Confirmed Disability Improvement and Its Sustainability Among Progressive Multiple Sclerosis Patients in Clinical Trial Placebo Arms

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BACKGROUND

- There is limited aggregate data on disability improvement and/or progression in progressive MS patients treated with placebo
- The natural history of progressive MS can be evaluated using the MSOAC Placebo Database, which includes pooled placebo arm data from nine clinical trials[1]
  - In aggregate, 2465 individual clinical records are available from patients with RRMS and progressive forms of MS
  - The database contains data on demographics, medical history, and outcome measures including the EDSS
- Analyzed data from the MSOAC database can be used to obtain an estimate for a control arm for disability improvement experienced by patients as part of the natural history of progressive MS which may help inform future clinical trials

OBJECTIVE

- To determine the percentage of the progressive MS populations with CDI and sustainability through 24 months in the MSOAC Placebo Database

STUDY DESIGN

- This study was a retrospective analysis of pooled EDSS data from the MSOAC Placebo Database
- Eligible patients met the following criteria:
  - Progressive MS (PPMS and SPMS)
  - Age between 18 and <61 years of age
  - Baseline EDSS score between 3 and 6.5

METHODS

- Outcomes of interest were the percentage of patients with CDI (calculated from confirmation), the duration of CDI, and the percentage of patients who sustained CDI status through 24 months
- CDI was defined by change in EDSS score at 9 months confirmed at 12 months, or at 12 months confirmed at 15 months (**Table 1**)
  - Analyses were also conducted for PPMS and SPMS to assess for group-dependent differences

Table 1. Confirmed disability improvement

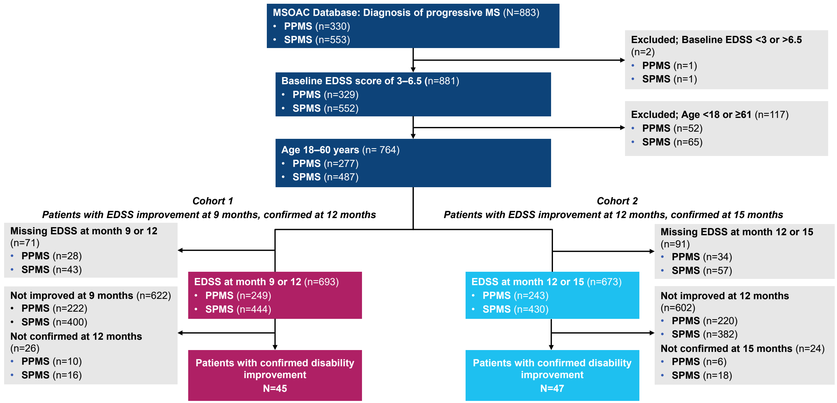
Definition	Details
Disability improvement	Change from baseline in EDSS score; minimal clinically significant change was defined as a decrease of: • ≥1.0 from an EDSS baseline score of ≤5.0 • ≥0.5 from an EDSS baseline score of ≥5.5
Confirmed disability improvement	• Disability improvement at 9 months and confirmed at 12 months (**Cohort 1**) • Disability improvement at 12 months and confirmed at 15 months (**Cohort 2**)

RESULTS – STUDY POPULATION

Study population

- In total, 883 patients with progressive MS were identified (n=330 PPMS, n=553 SPMS); 693 and 673 patients were eligible in Cohorts 1 and 2, respectively (**Figure 1**)

Figure 1. Patient selection



- Characteristics for eligible patients with progressive MS in Cohorts 1 and 2 are shown in **Table 2**
  - The mean age of patients with progressive MS was similar in both cohorts
  - The majority of patients in Cohorts 1 and 2 were female
  - Most patients with progressive MS in Cohorts 1 and 2 had a baseline EDSS score 5.5–6.5
  - In both cohorts, patients who improved tended to have a higher baseline EDSS score (i.e., 5.5–6.5) than patients who did not improve

Table 2. Patient characteristics

	Cohort 1			Cohort 2		
	Total Patients N=693	Patients with CDI N=45	*P* value*	Total Patients N=673	Patients with CDI N=47	*P* value*
Age, years						
Mean (SD)	48.7 (7.3)	49.7 (6.1)	0.32	48.7 (7.3)	49.3 (6.4)	0.56
Gender, n (%)						
Male	285 (41.1)	18 (40.0)	0.87	277 (41.2)	16 (34.0)	0.30
Female	408 (58.9)	27 (60.0)		396 (58.8)	31 (66.0)	
EDSS score, n (%)						
3–5	303 (43.7)	15 (33.3)	0.15	300 (44.6)	14 (29.8)	0.03
5.5–6.5	390 (56.3)	30 (66.7)		373 (55.4)	33 (70.2)	

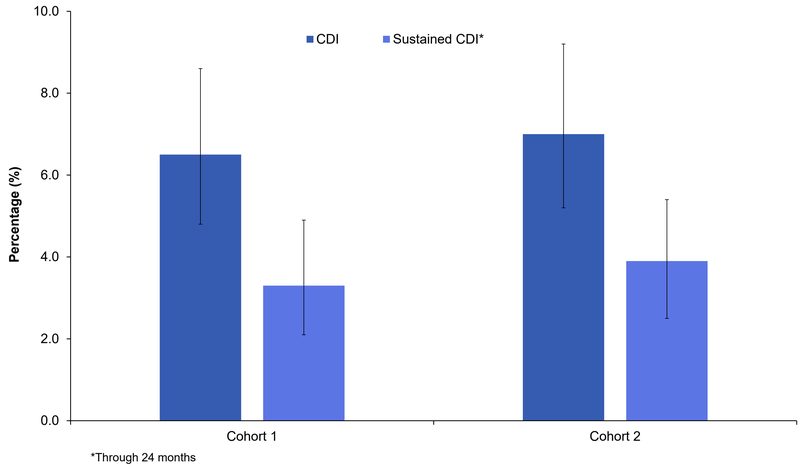
**P* values were conducted using t-test or chi-squared test as appropriate to assess for differences between patients who improved and patients who did not improve

RESULTS – CONFIRMED DISABILITY IMPROVEMENT

Confirmed disability improvement and sustained improvement

- Overall, 6.5% (45/693; 95% CI: 4.8%–8.6%) and 7.0% (47/673; 95% CI: 5.2%–9.2%) of eligible patients had CDI in Cohorts 1 and 2, respectively (**Figure 2**)
- The mean (SD) duration of CDI was 7.5 (5.1) months and 5.9 (3.8) months in Cohorts 1 and 2, respectively
- CDI was sustained through 24 months in 3.3% (95% CI: 2.1%–4.9%) and 3.9% (95% CI: 2.5%–5.6%) of all eligible patients with progressive MS in Cohorts 1 and 2, respectively (**Figure 2**)

Figure 2. Percentage of eligible subjects achieving CDI and once achieved, sustained CDI through 24 months



*Through 24 months

Confirmed disability improvement by PPMS vs SPMS

No differences were observed between patients with PPMS and SPMS in the percentage with a CDI or in those who sustained CDI through 24 months

- A logistic regression adjusting for age, gender, and baseline EDSS score showed:
  - There was no association between MS diagnosis (PPMS vs SPMS) and proportion of patients with CDI for Cohort 1 (OR=1.18, 95% CI: 0.62–2.24; *P*=0.62) or Cohort 2 (OR=1.19, 95% CI: 0.63–2.25; *P*=0.60)
  - Similarly, there was no association between MS diagnosis (PPMS vs SPMS) and proportion of patients with sustained CDI at 24 months for Cohort 1 (OR=1.17, 95% CI: 0.48–2.82; *P*=0.73) or for Cohort 2 (OR=1.21, 95% CI: 0.53–2.79; *P*=0.65)

CONCLUSIONS

Results from this study examining CDI in the MSOAC Placebo Database support low rates of CDI and similarities between the PPMS and SPMS populations, which in this analysis includes both active and nonactive patients

- At 9 months confirmed at 12 months, CDI measured in a mixed active and nonactive PMS population was observed in 6.5% of patients evaluated in clinical trial placebo arms, with 3.3% maintaining CDI through 24 months
- Importantly, these data do not clarify differences in CDI between active and nonactive progressive MS populations. However, a previous publication on SPMS showed the placebo CDI is lower in nonactive (4%) than active patients (7.4%), at 6 months confirmed at 12 months[2]
- No difference was seen in disability improvement between PPMS and SPMS patients in either cohort, supporting the similarity of patients with progressive MS

More transformative therapies are needed to improve disability in patients with progressive MS, especially in nonactive disease, where there are limited approved treatment options

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REFERENCES

1. Multiple Sclerosis Outcomes Assessment Consortium. Critical Path Institute. Available at: https://c-path.org/programs/msoac/ (Accessed April 13, 2022)
2. Xun P, Sadetsky N, Kresa-Reahl K, *et al*. American Academy of Neurology 2022 Annual Meeting (Virtual). April 24–26, 2022

ABBREVIATIONS

CDI = confirmed disability improvement; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; MSOAC = Multiple Sclerosis Outcomes Assessment Consortium; OR = odds ratio; PPMS = primary progressive multiple sclerosis; SD = standard deviation; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

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