DXT24

Two Expanded Disability Status Scale Subscales Evaluated in Patients With Relapsing-Remitting or Secondary Progressive Multiple Sclerosis

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Introduction

- Disability in multiple sclerosis (MS) is commonly rated using the Expanded Disability Status Scale (EDSS)[1]
- In relapsing-remitting MS (RRMS), increased disability is associated with incomplete recovery from relapses[2]
- Relapse-independent disability progression later in the disease is characteristic of transition from RRMS to secondary progressive multiple sclerosis (SPMS)[3]
  - Without disease-modifying therapy, most patients with RRMS transition to SPMS within 25 years of disease onset[4,5]
- Fingolimod and siponimod (sphingosine 1-phosphate receptor modulators) are disease-modifying therapies shown to reduce disability progression in RRMS and SPMS, respectively[6,7]
  - Fingolimod (Gilenya®) 0.5 mg/day reduced disability progression versus placebo over 24 months in RRMS (phase 3 FREEDOMS trial)[6]
  - Siponimod (Mayzent®) 2 mg/day reduced disability progression versus placebo over a period of up to 36 months in SPMS (phase 3 EXPAND trial)[7]
- EDSS scores are based on assessment of eight functional systems: bowel and bladder; brain stem; cerebellar; cerebral or mental; pyramidal; sensory; visual; and other[1]
  - However, each functional system contributes differentially to disease worsening at different disease stages[8,9]
  - EDSS assessments may also be burdensome for patients and clinicians
- Factor analysis can be used to reduce a large number of variables into a smaller number of factors, identifying hidden factors from observed variables
- Using data from FREEDOMS and EXPAND, two new subscales of the EDSS (Motor Integration; Collateral) capturing parameters most relevant to disability worsening were derived by factor analysis[10,11]

Objective

- Evaluate effects of fingolimod and siponimod using EDSS subscales derived by factor analyses of phase 3 trial data

Methods

- Based on previously published methodology,[7] PROC FACTOR (SAS) procedure determined a 'best fit' of Baseline EDSS item data to Motor Integration (ambulation, cerebellar and pyramidal functions) and Collateral (bowel and bladder, brain stem, cerebral or mental, sensory and visual functions) subscales in RRMS using data from FREEDOMS, and in SPMS using data from EXPAND
- Factor analyses of each trial data set were performed independently
- Statistical significance of treatment effect sizes (change from Baseline versus placebo) were assessed in FREEDOMS using rank analysis of covariance, and in EXPAND via analysis of covariance mixed-effect repeat-measurement model, with treatment, time point (as a categorical variable) and their interaction, country/region, and Baseline relapse status as factors, and corresponding Baseline values as covariates
- Treatment effect sizes on disability (mean change from Baseline versus placebo) were determined for overall EDSS score and for each subscale score
  - FREEDOMS: overall population up to 24 months
  - EXPAND: overall population, and subgroups stratified by relapse activity or presence of gadolinium-enhancing (Gd+) lesions before enrollment, up to 27 months
- Analyses were for hypothesis generation without multiple comparison adjustment

Results

EDSS factor analysis

- Each factor analysis (of FREEDOMS or EXPAND Baseline data) independently allocated the same EDSS functions to either Motor Integration or Collateral subscales (**Table 1**)
  - Each function was allocated to the subscale with the highest factor loading
  - Factor loadings can be interpreted as regression coefficients: the higher the factor loading, the greater the contribution of a specific functional system to a subscale
- Overall variance accounting for the Motor Integration and Collateral subscales was 53.6% and 46.4% in FREEDOMS, and 55.2% and 44.8% in EXPAND

Participants

- EDSS data were analyzed from
  - 843 patients with RRMS in FREEDOMS (fingolimod, N=425; placebo, N=418)
  - 1645 patients with SPMS in EXPAND (siponimod, N=1099; placebo, N=546)

Fingolimod efficacy by EDSS and subscale scores in RRMS (overall population)

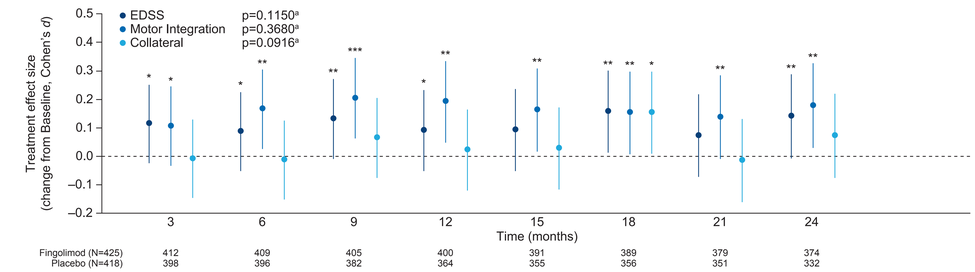
- Treatment effects significantly favoring fingolimod over placebo were evident at every time point except at Months 15 and 25 for EDSS scores and at every time point for Motor Integration subscale scores
- Nonsignificant numerical improvements with fingolimod versus placebo were also seen in Collateral subscale scores at Months 9, 12, 15, 18 and 24 (**Figure 1**)

Table 1. Factor loadings for each EDSS function

Function	RRMS (FREEDOMS)		SPMS (EXPAND)	
	Motor Integration	Collateral	Motor Integration	Collateral
Ambulation	**0.51965**	0.15027	**0.67393**	0.13383
Bowel and bladder	0.28569	**0.46376**	0.26431	**0.29866**
Brain stem	0.28084	**0.31573**	0.02655	**0.37926**
Cerebellar	**0.55937**	0.41471	**0.40102**	0.32998
Cerebral or mental	0.15110	**0.49448**	0.00792	**0.47418**
Pyramidal	**0.64202**	0.32217	**0.56629**	−0.06852
Sensory	0.31132	**0.41342**	0.08285	**0.35622**
Visual	0.11594	**0.29662**	0.06233	**0.33067**

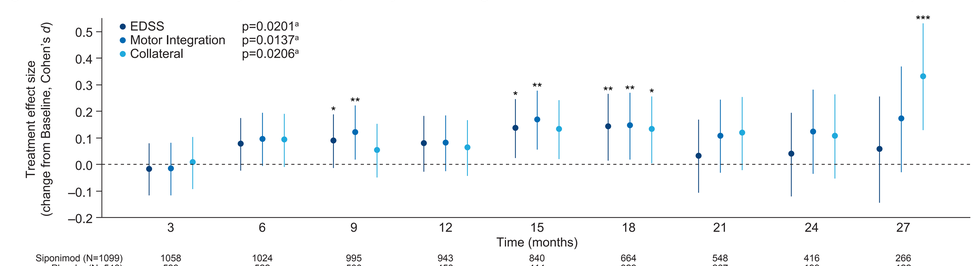
Each functional system was allocated to the subscale in which that functional system's factor-loading value was highest (bold text); range −1 to 1 in most cases
EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SMPS, secondary progressive multiple sclerosis

Figure 1. Treatment effect size by EDSS score, and by Motor Integration and Collateral subscale scores in RRMS (FREEDOMS)



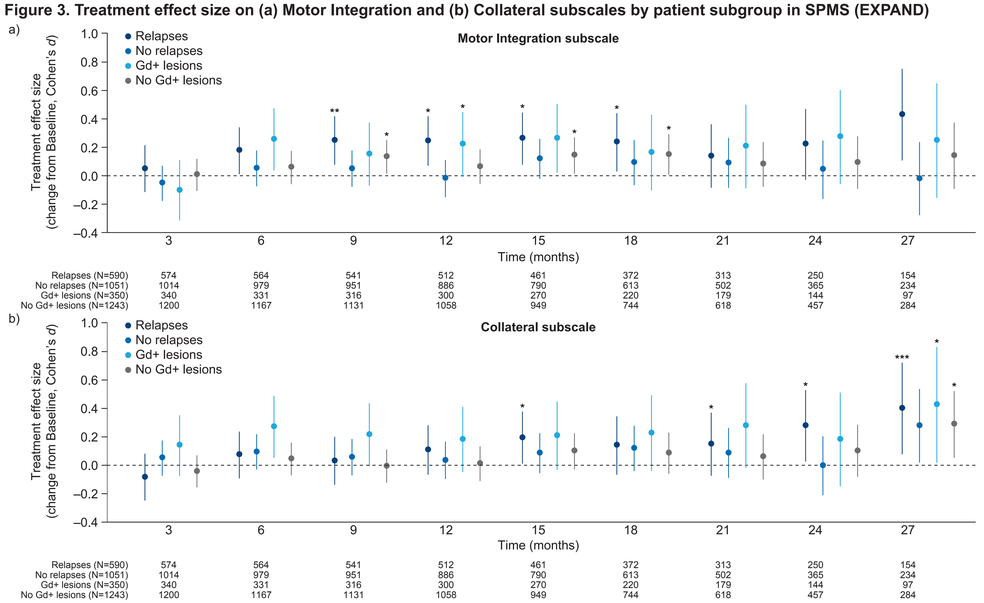
*p<0.05; **p<0.01; ***p<0.001 at individual time points. Data are mean (95% CI). [a]Overall p value for the entire study period
Effect sizes are standardized mean difference between fingolimod and placebo, expressed as Cohen's *d*; a positive effect size indicates a larger effect with fingolimod than with placebo
CI, confidence interval; EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis

Figure 2. Treatment effect size by EDSS score, and by Motor Integration and Collateral subscale scores in SPMS (EXPAND)



*p<0.05; **p<0.01; ***p<0.001 at individual time points. Data are mean (95% CI). [a]Overall p value for the entire study period
Effect sizes are standardized mean difference between siponimod and placebo, expressed as Cohen's *d*; a positive effect size indicates a larger effect with siponimod than with placebo
CI, confidence interval; EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis

Figure 3. Treatment effect size on (a) Motor Integration and (b) Collateral subscales by patient subgroup in SPMS (EXPAND)



*p<0.05; **p<0.01; ***p<0.001 at individual time points. Data are mean (95% CI). Patients in the 'No relapses' subgroup had no relapses in the 2 years before Baseline; patients in the 'No Gd+ lesions' subgroup had no Gd+ lesions at Baseline
Effect sizes are standardized mean difference between siponimod and placebo, expressed as Cohen's *d*; a positive effect size indicates a larger effect with siponimod than with placebo
CI, confidence interval; Gd+, gadolinium-enhancing; SPMS, secondary progressive multiple sclerosis

Siponimod efficacy by EDSS and subscale scores in SPMS (overall population)

- Treatment effects favoring siponimod were detected over the entire analysis period based on EDSS (p=0.020) and on both Motor Integration (p=0.014) and Collateral subscale (p=0.021) scores
- Marked treatment effects on EDSS and on Motor Integration disability were observed at Months 9, 15 and 18, and on Collateral disability at Months 18 and 27 (**Figure 2**)

Siponimod efficacy by EDSS and subscale scores in SPMS patient subgroups

- Across the analysis period, treatment effects favoring siponimod on the Motor Integration subscale were generally larger among relapsing patients and those with Gd+ lesions than nonrelapsing patients and those with no Gd+ lesions at Baseline (**Figure 3a**)
- Marked treatment effects on the Motor Integration subscale were seen:
  - from Months 9 to 18 in the relapsing subgroup
  - at Month 12 in the subgroup of patients with Gd+ lesions
  - at Months 9, 15 and 18 among patients with no Gd+ lesions at Baseline
- Across the analysis period, treatment effects on the Collateral subscale were larger among patients with Gd+ lesions than among those with no Gd+ lesions at Baseline (**Figure 3b**)
- For relapsing patients, treatment effects on the Collateral subscale appeared to manifest later than on the Motor Integration subscale, and were greater than effects among nonrelapsing patients from Month 12 onwards

Conclusions

- Independent factor analyses of data from FREEDOMS (RRMS, fingolimod) and EXPAND (SPMS, siponimod) allocated the same EDSS functional systems to two novel subscales, confirming validity of the findings
- Beneficial effects of fingolimod on disability in patients with RRMS were mainly seen in the Motor Integration subscale
- Benefits associated with siponimod in patients with SPMS were seen in both the Motor Integration and Collateral subscales
  - Motor Integration effects generally appeared before Collateral effects
  - Marked changes in Collateral effects were observed at later time points, although cohort effects cannot be ruled out
- Using factor analysis to consolidate EDSS functional systems into two subscales most relevant to disease worsening may improve their clinical usefulness and help to reduce the burden of disease assessment and management for patients and clinicians

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