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Original Research Paper

Greater sensitivity to multiple sclerosis disability worsening and progression events using a roving versus a fixed reference value in a prospective cohort study

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Abstract

Background: Confirmed Expanded Disability Status Scale (EDSS) progression occurring after a fixed-study entry baseline is a common measure of disability increase in relapsing-remitting multiple sclerosis (RRMS) studies but may not detect all disability progression events, especially those unrelated to overt relapses.

Objective: To evaluate possible measures of disability progression unrelated to relapse using EDSS data over ≈5.5 years from the Tysabri® Observational Program (TOP).

Methods: TOP is an ongoing, prospective, open-label study in RRMS patients receiving intravenous 300 mg natalizumab every 4 weeks. Measures of increasing disability were assessed using as a reference either study baseline score or a "roving" system that resets the reference score after ⩾24- or ⩾48-week confirmation of a new score.

Results: This analysis included 5562 patients. Approximately 70% more EDSS progression events unrelated to relapse and 50% more EDSS worsening events overall were detected with a roving reference score (cumulative probability: 17.6% and 29.7%, respectively) than with a fixed reference baseline score (cumulative probability: 10.1% and 20.3%, respectively).

Conclusion: In this long-term observational RRMS dataset, a roving EDSS reference value was more efficient than a study baseline EDSS reference in detecting progression/worsening events unrelated to relapses and thus the transition to secondary progressive disease.

Keywords: Multiple sclerosis, relapsing-remitting, natalizumab, disease progression, Expanded Disability Status Scale, secondary progressive multiple sclerosis

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Introduction

Prevention of disability accumulation in patients with relapsing-remitting multiple sclerosis (RRMS) is a common goal in clinical trials and clinical practice.[1] Disability worsening is typically measured by increases in Expanded Disability Status Scale (EDSS) score confirmed at 12 or 24 weeks or time points later in the trial, using the baseline EDSS score as reference. Confirmation of EDSS increase at 12 or 24 weeks or a later time point reduces the likelihood of capturing events that may subsequently revert,[2,3] and the European Medicines Agency[4] has recently recommended that disability worsening be confirmed by measurements taken at least 24 weeks apart.

Most RRMS studies enroll patients with clinical disease activity, and though the enrollment criteria of these studies require that the last relapse not have occurred within a certain timeframe before baseline (usually at least 30 days), a substantial fraction of patients will experience EDSS score regression,[5] especially during the first year, which may be associated with prolonged recovery from relapse. Such an initial decrease in EDSS score after treatment

initiation may reduce the detection rate of subsequent events of disability worsening or progression, as patients first have to progress back to the baseline level and then beyond it to register a worsening or progression event.

The typical disease course of multiple sclerosis (MS) begins with clinically active RRMS, characterized by the occurrence of relapses, acute or subacute episodes of new or increasing neurologic dysfunction, followed by full or partial recovery in the absence of fever or infection.[6] In most RRMS patients, the disease eventually advances to a secondary progressive stage.[7] Secondary progressive MS (SPMS) is characterized by an initial relapsing-remitting disease course followed by progression of variable rate with or without occasional relapses, minor remissions, and plateaus.[8] The median time to secondary progression has been estimated as 15–19 years from RRMS onset.[7,9] Reaching SPMS appears to be the strongest determinant of poor long-term disease prognosis and is more dependent on age than on disease duration.[10–14]

Clear metrics for sensitive and reliable identification of the transition from RRMS to SPMS have been lacking.[6] A comprehensive analysis using the large MSBase cohort to evaluate potential definitions found the highest specificity in a definition requiring an EDSS score increase of ⩾1.0 (or ⩾0.5 from a baseline score ⩾6.0), resulting in a minimum score of 4.0 in the absence of relapses that was confirmed after ⩾3 months within the leading functional system, along with a minimum pyramidal functional system score of 2.0.[15] Despite its high specificity, this definition would only capture progressive disease in a rather advanced stage that may be less amenable to treatment.

When referring to increases in disability, recent literature has suggested that the term "worsening" be used in place of "progression" to describe increasing disability in patients with relapsing forms of the disease, with the term "progression" reserved for patients in the progressive phase of MS, defined by progressively increasing disability unrelated to relapse activity.[6,15]

In this study, we explore the use of a roving EDSS reference value to enhance detection of EDSS worsening events. The use of a roving EDSS reference value should also allow more sensitive measurement (in the total study population) of disability progression within relapse-free epochs according to specific, time-based interval definitions (e.g. 24 or 48 weeks apart). Using data from a period of approximately 5.5 years in the Tysabri® Observational Program (TOP)[16] study of natalizumab-treated RRMS patients, we evaluate metrics using fixed and roving EDSS baseline criteria for identification of changes in disability.

Materials and methods

Study design

TOP (ClinicalTrials.gov: NCT00493298) is an ongoing, prospective, observational, 10-year open-label study of patients with RRMS in clinical practice settings in Europe, Australia, Argentina, and Canada.[16] The study protocol was approved by each center's independent ethics committee. A complete list of investigators and the countries in which they practice is included in the Supplementary Material. The study design was written in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and all enrolled patients provided written informed consent.

The TOP methodology and interim conventional disability progression outcomes have been published.[16] Briefly, patients who have received ⩽3 infusions of natalizumab prior to enrollment are eligible to enroll in TOP. Patients in TOP receive intravenous infusions of 300 mg natalizumab every 4 weeks.

Assessments

EDSS scores were assessed at regular clinical visits approximately every 24 weeks. For the sake of clarity and consistency with the revised definitions of the clinical course of MS in Lublin et al.,[6] throughout this article, we refer to a disability increase associated with relapses as EDSS *worsening*, whereas EDSS *progression* is reserved for a disability increase unrelated to overt relapse activity. EDSS worsening and progression events were defined as increases in EDSS score of ⩾1.5 points from an EDSS score of 0.0, ⩾1.0 point from an EDSS score of 1.0–5.5, or ⩾0.5 point from an EDSS score ⩾6.0. EDSS worsening and progression events were assessed using as a reference either the conventional fixed study baseline EDSS score or a roving EDSS score in which the increase or decrease had to be separated from the last EDSS assessment by at least 24 or 48 weeks (Figure 1). All EDSS worsening and progression events were required to be confirmed at 24 weeks.

Using the fixed space baseline EDSS score reference or the roving EDSS reference value, we

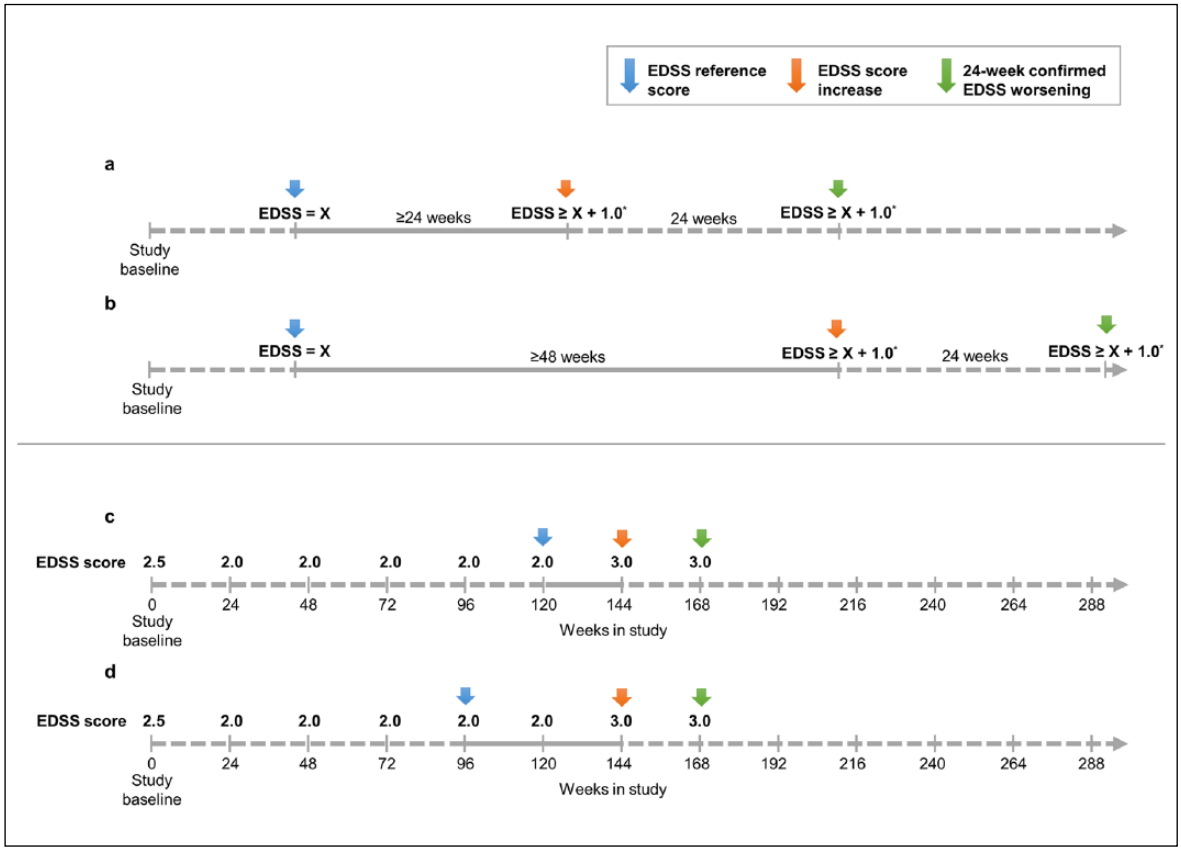


Figure 1. Schematic of the roving Expanded Disability Status Scale (EDSS) reference system. Confirmed EDSS worsening (a) ⩾24 or (b) ⩾48 weeks apart using a roving reference is illustrated. Also shown are hypothetical examples of confirmed EDSS worsening (c) ⩾24 or (d) ⩾48 weeks apart that would be captured using a roving EDSS reference and not accounted for using the conventional study baseline as EDSS.
*Increase in EDSS score of ⩾1.5 points from a score of 0.0, ⩾1.0 point from a score of 1.0–5.5, or ⩾0.5 points from a score ⩾6.0.

assessed both overall confirmed EDSS worsening and EDSS progression unrelated to relapse. An observed EDSS progression event was considered unrelated to any relapse if no concurrent relapse had been recorded from the 30 days prior to the reference EDSS assessment to either 30 days or 12 weeks after the progressed EDSS assessment time point (Figure 2). Using a roving EDSS score rather than the fixed study baseline EDSS score as reference reduced the potential bias toward the selection of entirely relapse-free patients when progression events unrelated to relapse were analyzed.

Sensitivity analysis

A sensitivity analysis of the roving EDSS reference system was performed with progression events unrelated to relapse (increases in EDSS score of ⩾1.5 points from an EDSS score of 0.0, ⩾1.0 point from an EDSS score of 1.0–5.5, or ⩾0.5 point from an EDSS score ⩾6.0) excluded if recorded in reference to an EDSS score that was both lower than study baseline EDSS score and not confirmed after ⩾12 weeks. (For example, if a recorded EDSS score was lower than the score at study baseline, then, to qualify for use as a progression reference, this EDSS score must also have been confirmed by a second EDSS score at least as low as the first score ⩾12 weeks later.)

Statistical analysis

Baseline characteristics are presented using summary statistics as appropriate. Cumulative probabilities of EDSS worsening and progression unrelated to relapse were estimated using the Kaplan–Meier method. If the onset of EDSS worsening or progression unrelated to relapse occurred ⩾12 weeks after the last dose of natalizumab, this event was excluded and the patient was censored 12 weeks after the last dose. However, confirmation of the worsening or

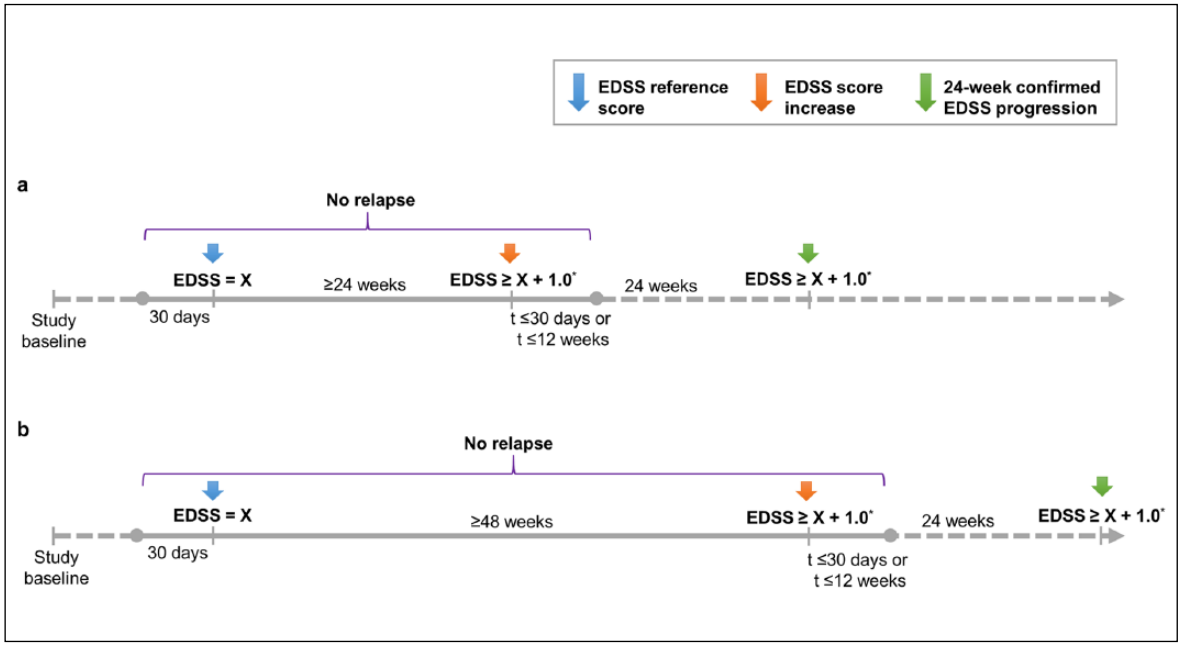


Figure 2. Schematic of methodological assessment of Expanded Disability Status Scale (EDSS) progression unrelated to relapses confirmed (a) ⩾24 or (b) ⩾48 weeks apart using a roving EDSS reference.
t: time following EDSS increase with no concurrent relapse.
*Increase in EDSS score of ⩾1.5 points from a score of 0.0, ⩾1.0 point from a score of 1.0–5.5, or ⩾0.5 points from a score ⩾6.0.

progression event could occur ⩾12 weeks after the last dose of natalizumab. The analysis allowed multiple events of progression; when a patient had ⩾2 confirmed progression events, the event with the earliest onset date was used. Patients who dropped out of the study before week 288 and who had not had any progression events were censored 12 weeks after the last dose or at week 288, whichever was earlier.

Cumulative probabilities of EDSS worsening and progression unrelated to relapse using a roving EDSS reference were also analyzed in subgroups based on age at baseline (⩽37 years and >37 years), baseline EDSS score (⩽3.5 and >3.5), the number of relapses prior to starting natalizumab (<2 and ⩾2), and MS disease duration at baseline (⩽7 years and >7 years) in which patients were stratified according to their distribution above or below the median value at study baseline. Analyses were conducted using SAS/STAT software (version 9.3, SAS Institute, Cary, NC, USA).

Results

As of 1 May 2014, a total of 5623 patients were enrolled in TOP. Of these patients, 5562 had baseline and follow-up EDSS scores and were included in the analysis (Table 1). At the time of data extraction, patients had been on natalizumab treatment for a median (25th percentile, 75th percentile) of 108.3 (57.4, 176.6) weeks.

Disability worsening and progression unrelated to relapse using study baseline EDSS score as a fixed reference

When the baseline EDSS score was used as a fixed reference point, the cumulative probabilities of 24-week-confirmed EDSS worsening ⩾24 and ⩾48 weeks apart (i.e. with ⩾24 or ⩾48 weeks between the reference and the EDSS score increase) were similar (20.3% and 19.5%, respectively; Figure 3(a) and (b); Table 2). Exclusion of relapse-associated events reduced the number of confirmed progression events by approximately 50%. Similar results were observed when the 30-day or 12-week relapse cutoff was used to ensure that the captured progression events did not reflect an emerging subsequent relapse.

Disability worsening and progression unrelated to relapse using a roving EDSS reference value

When a roving EDSS reference value was used, the cumulative probability at 288 weeks in TOP of 24-week-confirmed EDSS worsening between EDSS assessments ⩾24 weeks apart (37.1%; Figure 3(c))

Table 1. Baseline characteristics.

Characteristics	TOP patients ($n=5562$)
Age, years	
Mean (SD)	37.1 (9.73)
Median (min, max)	37.0 (12, 70)
Gender, *n* (%)	
Male	1556 (28.0)
Female	4006 (72.0)
MS duration, years ($n=5545$)	
Mean (SD)	8.61 (6.687)
Median (min, max)	7.15 (0.0, 43.9)
Baseline EDSS score ($n=5555$)	
Mean (SD)	3.45 (1.629)
Median (range)	3.5 (0.0, 9.5)
Prior DMTs, *n* (%)	
0	538 (9.7)
1	2506 (45.1)
⩾2	2518 (45.3)
Prior relapses in last year ($n=5561$)	
Mean (SD)	2.0 (1.01)
Median (min, max)	2 (0, 10)
Natalizumab doses received before enrollment, *n* (%)	
0	2374 (42.7)
1	1278 (23.0)
2	1010 (18.2)
3	900 (16.2)

DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; SD: standard deviation.

was similar to that between assessments ⩾48 weeks apart (34.9%; Figure 3(d); Table 2).

Events of confirmed disability progression unrelated to relapse (Figure 3; Table 2) represented 61%–66% of overall confirmed disability worsening. Furthermore, 2.4 and 2.2 times more progression events unrelated to relapse measured ⩾24 weeks apart and ⩾48 weeks apart, respectively, were captured using the roving EDSS value rather than the study baseline EDSS score as a reference (Table 2).

A sensitivity analysis using a roving EDSS reference value that required confirmation of the new reference if it was lower than the study baseline EDSS score reduced the overall number of identified worsening events by 17%–20% and reduced the number of progression events unrelated to relapse by 22%–27%. However, the analysis using the roving EDSS reference still detected approximately 50% more overall worsening events and approximately 70% more progression events unrelated to relapse than analyses using the study baseline EDSS score as a fixed EDSS reference (Figure 4; Table 2).

Confirmed EDSS worsening and progression unrelated to relapse stratified by baseline characteristics using a roving EDSS reference value

Patients in the TOP study population above the median age of 37 years at baseline had more EDSS worsening and progression events unrelated to relapse than patients ⩽37 years old at baseline (Table 3); analyses of both ⩾24 weeks and ⩾48 weeks apart (using both the primary analysis and the more stringent sensitivity analysis) showed approximately 1.6 to 2.0 times more progression events unrelated to relapse in older than in younger patients (Table 3).

Patients who initiated natalizumab after <2 relapses in the prior year had slightly higher rates of EDSS worsening and progression unrelated to relapse than patients with ⩾2 relapses (Table 3). EDSS progression events unrelated to relapse occurred at a similar rate in patients with baseline EDSS ⩽3.5 (the median score) and with baseline EDSS >3.5 in both the primary and sensitivity analyses (Table 3). EDSS worsening and progression unrelated to relapse events were also similar in patients with different MS disease durations at baseline (⩽7 years or >7 years; Table 3).

Discussion

In this study, the use of a roving EDSS reference captured more than twice as many EDSS worsening events as analyses using the study baseline EDSS score as a fixed reference. Assessment of changes in EDSS score based on a roving EDSS reference value rather than a conventional fixed study baseline EDSS reference may therefore serve as a more sensitive measure to capture events of disability progression in clinical trials and long-term observational MS studies. To address the potential variability of the new reference EDSS score used for the roving reference analysis, the more stringent sensitivity analysis criteria included only events using a roving EDSS reference that itself had to be confirmed when lower than the study baseline EDSS score. This sensitivity analysis still revealed approximately 50%–70% more worsening and progression events than analyses using the study baseline EDSS score as a fixed reference.

Analyses using the roving reference seem especially sensitive to the detection of events unrelated to relapses. According to the revised definitions of the clinical course of MS by Lublin et al.,[6] confirmed

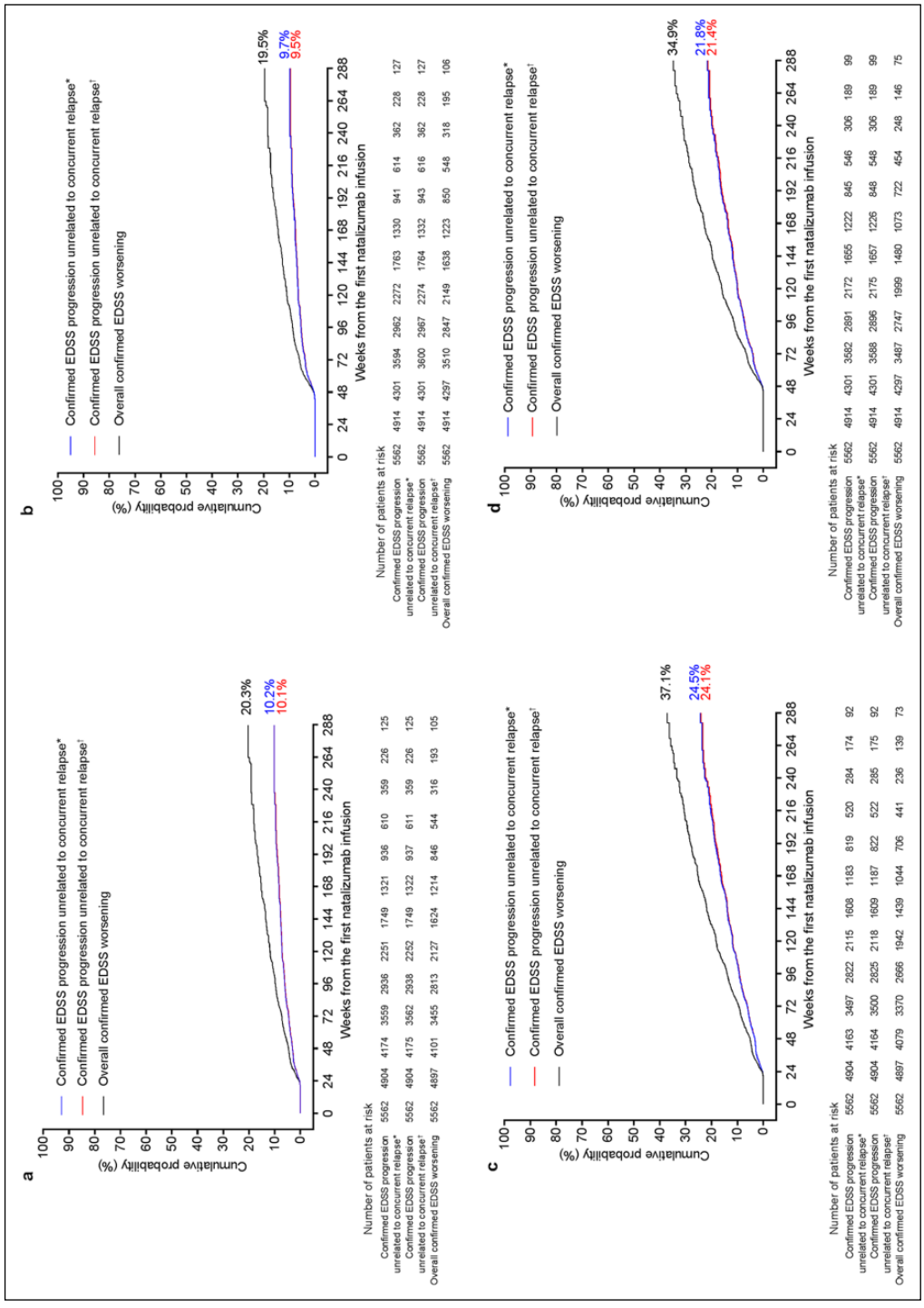


Figure 3. Cumulative probabilities (Kaplan–Meier analysis) of 24-week-confirmed Expanded Disability Status Scale (EDSS) overall worsening or progression and of 24-week-confirmed EDSS progression unrelated to relapses identified using a conventional study baseline reference for events occurring (a) ⩾24 weeks apart or (b) ⩾48 weeks apart or using a roving reference for events occurring between two EDSS assessments (c) ⩾24 weeks apart or (d) ⩾48 weeks apart.
*Defined as a relapse that was recorded from ⩽30 days prior to the reference EDSS assessment to ⩽30 days post progression assessment.
†Defined as a relapse that was recorded from ⩽30 days prior to the reference EDSS assessment to ⩽12 weeks post progression assessment.

Table 2. Cumulative probabilities (Kaplan–Meier analysis) at 288 weeks of 24-week-confirmed EDSS worsening or progression unrelated to relapse using a fixed study baseline or roving EDSS reference value ($n = 5562$).

Cumulative probability, % (95% CI)	Overall confirmed EDSS worsening	Confirmed EDSS progression unrelated to relapse[a]	
		⩽30 days	⩽12 weeks
Fixed study baseline EDSS reference			
EDSS assessments ⩾24 weeks apart	20.3 (18.0–22.5)	10.2 (8.9–11.6)	10.1 (8.7–11.4)
EDSS assessments ⩾48 weeks apart	19.5 (17.3–21.7)	9.7 (8.3–11.0)	9.5 (8.1–10.8)
Roving EDSS reference value			
EDSS assessments ⩾24 weeks apart	37.1 (33.5–40.5)	24.5 (21.6–27.3)	24.1 (21.2–26.9)
EDSS assessments ⩾48 weeks apart	34.9 (31.5–38.3)	21.8 (19.1–24.5)	21.4 (18.7–24.2)
Roving EDSS reference value (sensitivity analysis)			
EDSS assessments ⩾24 weeks apart	29.7 (26.4–32.9)	17.9 (15.4–20.3)	17.6 (15.1–20.0)
EDSS assessments ⩾48 weeks apart	28.9 (25.7–32.2)	17.1 (14.7–19.6)	16.8 (14.3–19.2)

EDSS: Expanded Disability Status Scale; CI: confidence interval.
[a]With no concurrent relapse from 30 days prior to reference score until indicated time after the increase in EDSS score.

disability progression unrelated to relapse (measured here using a roving window of EDSS assessment over an approximate 1-year period) may represent a reliable clinical diagnostic signature for SPMS. A defining feature of SPMS is ongoing disability progression, and our analysis assesses only the first on-study progression event. It is possible that "disability progression unrelated to relapse" as identified here was in fact due to a subclinical relapse in some patients. However, because the current definition of SPMS includes patients with or without occasional relapses,[6] patients with progression occurring over ⩾24 weeks and even more so over ⩾48 weeks would meet the current SPMS criteria. In parallel to the conventional definition of SPMS phenotype, such time-to-event analysis of confirmed disability progression unrelated to relapse could lead to a more sensitive and specific metric-based evaluation of SPMS onset and/or SPMS disease course.

The greater sensitivity of this assessment could allow detection of treatment effects in sample sizes that are smaller than those typically needed to assess disability progression. In this work, the sensitivity to detect events of EDSS worsening and progression unrelated to relapses refers to the greater ability of a roving EDSS methodology to identify disability change. This should be distinguished from the conventional definition of "sensitivity" used in the context of diagnostic tests, which refers more specifically to the proportion of true positives identified.[17]

Using a roving EDSS reference system to analyze specific baseline patient characteristics suggests that being part of the older age group but not disease duration or baseline EDSS score increased the risk of progression. This finding is consistent with the stronger correlation of age as compared to EDSS score or disease duration with risk of SPMS onset described in previous studies.[12–14] The similar number of events detected when applying more stringent criteria for confirmation intervals and absence of relapse should increase confidence in the specificity of this measure.

A limitation of this analysis is that, as with any assessment of disability progression, data are missing due to missing patient visits.

Caution is necessary if our proposed approach to the assessment of disability progression events unrelated to relapses was to be applied in the setting of comparative trials in patients with RRMS because of the bias related to the influence of post-randomization factors. For instance, any post-baseline change in relapse rate and/or improvement/decrease in EDSS due to differential treatment effects would impact sensitivity to detect subsequent progression events. This potential bias would need to be taken into account in the predefined statistical analysis plan and more importantly in the interpretation of the results. Implementation of adequate marginal structural models to account for post-randomization time-varying factors and interval censoring around the occurrence of relapses could help to reduce imbalance in the cumulative epoch time in which patients are at risk of disability progression events unrelated to relapse. Such prospectively implemented measures would reduce but not completely eliminate bias. This taken into account, the use of a roving reference system to

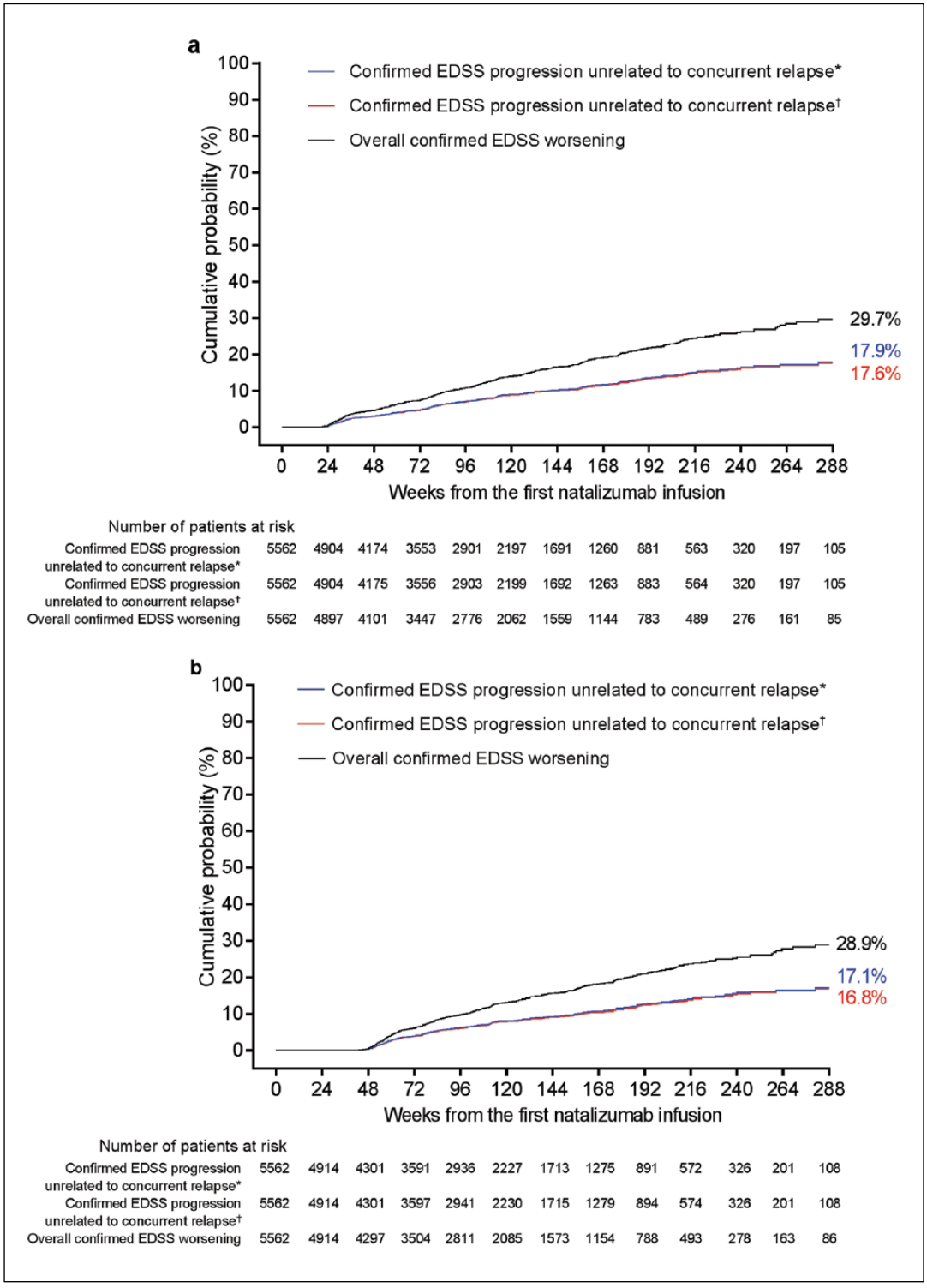


Figure 4. Cumulative probabilities (Kaplan–Meier analysis) of 24-week-confirmed Expanded Disability Status Scale (EDSS) overall worsening or progression and of 24-week-confirmed EDSS progression unrelated to relapses using sensitivity analysis criteria (roving baseline confirmed at 12 weeks). Kaplan–Meier plots show the cumulative probability of events occurring between two EDSS assessments: (a) ⩾24 weeks apart or (b) ⩾48 weeks apart.

*Defined as a relapse that was recorded from ⩽30 days prior to the reference EDSS assessment to ⩽30 days post progression assessment.

†Defined as a relapse that was recorded from ⩽30 days prior to the reference EDSS assessment to ⩽12 weeks post progression assessment.

Table 3. Cumulative probabilities (Kaplan–Meier analysis) at 288 weeks of confirmed EDSS worsening or progression unrelated to relapse using a roving EDSS reference value and stratified by the baseline characteristics of age, EDSS score, number of relapses in the prior year, and MS disease duration.

Cumulative probability, % (95% CI)	Overall confirmed EDSS worsening		Confirmed EDSS progression unrelated to relapse[a]			
			⩽30 days		⩽12 weeks	
	Primary analysis	Sensitivity analysis	Primary analysis	Sensitivity analysis	Primary analysis	Sensitivity analysis
Age ⩽37 years (n=2932)						
EDSS assessments ⩾24 weeks apart	31.8 (27.4–36.1)	25.5 (21.5–29.6)	18.9 (15.8–22.0)	12.6 (10.3–14.9)	18.4 (15.4–21.5)	12.2 (10.0–14.5)
EDSS assessments ⩾48 weeks apart	30.2 (26.0–34.5)	25.0 (21.0–29.1)	16.6 (13.7–19.5)	11.8 (9.5–14.1)	16.3 (13.4–19.2)	11.5 (9.2–13.7)
Age >37 years (n=2630)						
EDSS assessments ⩾24 weeks apart	42.8 (37.6–48.0)	34.3 (29.3–39.3)	30.6 (25.9–35.3)	23.8 (19.4–28.2)	30.3 (25.6–35.0)	23.5 (19.2–27.9)
EDSS assessments ⩾48 weeks apart	39.9(34.8–45.1)	33.2 (28.2–38.2)	27.5 (23.0–32.1)	23.1 (18.7–27.5)	27.2 (22.6–31.7)	22.7 (18.3–27.1)
EDSS score ⩽3.5 (n=3202)						
EDSS assessments ⩾24 weeks apart	35.3 (30.7–40.0)	28.9 (24.4–33.3)	24.0 (20.1–27.9)	17.8 (14.3–21.2)	23.6 (19.7–27.4)	17.5 (14.1–20.9)
EDSS assessments ⩾48 weeks apart	33.4 (28.8–38.0)	28.1 (23.7–32.5)	21.6 (17.8–25.4)	17.2 (13.8–20.7)	21.4 (17.6–25.2)	17.0 (13.6–20.4)
EDSS score >3.5 (n=2353)						
EDSS assessments ⩾24 weeks apart	39.8 (34.4–45.2)	31.1 (26.2–35.9)	25.3 (21.2–29.4)	18.2 (14.7–21.6)	25.0 (20.8–29.1)	17.8 (14.3–21.3)
EDSS assessments ⩾48 weeks apart	37.2 (31.9–42.4)	30.3 (25.4–35.2)	22.1 (18.4–25.9)	17.1 (13.6–20.6)	21.6 (17.8–25.4)	16.6 (13.1–20.1)
Relapses in the prior year <2 (n=1959)						
EDSS assessments ⩾24 weeks apart	40.6 (34.6–46.6)	32.5 (27.1–37.9)	28.3 (23.4–33.1)	21.6 (17.4–25.9)	27.8 (23.0–32.6)	21.5 (17.2–25.7)
EDSS assessments ⩾48 weeks apart	37.5 (31.8–43.3)	31.6 (26.2–37.0)	25.1 (20.7–29.6)	20.9 (16.7–25.2)	24.8 (20.4–29.3)	20.7 (16.4–24.9)
Relapses in the prior year ⩾2 (n=3602)						
EDSS assessments ⩾24 weeks apart	35.3 (31.1–39.6)	28.1 (24.2–32.1)	22.5 (19.0–26.0)	15.9 (12.9–18.9)	22.2 (18.7–25.6)	15.6 (12.6–18.5)
EDSS assessments ⩾48 weeks apart	33.5 (29.3–37.7)	27.5 (23.5–31.5)	20.1 (16.7–23.5)	15.2 (12.2–18.2)	19.7 (16.3–23.1)	14.8 (11.8–17.8)
MS disease duration ⩽7 years (n=2732)						
EDSS assessments ⩾24 weeks apart	35.4 (30.2–40.6)	27.5 (23.0–32.0)	23.8 (19.1–28.6)	17.0 (13.0–21.0)	23.6 (18.9–28.4)	16.8 (12.8–20.9)
EDSS assessments ⩾48 weeks apart	32.7 (27.8–37.7)	27.0 (22.5–31.6)	21.1 (16.6–25.6)	16.4 (12.4–20.5)	20.8 (16.3–25.3)	16.2 (12.2–20.2)
MS disease duration >7 years (n=2813)						
EDSS assessments ⩾24 weeks apart	38.5 (33.8–43.2)	31.6 (26.9–36.2)	25.1 (21.8–28.5)	18.7 (15.7–21.7)	24.5 (21.2–27.9)	18.3 (15.3–21.3)
EDSS assessments ⩾48 weeks apart	36.7 (32.0–41.4)	30.6 (26.0–35.2)	22.6 (19.2–25.9)	17.8 (14.9–20.8)	22.1 (18.8–25.4)	17.4 (14.4–20.4)

EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; CI: confidence interval.
[a]With no concurrent relapse from 30 days prior to reference score until indicated time after the EDSS score increase.

more accurately capture confirmed disability worsening or progression unrelated to relapse could be applied beyond the EDSS to other clinical disability outcome measures such as the Timed 25-Foot Walk, the 9-Hole Peg Test, low contrast letter acuity, cognitive function testing,[18–21] or multicomponent endpoints using various combinations of the above.[22]

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