How do patients with secondary progressive multiple sclerosis enrolled in the EXPAND randomized controlled trial compare with those seen in German clinical practice in the NeuroTransData multiple sclerosis registry?

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ABSTRACT

BACKGROUND: In EXPAND (NCT01665144), a phase 3 randomized clinical trial, siponimod reduced disability progression versus placebo in patients with secondary progressive multiple sclerosis (SPMS).

AIM: To understand how a real-world population with SPMS relates to that in EXPAND, we conducted a retrospective, observational cohort study using the German NeuroTransData (NTD) multiple sclerosis (MS) registry.

METHODS: The NTD MS registry is run by a Germany-wide network of physicians. Two cross-sectional analyses were performed using the NTD MS registry. The first included patients with SPMS, as recorded in the registry, and compared their characteristics between 1 January 2018 and 31 December 2018 with patients in EXPAND. The second described the characteristics of patients in the registry at the time of diagnosis of SPMS between 1 January 2010 and 31 December 2018.

RESULTS: The first analysis included 773 patients: patients were older in the NTD MS registry than in EXPAND (mean age, 57.9 vs 48.0 years) and had a longer duration of SPMS (mean, 6.2 vs 3.8 years). In the NTD MS registry, median Expanded Disability Status Scale (EDSS) scores were comparable to EXPAND (6.0 versus 6.0), although fewer patients had relapses in the previous 24 months (16% vs 36% [siponimod] and 37% [placebo]). Data on gadolinium-enhancing lesions were only available for 5.8% of patients in the NTD MS registry. The second analysis included 916 patients: at the time of SPMS diagnosis, the mean age was 53.2 years and the median EDSS score was 5.0.

CONCLUSION: The population in the NTD MS registry was older to that in EXPAND, but were similar in terms of disability. Differences likely reflect the inclusion criteria of EXPAND but also highlight that real-world populations encompass a wider range of patient characteristics.

KEYWORDS: multiple sclerosis, secondary progressive multiple sclerosis, real-world population, observational study, randomized clinical trial.

Introduction

Randomized controlled trials (RCTs) are the gold standard for assessing the safety and efficacy of new treatments. To minimize confounding factors, they use strict inclusion criteria and are conducted under highly controlled conditions.1-3 However, this means that the population included in RCTs, and patient management, may not always represent that seen in clinical practice.1-3 Indeed, the specific monitoring protocols applied in RCTs may vary from those in real-world clinical practice, and there is evidence that this can lead to discrepancies between the results of RCTs and real-world outcomes.3,4 Real-world studies help to bridge the gap between RCTs and clinical practice. They can help us to understand how the populations of RCTs reflect patients seen in clinical practice and the relevance of the procedures conducted in RCTs.3 These insights can help payers and regulators to interpret results from RCTs and can guide decision-making.

In secondary progressive multiple sclerosis (SPMS), patients experience irreversible disability progression. However, few approved disease-modifying therapies (DMTs) for SPMS have been shown to slow disability progression in RCTs.7-10 Guidelines developed by the European Academy of Neurology...
and the European Committee for Treatment and Research in Multiple Sclerosis report that only interferon-β and mitoxantrone had been compared with placebo or another DMT in patients with SPMS in RCTs. Interferon-β showed inconsistent effects on disability progression and mitoxantrone reduced the risk of disability progression but its use is limited by safety concerns.11

EXPAND is an international, phase 3, placebo-controlled RCT that evaluated the efficacy and safety of the DMT siponimod, a sphingosine-1-phosphate receptor modulator, in patients with SPMS.12,13 In the EXPAND trial, siponimod showed a significantly lower risk of 6-month confirmed disability progression compared with placebo in patients with SPMS, and was well tolerated.13 When looking at patient subgroups in EXPAND, the risk of 6-month confirmed disability progression was significantly reduced with siponimod versus placebo in patients with relapses in the previous 2 years and in patients with gadolinium-enhancing (Gd+) lesions at baseline. In patients without relapses in the previous 2 years and in those without Gd+ lesions at baseline, 6-month confirmed disability progression trended towards a reduction with siponimod versus placebo but did not reach statistical significance.13 Based on the results from EXPAND, siponimod was approved by the European Medicines Agency (EMA) for use in adults with relapses or imaging features of inflammatory activity (i.e., active SPMS).14 The EXPAND long-term extension study demonstrated that patients with inactive SPMS may progress more slowly than patients with active SPMS and therefore a longer follow-up for disability progression than 6 months is needed to see the treatment benefit with siponimod.15

EXPAND enrolled patients aged 18-60 years who had a diagnosis of SPMS, an Expanded Disability Status Scale (EDSS) score of 3.0-6.5, documented EDSS progression in the 2 years before the study and no relapses in the 3 months before randomization (Supplemental Table 1). How patients enrolled in EXPAND reflect patients with SPMS in clinical practice has not been evaluated, owing to a paucity of real-world data describing patient populations with SPMS.

To assess the characteristics of patients with SPMS in the real world and how these patients relate to those enrolled in EXPAND, we conducted a retrospective, observational cohort study using the German NeuroTransData (NTD) multiple sclerosis (MS) registry.

Methods
The NTD MS registry, founded in 2008, is run by a Germany-wide network of physicians in the fields of neurology and psychiatry. It consists of 78 neurologists across 153 private practices who see approximately 600 000 outpatients per year. The NTD MS registry includes about 25 000 outpatients with MS, which represents approximately 15% of all MS patients in Germany. For inclusion in this study, patients enrolled in the NTD MS registry were required to be aged ≥18 years and to have a diagnosis of SPMS, as had been recorded in the registry by their physician. Patients enrolled in RCTs were not eligible for inclusion.

Two separate cross-sectional analyses were performed using the NTD MS registry. The first analysis included all patients with SPMS included in the NTD MS registry and described the characteristics of these patients between 1 January 2018 and 31 December 2018. These data were compared with the baseline characteristics of patients enrolled in EXPAND. The eligibility criteria of EXPAND are reported in the supplemental materials (Supplemental Table 1) and full details of the study design and methodology are reported by Kappos et al.18 The second analysis evaluated patients included in the NTD registry diagnosed with SPMS between 1 January 2010 to 31 December 2018 with a minimum of 12 months’ follow-up after their diagnosis of SPMS, and described the characteristics of these patients at the time of diagnosis of SPMS.

Data collection
In the NTD MS registry, demographic characteristics, clinical history and clinical variables are captured in real time during clinical visits using a web-based patient management platform. Standardized clinical assessments of EDSS scores are performed by certified raters (https://www.neurostatus.net/). If magnetic resonance imaging (MRI) is clinically indicated, results are documented as predefined, structured categorical variables, including evidence of Gd+ lesions.

To ensure data quality in the NTD MS registry, all personnel undergo regular training. In addition, data quality in the NTD MS registry is monitored upon entry, on a regular basis via queries, and retrospectively every quarter. Following extraction of data from the NTD MS registry, defined standardized data-cleansing procedures are performed. All data are pseudonymized and pooled to form the NTD MS registry database.

Patients provided written informed consent for their inclusion in the NTD MS registry and for processing of their personalized data, as per General Data Protection Regulation. The NTD MS registry data acquisition and management protocol was approved by the Ethical Committee of the Bavarian Medical Board (Bayerische Landesärztekammer; 14 June 2012; approval number 11144) and was re-approved by the Ethical Committee of the Medical Board North-Rhine (Ärztekammer Nordrhein, 25 April 2017; approval number 20170701). The study was conducted in concordance with the ethical principles laid down in the Declaration of Helsinki.

Statistical analysis
Statistical analyses followed a pre-defined statistical analysis plan. Continuous data were summarized using mean and standard deviation (SD), or median and range or interquartile range (IQR), as appropriate, and missing data were not imputed. Categorical data were summarized as the number of patients and the percentage of
the cohort with available data, and missing data were considered a separate category of data with no data imputation. In the analysis of patients at the time of diagnosis of SPMS, EDSS score at the date of diagnosis of SPMS or the closest value within ±90 days of this date was taken to be the EDSS score at the time of the diagnosis of SPMS. SAS version 9.2 was used to analyse the data.

Table 1. Characteristics of patients in the 2018 NTD MS registry cohort and the EXPAND trial at enrolment.

|                      | NTD MS REGISTRY (N = 773) | EXPAND | PLACEBO | TOTAL \textsuperscript{12} (N = 1651) |
|----------------------|---------------------------|--------|---------|-----------------------------------|
|                      | SIPONIMOD (N = 1105)      | PLACEBO (N = 546) | TOTAL (N = 1651) |
| Age, years           |                           |        |         |                                   |
| Mean (SD)            | 57.9 (10.0)               | 48.0 (7.8) | 48.1 (7.9) | 48.0 (7.9) |
| Median (range)       | 57.2 (26-86)              | 49.0 (22-61) | 49.0 (21-61) | — |
| Time since diagnosis of MS, years |               |        |         |                                   |
| Mean (SD)            | 20.3 (9.4)                | 12.9 (7.9) | 12.1 (7.5) | 12.6 (7.8) |
| Median (range)       | 19.5 (4.4-56.0)           | 12.0 (4.1-44.4) | 11.2 (4.1-39.4) | — |
| Time since onset of MS symptoms, years |               |        |         |                                   |
| Mean (SD)            | 23.9 (10.3)               | 17.1 (8.4) | 16.2 (8.2) | 16.8 (8.3) |
| Median (range)       | 23.0 (2.7-56.0)           | 16.4 (1.4-45.0) | 15.4 (1.3-43.0) | — |
| Time since conversion to SPMS, years |               |        |         |                                   |
| Mean (SD)            | 6.2 (4.8)                 | 3.9 (3.6)  | 3.6 (3.3)  | 3.8 (3.5)  |
| Median (IQR)         | 5.7 (2.5-8.3)             | 2.6 (-1.24.4) | 2.5 (-1.21.7) | — |
| Women, n (%)         | 550 (71)                  | 669 (61) | 323 (59) | 992 (60) |
| EDSS score           |                           |        |         |                                   |
| Median (range)       | 6.0 (.9-9.0)              | 6.0 (2.0-7.0) | 6.0 (2.0-7.0) | 6.0 (NR) |
| EDSS score frequency, n (% of evaluable) |   |        |         |                                   |
| <3                   | 34 (6)                    | 6 (1)   | 2 (<1) | — |
| 3-4.5                | 171 (30)                  | 312 (28) | 148 (27) | — |
| 5-5.5                | 68 (12)                   | 165 (15) | 100 (18) | — |
| 6-6.5                | 172 (30)                  | 620 (56) | 295 (54) | — |
| >6.5                 | 124 (22)                  | 2 (<1)  | 1 (<1) | — |
| Missing              | 206 (NA)                  | 0       | 0       | — |
| Relapses in the previous 12 months |   |        |         |                                   |
| ≥1 relapse, n (%)    | 67 (9)                    | 227 (21) | 130 (24) | — |
| Mean (SD)            | .1 (.4)                   | .2 (.5)  | .3 (.6)  | — |
| Median (range)       | 0 (0-3)                   | 0 (0-4)  | 0 (0-4)  | — |
| Relapses in the previous 24 months |               |        |         |                                   |
| ≥1 relapse, n (%)    | 123 (16)                  | 393 (36) | 203 (37) | — |
| Mean (SD)            | .2 (.6)                   | .7 (1.2) | .7 (1.2) | — |
| Median (range)       | 0 (0-6)                   | 0 (0-12) | 0 (0-8)  | — |
| Gd+ lesions present, n (% of evaluable) |               |        |         |                                   |
| Yes                  | 7 (16)                    | 237 (22) | 114 (22) | — |
| No                   | 38 (84)                   | 833 (78) | 415 (78) | — |
| Not evaluable        | 728 (NA)                  | 35 (NA)  | 17 (NA)  | — |
| No use of DMTs after conversion to SPMS, n (%) | 193 (25.0) | 245 (22) | 114 (21) | — |

\*Data for total population not available for all characteristics.  
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IQR, interquartile range; MS, multiple sclerosis; NA, not applicable; NTD, NeuroTransData; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.
Results
Comparison between patients with SPMS in the NTD MS registry in 2018 and the EXPAND trial
The German cohort comprised 773 outpatients with SPMS who were enrolled in the NTD MS registry in 2018. The characteristics of the 2018 NTD MS registry cohort and the patients in EXPAND at baseline are shown in Table 1. All patients included in the NTD MS registry were Caucasian. There was a higher proportion of female patients in the 2018 NTD MS registry cohort (71%) than in the EXPAND trial (60%). Patients in the 2018 NTD MS registry cohort were almost a decade older (mean age 57.9 years) than those in the EXPAND trial (mean age 48.0 years). The median time since conversion to SPMS was approximately twice as long in the 2018 NTD MS registry cohort (5.7 years) than in the EXPAND trial (siponimod arm, 2.6 years; placebo arm, 2.5 years). The proportion of patients who had not received any DMTs since their SPMS diagnosis was slightly higher in the 2018 NTD MS registry cohort (25%) than in the EXPAND trial (siponimod arm, 22%; placebo arm, 21%).

When looking at disease characteristics, severity of disability was comparable between patients in the NTD MS registry and those in EXPAND, with median EDSS scores of 6.0 for both cohorts. However, patients in the NTD MS registry displayed a wider range of EDSS scores because they were not subject to the EXPAND inclusion criteria (Figure 1). A greater proportion of patients in the NTD MS registry (84%) experienced no relapses in the previous 24 months before the study than those in EXPAND (siponimod arm, 64%; placebo arm, 63%). Of patients with evaluable data, the proportion of patients who had Gd+ lesions was similar between the NTD registry (16%) and EXPAND (siponimod arm, 21%; placebo arm, 21%), although in the NTD MS registry, MRI is only performed for clinical reasons and therefore only 5.8% of patients in the NTD MS registry had evaluable MRI data. By contrast, nearly all patients in EXPAND had evaluable MRI data (siponimod arm, 96.8%; placebo arm, 96.9%) (Table 1).

Discussion
Real-world studies complement RCTs by providing valuable insights into the characteristics of patients within a particular indication, which can help the medical community and payers to understand the applicability of RCT results in clinical practice. This study used data from the German NTD MS registry to assess the characteristics of outpatients with SPMS in clinical practice and to compare these with patients enrolled in the phase 3, placebo-controlled RCT EXPAND, which evaluated the efficacy and safety of siponimod. Overall, while there were differences between patients in the NTD MS registry and those in the EXPAND trial, the population in NTD MS registry had a broader range of characteristics and encompassed the population enrolled in the EXPAND trial.

On average, patients in the NTD MS registry were older than those in the EXPAND trial, both in the 2018 cohort and at the time of diagnosis of SPMS. In addition, the duration of SPMS was longer in the 2018 NTD MS registry cohort than in the EXPAND trial. There are several possible reasons for these differences. For example, physicians may be more likely to enrol their patients into RCTs soon after their conversion to SPMS because they are seeing these patients regularly in this dynamic phase of the disease. Furthermore, older patients may engage with medical services less frequently and be less interested in enrolment in a clinical trial than younger patients. This may introduce bias in the patient identification process for RCTs. In addition, the eligibility
Table 2. Characteristics of patients in the German NeuroTransData multiple sclerosis registry at the time of diagnosis of secondary progressive multiple sclerosis.

| Characteristic                                      | NTD MS REGISTRY (N = 916)                        |
|-----------------------------------------------------|--------------------------------------------------|
| Age, years                                          | Mean (SD) 53.2 (10.1)                             |
|                                                     | Median (range) 52.4 (24.8-83.2)                  |
| Time since onset of MS symptoms, years              | Mean (SD) 18.5 (10.3)                             |
|                                                     | Median (range) 16.9 (0-49.8)                      |
| Time since diagnosis of MS, years                   | Mean (SD) 15.1 (9.4)                             |
|                                                     | Median (IQR) 14.0 (8.2-20.8)                     |
| Women, n (%)                                        | 643 (70.2)                                       |
| EDSS score                                          | Median (IQR) 5.0 (4.0-6.5)                        |
| EDSS score frequency, n (%)                         |                                                   |
| <3                                                  | 73 (8.0)                                         |
| 3-4.5                                               | 328 (35.8)                                       |
| 5-5.5                                               | 133 (14.5)                                       |
| 6-6.5                                               | 192 (21.0)                                       |
| >6.5                                                | 190 (20.8)                                       |
| Relapses in the 12 months prior to diagnosis        |                                                   |
| ≥1 relapse, n (%)                                   | 142 (15.5)                                       |
| Mean (SD)                                           | .2 (.5)                                          |
| Median (range)                                      | 0 (0-4)                                          |
| Relapses in the 24 months prior to diagnosis        |                                                   |
| ≥1 relapse, n (%)                                   | 201 (21.9)                                       |
| Mean (SD)                                           | .3 (.7)                                          |
| Median (range)                                      | 0 (0-7)                                          |
| Gd+ lesions present, n (% of evaluable)             |                                                   |
| Yes                                                 | 25 (17.7)                                        |
| No                                                  | 116 (82.3)                                       |
| Not evaluable                                       | 775 (NA)                                         |
| Last DMT started before conversion to SPMS, n (%)   |                                                   |
| Interferon                                           | 240 (26.2)                                       |
| Mitoxantrone                                        | 103 (11.2)                                       |
| Glatiramer acetate                                  | 87 (9.5)                                         |
| Azathioprine                                        | 14 (1.5)                                         |
| Cyclophosphamide                                   | 1 (.1)                                           |
| Fingolimod                                          | 26 (2.8)                                         |
| Methotrexate                                        | 4 (.4)                                           |
| Natalizumab                                         | 36 (3.9)                                         |
| Dimethyl fumarate                                   | 16 (1.7)                                         |
| Immunoglobulin                                      | 3 (.3)                                           |
| Teriflunomide                                       | 10 (1.1)                                         |
| Rituximab                                           | 2 (.2)                                           |
| Alemtuzumab                                         | 3 (.3)                                           |
| Daclizumab                                          | 2 (.2)                                           |
| No prior use of DMTs before conversion to SPMS      | 369 (40.3)                                       |

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IQR, interquartile range; MS, multiple sclerosis; NTD, NeuroTransData; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.
criteria in the EXPAND trial may explain the difference in age because patients older than 60 years were excluded.\(^{13}\) Finally, there may be demographic differences between patient populations and/or their access to specialized neurology services in Germany and the other countries that were involved in EXPAND. To achieve outcomes with siponimod in clinical practice that are similar to those seen in the EXPAND trial, it may be important to consider treating patients in the real world as early as possible, to ensure that they are as close in age to those in the EXPAND trial as possible.

The degree of disability was similar between patients in the 2018 NTD MS registry cohort and those in the EXPAND trial, as measured using the EDSS scale, with a median EDSS score of 6.0 in all populations. The EDSS scale is a well-accepted tool to measure disability in people with MS and is the primary tool used for diagnosing SPMS. Baseline EDSS score is also known to influence the effectiveness of treatment in MS.\(^{17}\) As expected, there was much greater variation in disability in the 2018 real-world cohort than in the EXPAND trial because only patients with an EDSS score of 3-6.5 were eligible for inclusion in EXPAND. Indeed, 28% of patients in the 2018 NTD MS registry cohort had EDSS scores outside of the EXPAND inclusion criteria, with 6% having scores below 3 and 22% having scores of 7 or more. This indicates that, with regard to the degree of disability, the real-world, 2018 NTD MS registry cohort in Germany encompassed the full range included in the EXPAND population. Some patients in the NTD MS registry had an EDSS score below 3, indicating minimal disability. SPMS is typically diagnosed based on disability progression that occurs independently to relapse activity and therefore this may indicate that specialized neurological outpatient care centres are very aware of the risk of their patients transitioning from RRMS to SPMS and can identify this transition early.

In total, 84% of patients in the real-world, 2018 NTD MS registry cohort had no relapses in the 24 months prior to the study, compared with 64% and 63% of patients in the siponimod and placebo arms of EXPAND, respectively (Table 1). Relapse activity during the progressive course of MS has been shown to accelerate irreversible disability progression in a small number of studies,\(^{18,19}\) with this effect limited to 5 years after the onset of SPMS.\(^{19}\) Combined with the older age and longer duration of disease, the difference in relapses suggests that a sizable proportion of real-world patients may be further along in the disease course than those in the EXPAND population because reduced relapse rates are generally observed in the later stages of the disease and in older patients.\(^{20}\)

In clinical practice, a diagnosis of SPMS can be avoided or delayed by several years, owing to the uncertainty in establishing a diagnosis of SPMS during the course of slowly progressing disability, the lack of available treatments and the fear of withdrawing treatment leading to a rebound in inflammatory disease activity.\(^{21-23}\) Indeed, a recent study found SPMS to be widely underdiagnosed in Germany and the UK.\(^{24}\) Comparing the real-world, 2018 NTD MS registry cohort and the RCT population in the EXPAND trial, it appears that the opportunity to participate in clinical trials with promising treatments attracts younger patients with disability progression and a short course of SPMS. By contrast, real-world populations include patients with a wider range of demographic and clinical characteristics. The higher proportion of patients with non-relapsing SPMS in the 2018 NTD MS registry cohort might explain why the proportion of patients who had not received any DMTs since their diagnosis of SPMS was slightly higher in the real-world NTD MS registry cohort than in EXPAND, because none of the DMTs available at the time of this study had been shown to slow disability progression that is independent to relapses.\(^{25}\)

Only 5.8% of patients in the 2018 NTD MS registry cohort had evaluable data to assess Gd+ lesions (Table 1). This highlights the fact that MRI data are not routinely collected for patients with SPMS in clinical practice because at the time of this analysis, MRI results were not considered to be relevant to the therapeutic decision algorithm in this type of MS. Indeed, a real-world study found that MRI was conducted less frequently in patients with inactive SPMS than in those with active SPMS, meaning that the chance of detecting disease activity was reduced in these patients.\(^{26}\) The EMA has approved siponimod for use in patients with active SPMS, defined by the presence of relapses or imaging features of inflammatory activity.\(^{14}\) This is likely to lead to an increase in MRI diagnostics for patients with SPMS in European markets, driven by the need to identify patients with active SPMS to meet the European label criteria for siponimod in patients with SPMS without relapses.

The approval of siponimod, which has demonstrated efficacy and a well-tolerated safety profile in patients with active SPMS, will improve the therapeutic options in the population eligible to receive siponimod, as per the EMA label. The unmet need in this population is highlighted by the considerable proportion (21-25%) of patients in the 2018 NTD MS registry cohort and the EXPAND trial who had not received any DMTs following conversion to SPMS. However, the challenge remains of how to identify all eligible patients as soon as possible after conversion to SPMS, to ensure that they receive a treatment that specifically targets the progressive nature of the disease. Indeed, there are efforts to identify algorithms that would allow early detection of deterioration that is independent to relapses, with external validation of how clinically meaningful these algorithms currently pending.\(^{27,28}\)

A major strength of this study is that the data were captured from a large number of patients, across many centres in Germany, who were enrolled in the NTD MS registry. Furthermore, owing to established protocols and data-quality activities on both operational and management levels,\(^{29}\) data captured from the registry are standardized and of a high quality and information on data quality can be demonstrated.\(^{30}\)

In the real world, the majority of neurological care in SPMS takes place in an outpatient setting. However, by only capturing patients in the outpatient setting as part of the NTD MS registry, bias in population characteristics may arise.
Furthermore, the centres participating in the NTD registry are private neurologist practices, whereas RCTs typically recruit patients from specialized MS centres or centres affiliated with a university; there may be some differences between the patient populations seen in different healthcare settings. In addition, the NTD registry only includes patients from Germany — diagnostic and therapeutic procedures can differ across countries and this may limit the applicability of this study to other countries. Finally, although multiple activities to ensure data quality in the NTD MS registry are in place, real-world data and its quality can be biased by known and unknown confounders.

Conclusion
The population in the NTD MS registry were older, had a longer time since conversion to SPMS, had fewer relapses and a broader range of EDSS scores than the population in EXPAND, although the two populations were similar in terms of median EDSS scores. These differences between the real-world, 2018 NTD MS registry cohort compared with EXPAND mainly reflect the inclusion criteria in EXPAND but also underline that real-world patient care encompasses a wider range of demographic and clinical patient characteristics. This study highlights that the definition of active SPMS, as per the EMA label of siponimod, limits the number of patients who will be eligible in Germany, with a relatively small proportion of patients with SPMS experiencing relapse activity and even fewer patients undergoing MRI in clinical practice at the time of this analysis. As a consequence, the use of MRI in patients with SPMS without relapses is likely to increase as the importance of distinguishing between active and inactive SPMS increases within healthcare systems.

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