symptoms of idiopathic PD ≤48 months prior to Screening and an MDS-UPDRS Part III score >11
 - Prior treatment with L-dopa or dopamine receptor agonist was exclusionary; a diagnostic L-dopa challenge was allowed if the L-dopa exposure was ≤42 days and ended ≥3 months prior to Screening
 - Prior use of a monoamine oxidase B (MAO-B) inhibitor was permitted if discontinued 6 weeks prior to Screening
- Eligible participants (N=57) were randomized 1:1 to a 12-week treatment phase of oral bezisterim 20mg (n=28) or placebo (n=29) twice daily with a subsequent 4-week safety follow-up phase
- The MDS-UPDRS Parts I, II, and III were used to evaluate disease severity
 - Motor symptoms were assessed with a modified MDS-UPDRS Part III that excluded item 3.3 Rigidity and 3.12 Postural Stability
 - Part III assessments were video recorded and centrally rated by movement disorder specialists. (Table 1)
- Safety and Tolerability were monitored for treatment-emergent adverse events (TEAEs), by physical examination and suicidality, as measured by the Columbia Suicide Severity Rating Scale (C-SSRS)

Table 1. Select Endpoints and Instruments of Measure

Pharmacodynamic and Clinical Endpoints ^a
- Hematologic inflammatory biomarker indices at week 12 vs baseline - Change in the MDS-UPDRS Total, Part I, Part II and modified Part III scores at week 12 - Change in Parkinson’s Disease Questionnaire-39 (PDQ-39), Clinical Global Impression-Improvement (CGI-I) and an adjusted Parkinson’s Composite Scales (PARCOMS) scores at week 12
Select Exploratory Endpoints ^a
- Change in a fit-for-purpose Composite Benefit Score (CBS), a select set of items modeled to pool most informative data from^b: - MDS-UPDRS Part I - sleep problems - MDS-UPDRS Part I - daytime sleepiness - MDS-UPDRS Part I - constipation - MDS-UPDRS Part II - hobbies - MDS-UPDRS Part II - tremor - MDS-UPDRS Part II - walking and balance - MDS-UPDRS Part III – speech - MDS-UPDRS Part III - toe tapping, left and right - MDS-UPDRS Part III - left leg agility - MDS-UPDRS Part III – posture - MDS-UPDRS Part III - resting tremor constancy - Parkinson’s Disease Sleep Scale (PDSS-2) - staying asleep - Parkinson’s Disease Sleep Scale (PDSS-2) – nocturia - Parkinson’s Disease Sleep Scale (PDSS-2) - morning tiredness - Sub-group analyses by baseline biological characteristics and disease phenotype
Safety and Tolerability ^c

^aThe MDS-UPDRS Part III was modified to facilitate in-home video with central assessments by excluding Section 3.3 (Rigidity) and Section 3.12 (Postural Stability).
^bChange from baseline to Week 12 was calculated; the composite score is the mean of available item-level change scores per subject.
^cThe analyzed mITT and Safety populations included randomized participants who took at least 1 dose of study drug.

BASELINE PATIENT CHARACTERISTICS

- Baseline characteristics were similar for patients receiving bezisterim and placebo

Characteristic	Bezisterim (n = 28)	Placebo (n = 29)
Age, years (mean ± SD)	65.8 ± 7.8	65.8 ± 7.8
Sex, Male/Female (n)	20/8	16/13
MDS-UPDRS Part I (mean ± SD)	6.2 ± 3.9	5.0 ± 3.9
MDS-UPDRS Part II (mean ± SD)	6.9 ± 3.9	7.0 ± 4.8
MDS-UPDRS Part III (mean ± SD)	25.0 ± 7.6	25.5 ± 8.8
CGI-S (mean ± SD)	2.9 ± 0.7	2.8 ± 0.6
ESS (mean ± SD)	4.6 ± 2.2	5.3 ± 2.6
Platelets, x 10 ⁹ /L (mean ± SD)	235.1 ± 49.9	241.0 ± 70.7
Platelets >230 x 10 ⁹ /L, n (%)	14 (50.0)	14 (48.3)
Platelets ≤230 x 10 ⁹ /L, n (%)	11 (39.3)	13 (44.8)

ESS=Epworth Sleepiness Scale

RESULTS

Figure 1. Meaningful Change in CBS in the mITT Population (N=57)^{a,b}

- Meaningful change in CBS demonstrated improvement with bezisterim (mean Δ = -0.04) vs placebo (mean Δ = +0.18) [Cohen’s d = -0.94; P = 0.0011]^c
- 25% of patients receiving bezisterim showed a meaningful trend toward improvement vs 4% of patients taking placebo

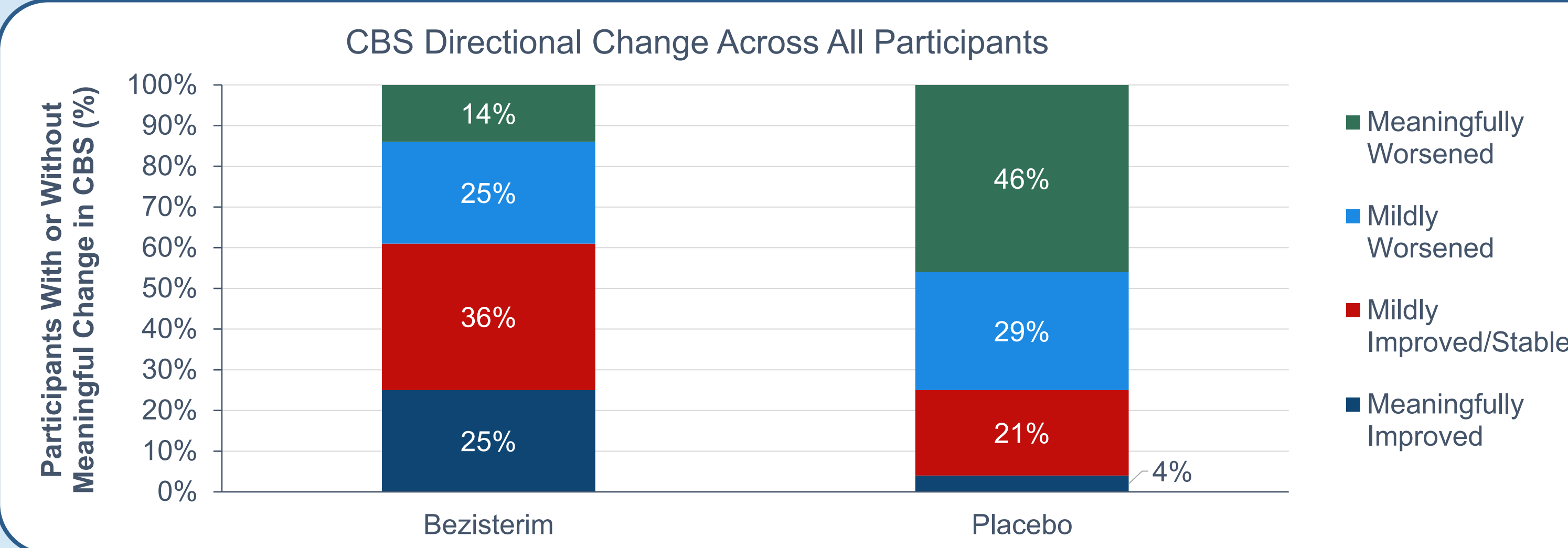


Figure 2. Score Changes in Participants With Higher Baseline Platelet (>230 x 10⁹/L) [n=27]^c

- Change effect size was significant for both the CBS [P = 0.0004], and for the MDS-UPDRS Part I, Part III and total scores [P < 0.05] with bezisterim (n = 13) vs placebo (n = 14)

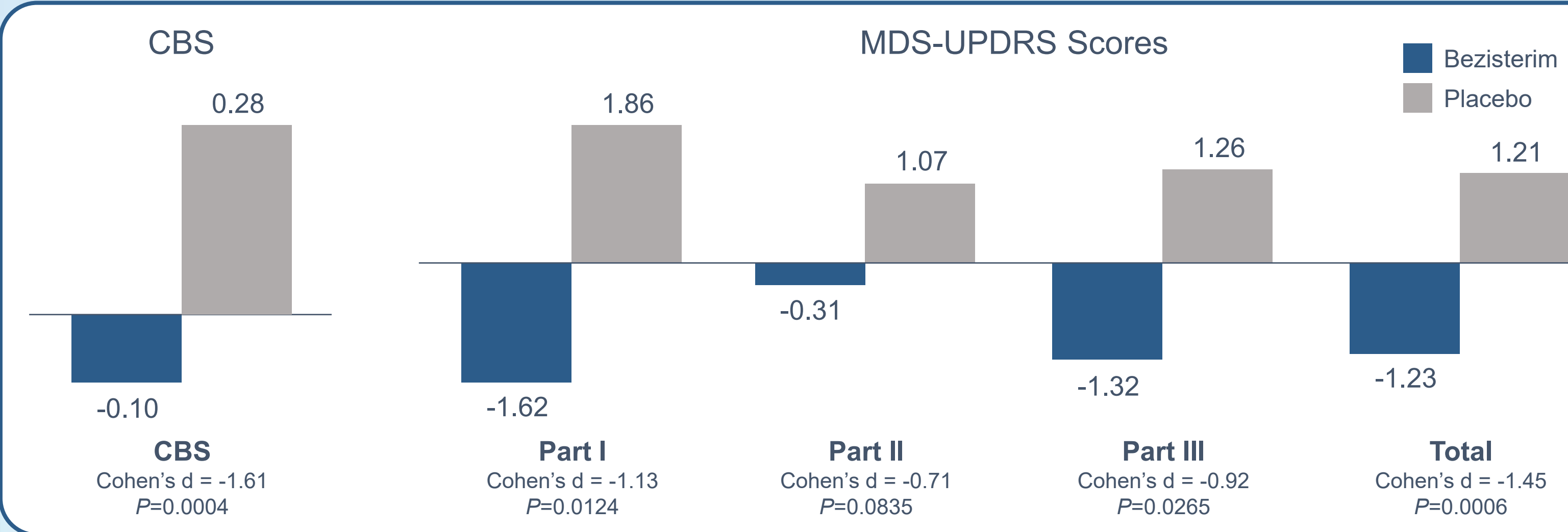


Figure 3: Score Changes in Patients With Platelets ≤230 x 10⁹/L (n=23) vs Participants With Platelets >230 x 10⁹/L (n=27)^c

- Treatment improvement reached statistical significance in patients with baseline evidence of inflammation, as noted with a platelet count >230 x 10⁹/L
- CBS in those participants with baseline platelets ≤230 x 10⁹/L (n=23) favored placebo slightly, but bezisterim imparted significant improvement vs placebo for those with platelets >230 x 10⁹/L (n = 27), a biomarker of systemic inflammation [P = 0.0002]^d
- Similarly, total MDS-UPDRS scores in those participants with baseline platelets ≤230 x 10⁹/L (n=23) favored placebo slightly, but bezisterim provided significant improvement in motor and non-motor symptoms vs placebo for those with platelets >230 x 10⁹/L (n = 27) [P = 0.0198]^d

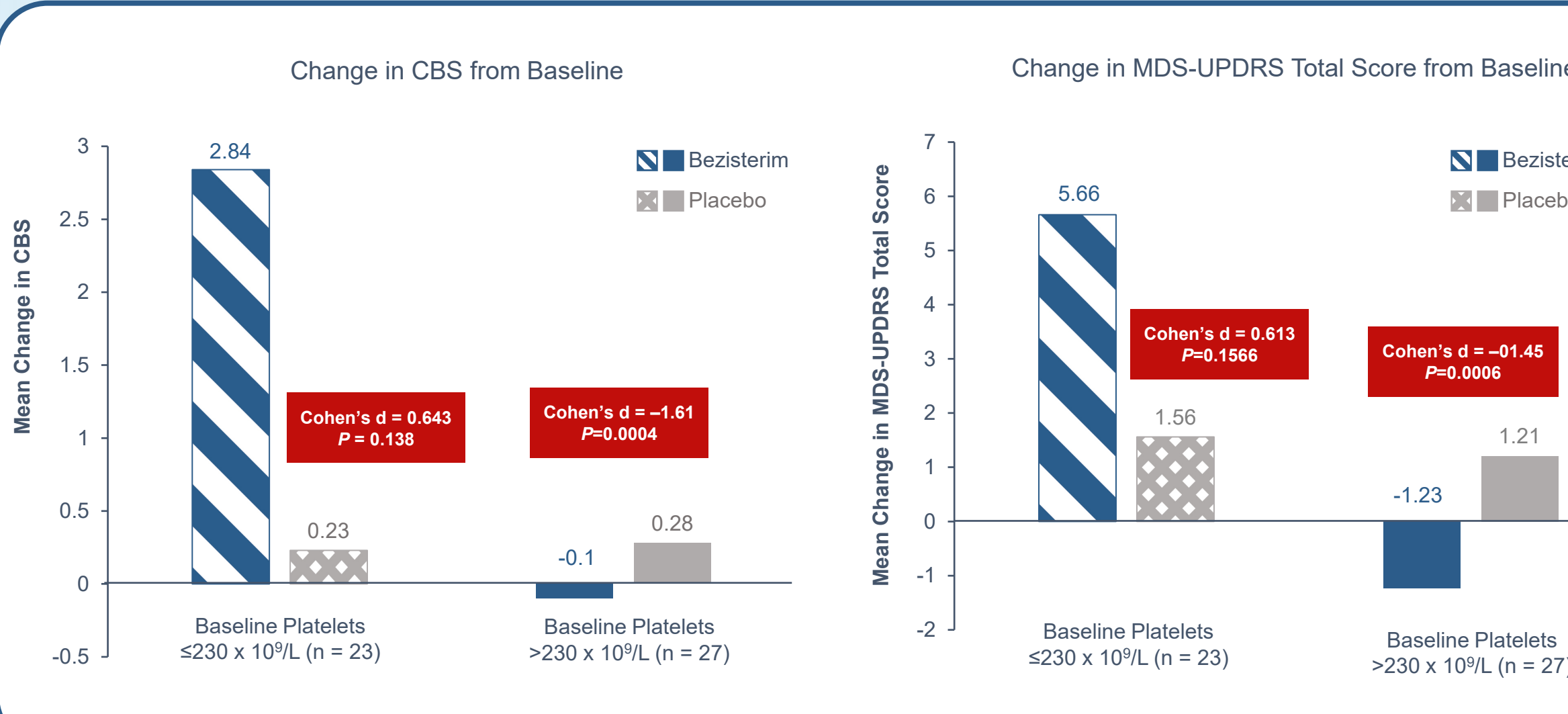
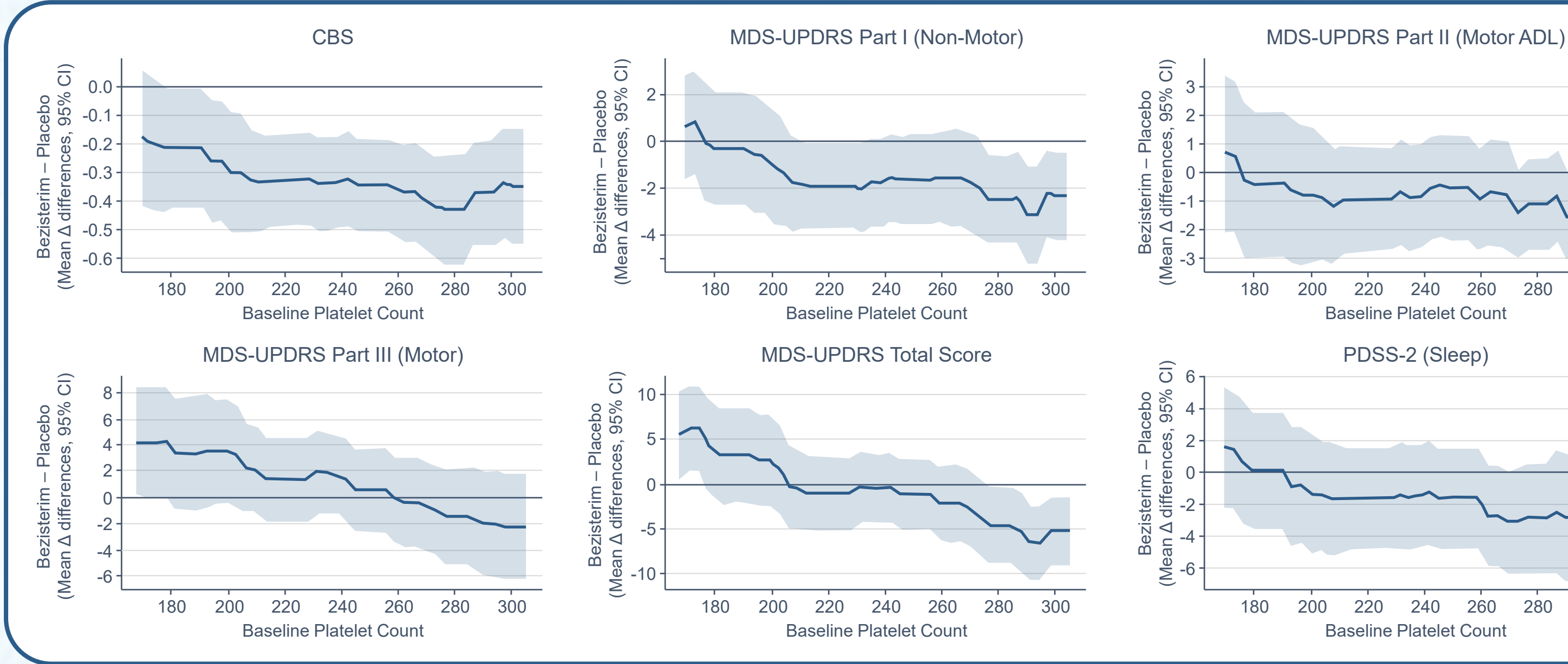


Figure 4. Mean Difference in Motor and Non-Motor Effects Across Baseline Platelet Range

- Increasing platelet count has been correlated to clinical disease activity in inflammatory disorders^{6,d}

- As platelet count rises, the difference in mean change from baseline between patients receiving bezisterim vs placebo increased^e
 - This supports a potential future enrichment strategy for patients likely to respond⁷
- Similar trends in between-group change differences were observed for MDS-UPDRS I, II, III, and Total scores, as well as PDSS-2 scores^e



ADL=activities of daily living

^dBased upon the standard of defining minimally important difference as a change that is 0.5 standard deviations (0.5 SD) from the mean; “Meaningfully Improved” and “Meaningfully Worsened” reflect scores that improved or worsened more than 0.5 SD from the mean change.⁵ Unless otherwise noted, all P-values reported are nominal and unadjusted for multiplicity, consistent with the exploratory, signal-finding objectives. *Treatment improvement is reflected by smaller or negative Cohen d value. ^eThe mean difference between bezisterim vs placebo at week 12 was plotted vs baseline platelet count; the solid blue line is the mean change with confidence intervals shown as grey shading. ^fAnalysis based on values are for those patients with available platelet counts at baseline (visit 1).

SAFETY

Reported AE	Bezisterim (n = 28)	Placebo (n = 29)
Patients with any AE, n (%)	16 (57.1)	17 (58.6)
Total AEs, n	28	39
Serious AEs, n	0	0
Severe AEs, n	0	0
Treatment-Related AEs, n	1	1
AEs, incidence >5% in either treatment arm		
Upper respiratory infection, n (%)	5 (17.9)	5 (17.2)
Diarrhea, n (%)	1 (3.6)	2 (6.9)
Back pain, n (%)	0 (0)	2 (6.9)
Fall, n (%)	0 (0)	2 (6.9)

AE= adverse event

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DISCLOSURES

CLR, CA, and JP are employees of BioVie Inc. JZ, MS, and SOQ are consultants for BioVie Inc.

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CONCLUSIONS

- In this signal-seeking trial, bezisterim shows statistically significant improvement vs placebo in the Composite Benefit Score (CBS) in the mITT population (Cohen’s d = -0.94; P = 0.0011) with meaningful clinical improvement in motor and non-motor symptoms
- Bezisterim demonstrated descriptive clinical benefit in this study, and improvements rose to statistical significance in those with a platelet count >230 x 10⁹/L
- Enhanced response in non-motor, motor, and motor ADL symptoms, with clinical motor engagement observed in those with baseline platelet counts above the study median
 - This represents an inflammation signal that informs an enriched study population and a biomarker for future phase 3 trials
- Bezisterim safety reports were similar to placebo, with 57.1% of patients receiving bezisterim vs 58.6% receiving placebo reporting any AEs; no serious or severe AEs were reported