DMT52

Inverse relationship between plasma neurofilament light chain concentration and symbol digit modalities test scores in the phase 3 SUNBEAM trial of ozanimod in relapsing multiple sclerosis

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Introduction

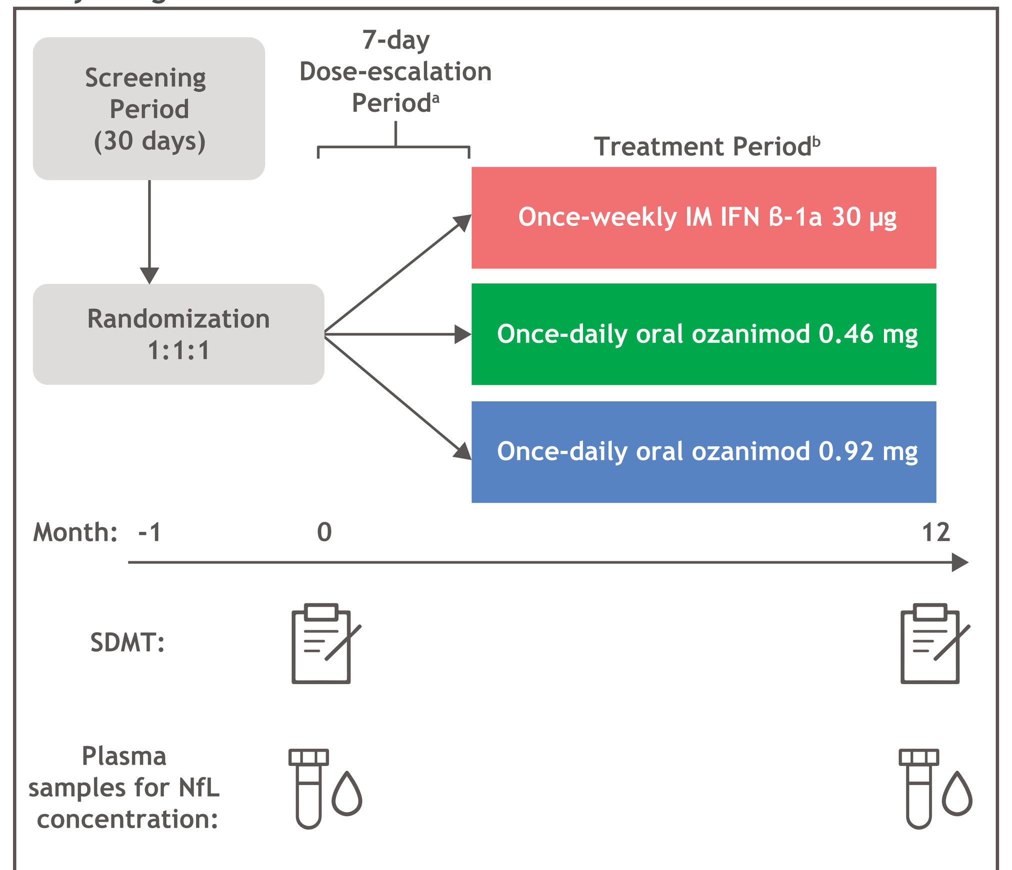
- Cognitive dysfunction, including diminished cognitive processing speed, is a major source of impairment in patients with multiple sclerosis (MS)[1]
- Ozanimod, a sphingosine 1-phosphate receptor 1 and 5 modulator,[2] is approved in multiple countries for the treatment of adults with either relapsing forms of MS (RMS) or moderately to severely active ulcerative colitis[3,4]
- In the phase 3 SUNBEAM trial, ozanimod reduced the concentration of plasma neurofilament light chain[5] (pNfL, a marker of neurodegeneration[6]) and improved cognitive processing speed, based on the Symbol Digit Modalities Test (SDMT), compared with intramuscular interferon (IFN) β-1a[7]
- Objective: To evaluate relationships between pNfL concentrations and SDMT scores at baseline and after 12 months of treatment with ozanimod or IFN β-1a in SUNBEAM

Methods

Study design

- Exploratory, post hoc analysis of pNfL concentration and SDMT score data from SUNBEAM (NCT02294058), a multicenter, randomized, double-blind, parallel-group, active-controlled, double-dummy phase 3 trial of ozanimod vs IFN β-1a in adults with RMS[8]

Study design



[a]Patients received ozanimod 0.23 mg/d on days 1-4, ozanimod 0.46 mg/d on days 5-7, and the assigned dose of ozanimod 0.46 or 0.92 mg/d starting on day 8 of ozanimod treatment.
[b]All patients remained on treatment until the last patient enrolled completed 12 months.
HCl, hydrochloride; IM, intramuscular; NfL, neurofilament light chain.

Assessments

- pNfL concentration was measured with a Simoa® NfL digital immunoassay (Quanterix, Billerica, MA)
- The SDMT is a timed test that provides patients with a key that pairs symbols and numerals, then presents the symbols out of sequence and asks patients to match them to the correct numerals[9]
  - Scoring is based on the correct number of responses given in 90 seconds, with higher scores indicating faster processing[9]
  - A 4-point change is considered clinically meaningful[9]
    - Patients were categorized by clinically meaningful SDMT improvement (≥ 4-point increase), worsening (≥ 4-point decrease), or stability (< 4-point ± change) at month 12

Statistical analysis

- Kendall's τ correlation was used to characterize the strength of relationships between pNfL concentrations and SDMT scores at baseline
- Relationships between mean change from baseline in SDMT scores and median percentage change in pNfL concentrations after 12 months of treatment were assessed by treatment-stratified bootstrap sampling (1000 samples)

Baseline demographics and clinical characteristics, SUNBEAM ITT population

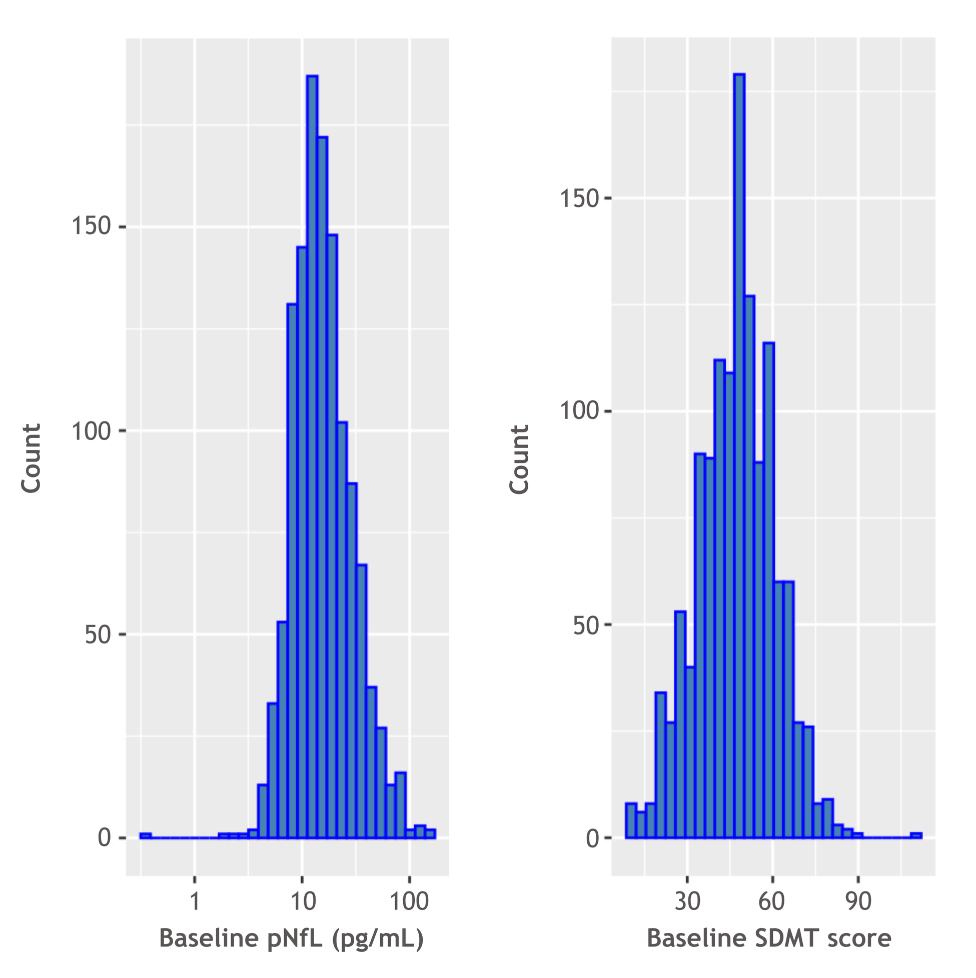
Parameter	IFN β-1a 30 μg/wk n = 448	Ozanimod 0.46 mg/d n = 451	Ozanimod 0.92 mg/d n = 447
Age, mean (SD), years	35.9 (9.1)	36.0 (9.4)	34.8 (9.2)
Sex, n (%)			
Female	300 (67.0)	311 (69.0)	283 (63.3)
Male	148 (33.0)	140 (31.0)	164 (36.7)
Time since symptom onset, mean (SD), years	6.9 (5.9)	7.2 (6.3)	6.9 (6.4)
EDSS score, mean (SD)	2.6 (1.1)	2.7 (1.1)	2.6 (1.2)
Baseline pNfL (pg/mL), median (Q1-Q3)	14.8 (9.8-24.4) n = 413	14.1 (9.7-22.4) n = 421	15.1 (10.9-22.8) n = 410
Baseline SDMT score, median (Q1-Q3)	49.0 (39.0-56.0) n = 426	48.0 (38.0-56.0) n = 430	49.0 (38.0-57.0) n = 427

EDSS, Expanded Disability Status Scale; SD, standard deviation.

Results

- Median (interquartile range [IQR]; Q1–Q3) pNfL concentration was 14.7 (10.2–23.3) pg/mL and median (IQR) SDMT score was 48.0 (38.0–56.0) at baseline

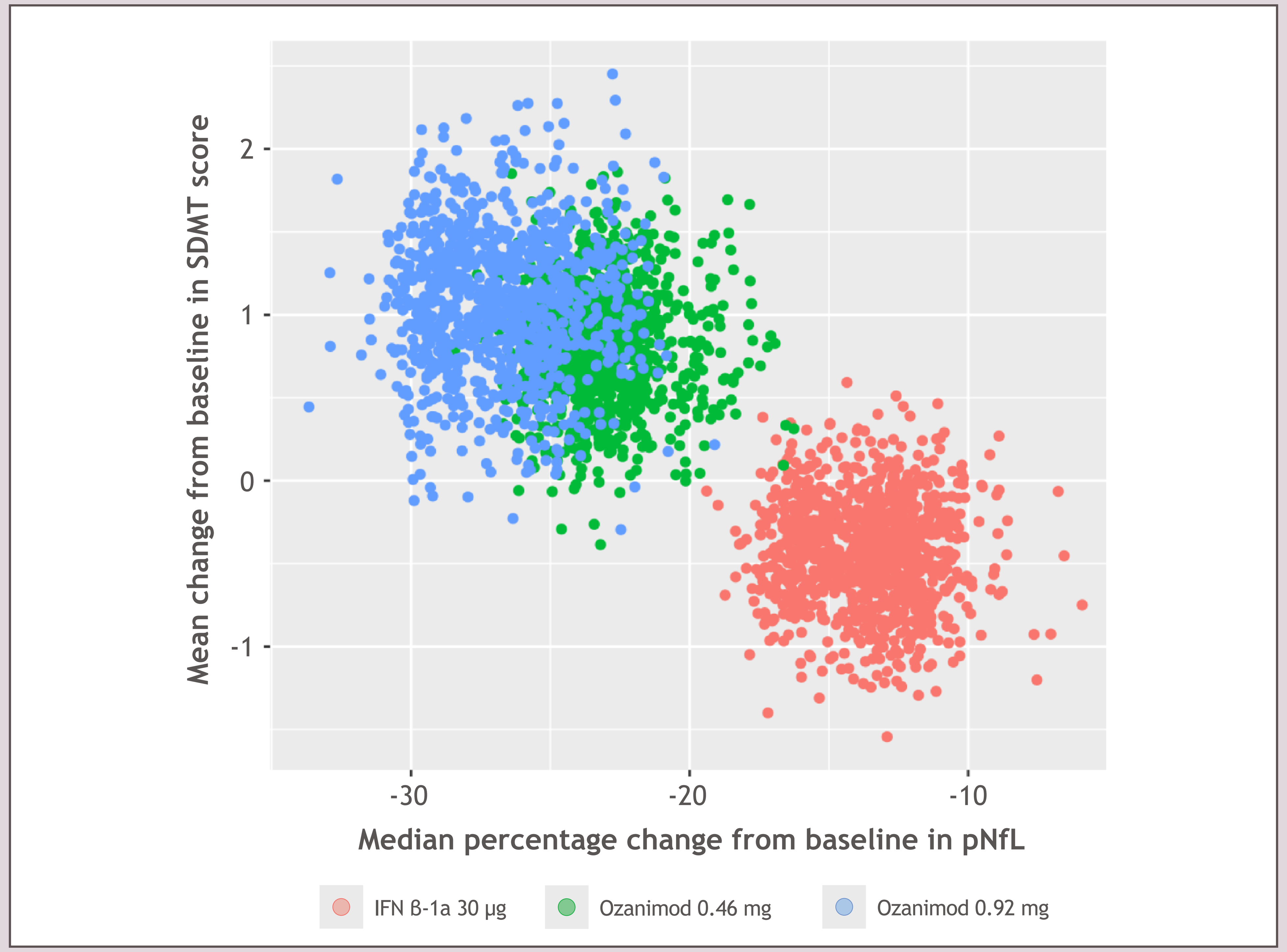
Baseline pNfL concentrations and SDMT scores



Greater median percentage reduction in pNfL concentration was associated with greater mean SDMT score change from baseline at month 12

Ozanimod 0.92 mg was associated with greater reductions in pNfL concentration (nominal $P < 0.0001$ based on robust linear models)[5] and improvements in SDMT score than IFN β-1a (nominal $P = 0.0019$ based on regression models)

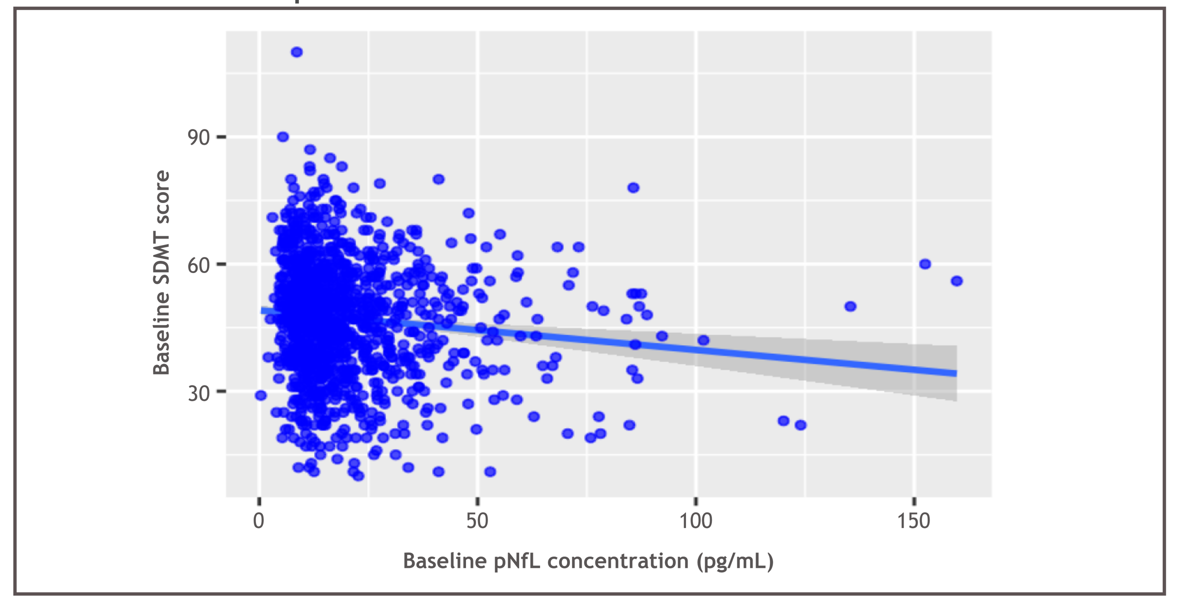
Association between change in pNfL concentration and change in SDMT score by treatment group[a]



[a]Relationship between mean change from baseline SDMT score and median % change in pNfL based on bootstrap sampling.
Individual dots on each plot represent the individual simulations from the bootstrap procedure.

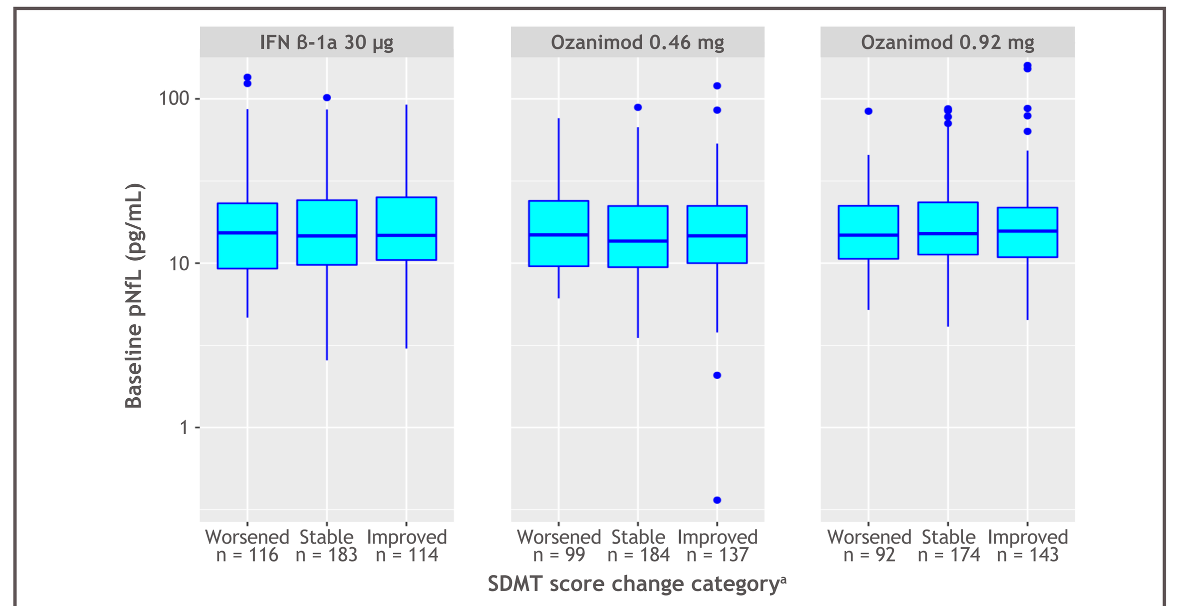
- Kendall's correlation (95% CI) between baseline pNfL concentration and SDMT score was −0.10 (−0.14 to −0.06), indicating a slight negative association

Association between pNfL concentration and SDMT score at baseline



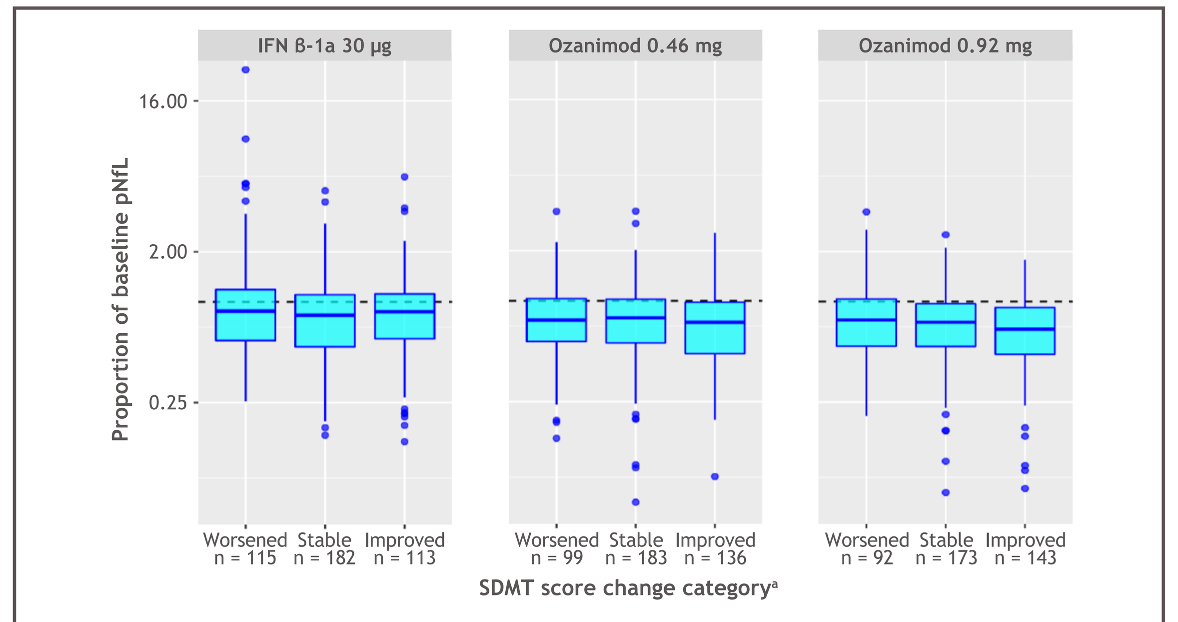
- There were no relationships noted between baseline pNfL concentration or change from baseline at month 12 in pNfL concentration and any specific SDMT score change category (worsened/stable/improved based on ≥ 4-point change from baseline at month 12)

Association between baseline pNfL concentration and clinically meaningful change in SDMT score by treatment group



[a]Worsened = ≥ 4-point decrease; stable = < 4-point ± change; improved = ≥ 4-point increase.

Association between change in pNfL concentration and clinically meaningful change in SDMT score by treatment group



[a]Worsened = ≥ 4-point decrease; stable = < 4-point ± change; improved = ≥ 4-point increase.

Conclusions

- In this analysis of the SUNBEAM trial, baseline pNfL concentration correlated weakly and inversely with baseline SDMT score
- Ozanimod treatment decreased pNfL concentrations and improved SDMT scores to a greater extent than IFN β-1a
- Future prospective analyses are warranted to determine the clinical utility of pNfL concentration as a marker of cognitive processing speed

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