

# Transition to Non-active Secondary Progressive Multiple Sclerosis (SPMS) After up to 9.5 Years of Natalizumab Treatment in the Real-World TYSABRI Observational Program (TOP)

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American Academy of Neurology Annual Meeting, 2020

**Disclosures:** This study was sponsored by Biogen (Cambridge, MA). LK (institution (University Hospital Basel) received and used exclusively for research support steering committee, advisory board, consultancy fees from Actelion, Addex, Bayer HealthCare, Biogen, Biotech, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Recaptos, Sanofi, Santhera, Siemens, Teva, UCB, Xenoport; speaker fees from Bayer HealthCare, Biogen, Merck, Novartis, Sanofi, Teva; support of educational activities from Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi, Teva; grants from Bayer HealthCare, Biogen, F. Hoffmann-La Roche, Merck, Novartis, the European Union, Inno-Swiss, the Roche Research Foundations, the Swiss Multiple Sclerosis Society, the Swiss National Research Foundation. HB: institution (Monash University) received compensation for consulting, talks, advisory/steering board activities from Alfred Health, Biogen, Genzyme, Merck, Novartis; research support from Biogen, Merck, MS Research Australia, National Health and Medical Research (Australia), Novartis, the Oxford Health Policy Forum, the Pennycook Foundation, Roche. MT: compensation for consulting from Biogen, Merck, Serono, Novartis, Roche; speaker honoraria from Biogen, Merck, Serono, Novartis, Roche, Sanofi, Genzyme, Teva; research grants from Biogen, Merck, Serono, Novartis, Roche. HW: honoraria from AbbVie, Actelion, Alexion, Biogen, Cognomed, Evgen, F. Hoffmann-La Roche, MedDay, Merck, Serono, Novartis, Roche Pharma AG, Sanofi, Genzyme, Teva; research support from Biogen, GlaxoSmithKline GmbH, Roche Pharma AG, Sanofi. TS: honoraria for consultancy and funding for travel from Biogen, Novartis. SB, RS, NC, SL: employees of and own stock and/or stock options in Biogen. P-RH: former employee of Biogen; may own stock and/or stock options in Biogen.

**Acknowledgments:** Biogen provided funding for medical writing and editorial support in the development of this poster; Alexandra D'Agostino, Ph.D, of Ashfield Healthcare Communications (Middletown, CT) wrote the first draft of the poster based on input from authors, and Joshua Safran of Ashfield Healthcare Communications copyedited and styled the poster per congress requirements. Biogen reviewed and provided feedback on the poster to the authors. The authors provided final approval of all content.



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- To explore the transition to non-active secondary progressive multiple sclerosis (SPMS) in patients with relapsing-remitting multiple sclerosis (RRMS) treated with natalizumab in the TYSABRI Observational Program (TOP).



## Conclusions

- In TOP, rates of transitioning to 4 exploratory definitions of non-active SPMS were documented using stringent criteria to ensure relapse-free progression events.
  - Across the 4 definitions, 11.8%–16.2% of patients met the criteria for non-active SPMS after a mean follow-up time of 5.2 years
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1. Ontaneda D, et al. *Lancet Neurol.* 2015;14:208-223. 2. Lublin FD, Reingold SC. *Neurology.* 1996;46:907-911. 3. Tremlett H, et al. *Mult Scler.* 2008;14:314-324;

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Introduction



Methods



Results



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American Academy of Neurology Annual Meeting, 2020

## Introduction

- The majority of patients with relapsing-remitting multiple sclerosis (RRMS) transition to SPMS.<sup>1,2</sup>
  - SPMS may be active, as determined by the presence of clinical relapses and/or magnetic resonance imaging activity, or non-active.<sup>3</sup>
- Previous studies have attempted to define the criteria for the transition from RRMS to SPMS, but none of these definitions has been widely accepted.<sup>4</sup>
- TOP is the largest real-world study of patients with RRMS treated with natalizumab and still ongoing, .<sup>5</sup>
  - In TOP, long-term natalizumab treatment was associated with low rates of disability worsening<sup>6</sup> and a low probability of reaching major EDSS milestones.<sup>7</sup>
- This analysis of TOP explored confirmed disability progression that was neither preceded nor followed by relapse, suggestive of a transition from relapsing MS to non-active (ie, non-relapsing) disease.

1. Murray T. *BMJ*. 2006;332:525-527; 2. Doshi A, Chataway J. *Clin Med (Lond)*. 2017;17:530-536; 3. Lublin FD, et al. *J Neurol*. 2014;83:278-286; 4. Lorscheider J, et al. *Brain*. 2016;139:2395-2405; 5. Butzkueven H, et al. *J Neurol Neurosurg Psychiatry*. 2020. In press. doi:10.1136/jnnp-2019-322326; 6. Kappos L, et al. Presented atECTRIMS; October 10–12, 2018; Berlin, Germany; 7. Trojano M, et al. *Mult Scler Relat Disord*. 2018;24:11-19.

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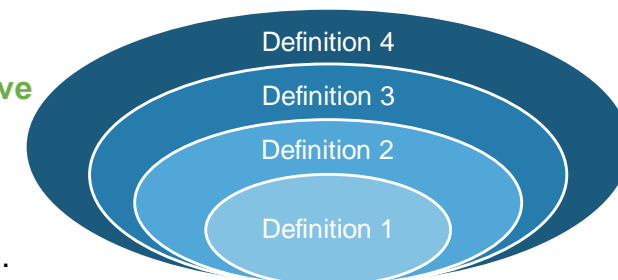
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## Methods

- RRMS patients enrolled in TOP as of November 2018 with baseline and  $\geq 3$  additional EDSS measurements were included.
  - To capture relapse-free progression events, EDSS scores were rebaselined after the last reported relapse.
- Kaplan-Meier–estimated cumulative probabilities of transitioning to non-active SPMS were assessed with 4 exploratory definitions.
  - All definitions required a 1.0-point increase from an EDSS score  $\leq 5.5$  or a 0.5-point increase from an EDSS score of  $\geq 6.0$  that occurred in the absence of relapse, was confirmed  $\geq 3$  months later, and resulted in either:
    - An overall EDSS score  $\geq 4.0$  along with a minimum pyramidal functional system score  $\geq 2$  (adapted from the definition used by Lorscheider et al<sup>1</sup>);
    - An overall EDSS score  $\geq 4.0$ ;
    - An overall EDSS score  $\geq 3.0$ ; or
    - No specific EDSS threshold.

**Figure 1. Overlap between non-active SPMS definitions**



- Non-active SPMS definitions were nested as indicated in Figure 1.
- Predictors of meeting a definition of non-active SPMS were identified using a Cox proportional hazards model that included the following covariates: age (10-year increase), sex, baseline EDSS score, the number of relapses in the 12 months prior to study initiation, the number of prior DMTs (including any natalizumab exposure prior to enrollment in TOP), disease duration (time from symptom onset), and the last DMT used.
- To assess potential variability in the frequency of EDSS measurements, the mean (standard deviation [SD]) time between consecutive EDSS measurements during natalizumab treatment was calculated for each patient.
- The time for  $\geq 50\%$  of patients to reach definition 1 of non-active SPMS following disease onset was extrapolated with Kaplan-Meier estimates and compared with a previously published natural history cohort.<sup>2</sup>
  - Because the Kaplan-Meier curve showed a fairly linear trend, a linear extrapolation was used for this survival analysis.

DMT=disease-modifying therapy.

1. Lorscheider J, et al. *Brain*. 2016;139:2395-2405; 2. Tremlett H, et al. *Mult Scler*. 2008;14:314-324.



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# Results (1 of 3)

## Patient characteristics

- Of the 6295 patients enrolled in TOP, 3871 were included in these analyses, with a mean (SD) time between EDSS evaluations of 6.6 (2.2) months.
- Across the 4 definitions, 11.8%–16.2% of patients met the criteria for non-active SPMS (Table 1).
  - The mean follow-up time across all 4 definitions was 5.2 years.
- Patients who met a non-active SPMS definition were older at study baseline and had longer disease duration, higher EDSS scores, fewer relapses in the year prior to treatment initiation, and more prior DMTs than patients who did not meet a non-active SPMS definition (Table 1).
  - However, only baseline age (hazard ratio [HR]=1.038; 95% confidence interval [CI], 1.027–1.049; *P*<0.0001) and EDSS score (HR=1.394; 95% CI, 1.310–1.484; *P*<0.0001) were significant predictors of meeting a definition of non-active SPMS.

Table 1. Baseline characteristics in patients who did or did not meet each non-active SPMS definition

Characteristic	Definition 1		Definition 2		Definition 3		Definition 4	
	Met (n=458)	Not met (n=3413)	Met (n=489)	Not met (n=3382)	Met (n=562)	Not met (n=3309)	Met (n=629)	Not met (n=3242)
<b>Percentage of analysis population (N=3871)</b>	11.8	88.2	12.6	87.4	14.5	85.5	16.2	83.8
<b>Age, mean (SD), years</b>	42.1 (9.21)	37.0 (9.76)	41.9 (9.3)	36.9 (9.76)	41.2 (9.43)	36.9 (9.77)	40.3 (9.74)	37.0 (9.77)
<b>Female, n (%)</b>	306 (66.8)	2432 (71.3)	326 (66.7)	2412 (71.3)	377 (67.1)	2361 (71.4)	427 (67.9)	2311 (71.3)
<b>Disease duration at baseline, median (range), years</b>	10.5 (0.5–42.5)	7.3 (0.1–44.4)	10.1 (0.5–42.5)	7.3 (0.1–44.4)	9.6 (0.5–42.5)	7.3 (0.1–44.4)	9.2 (0.5–42.5)	7.4 (0.1–44.4)
<b>Baseline EDSS score, mean (SD)</b>	4.4 (1.39)	3.3 (1.59)	4.3 (1.41)	3.3 (1.59)	4.0 (1.53)	3.3 (1.59)	3.7 (1.75)	3.4 (1.56)
<b>Relapses in year prior to natalizumab initiation, mean (SD)</b>	1.8 (0.93)	2.0 (0.98)	1.8 (0.93)	2.0 (0.98)	1.9 (1.00)	2.0 (0.97)	1.8 (0.93)	2.0 (0.98)
<b>Prior DMTs, n (%)</b>								
0	29 (6.3)	302 (8.8)	34 (7)	297 (8.8)	46 (8.2)	285 (8.6)	56 (8.9)	275 (8.5)
1	250 (54.6)	1872 (54.8)	264 (54)	1858 (54.9)	308 (54.8)	1814 (54.8)	347 (55.2)	1775 (54.8)
≥2	179 (39.1)	1239 (36.3)	191 (39.1)	1227 (36.3)	208 (37)	1210 (36.6)	226 (35.9)	1192 (36.8)

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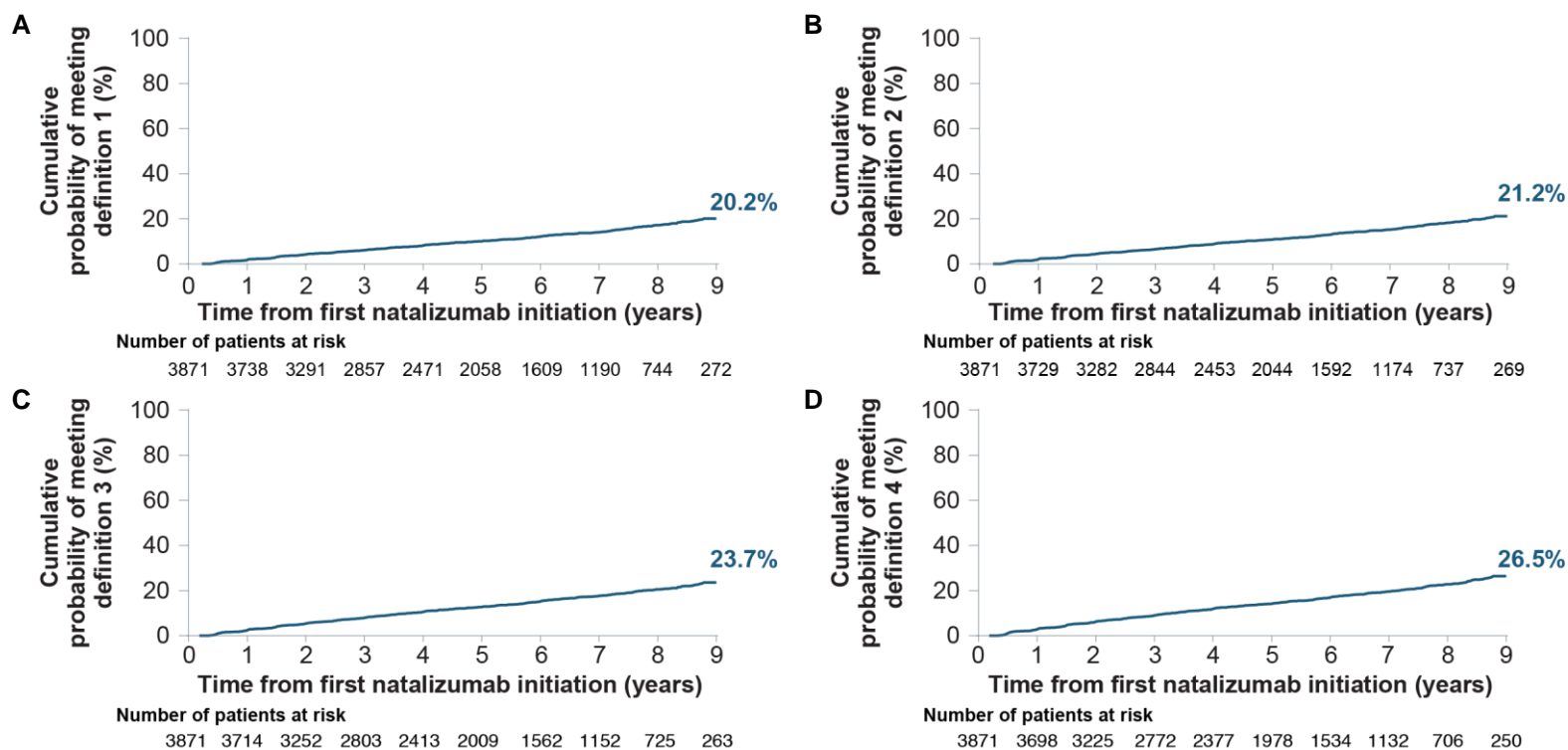


## Results (2 of 3)

### Cumulative probability of transition to non-active SPMS

- The cumulative probabilities of meeting each non-active SPMS definition over 9 years of study follow-up ranged from 20.2% to 26.5% (Figure 2A–D).
  - In those patients who transitioned to non-active SPMS, the mean (SD) time from enrollment in TOP to meeting a non-active SPMS definition ranged from 3.4 (2.3) to 3.6 (2.4) years.
  - Mean (SD) EDSS scores at the defining progression event ranged from 5.0 (1.7) to 5.8 (1.2).

Figure 2. Cumulative probability of meeting (A) definition 1, (B) definition 2, (C) definition 3, and (D) definition 4 of non-active SPMS



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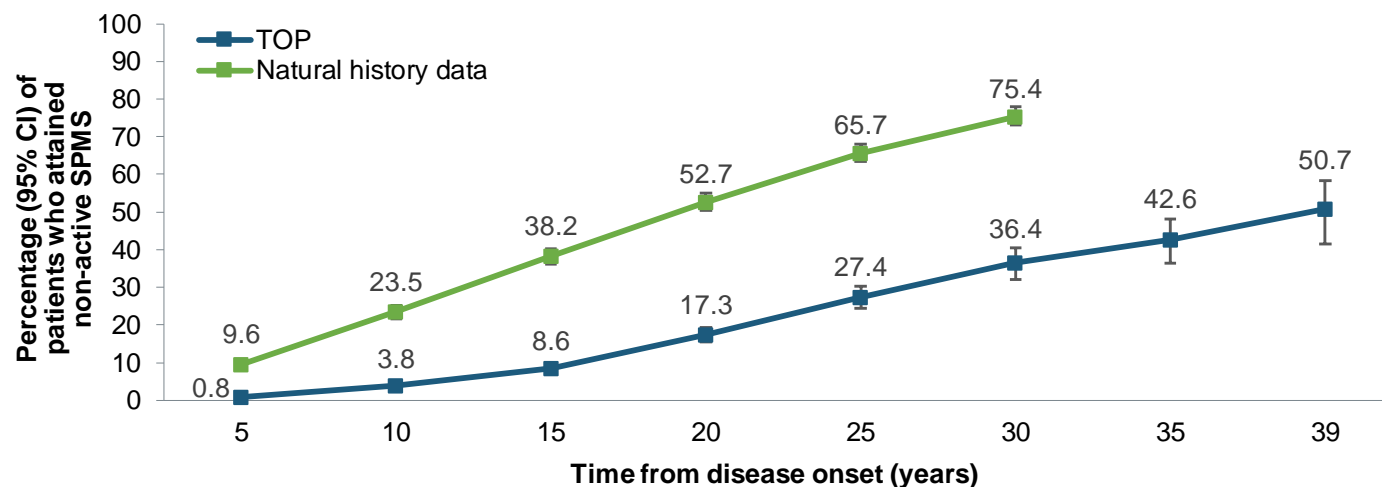
### Maintenance of progression

- Most patients (84.7%–87.5%) who met a definition of non-active SPMS maintained progression at the last available EDSS score while on natalizumab, which occurred a mean of 2.6 years after the progression event.
- The median last available EDSS score on treatment was 6.0 for all 4 definitions of non-active SPMS.

### Comparison with natural history

- In TOP, the estimated time for 50.7% of patients to meet definition 1 of non-active SPMS was 38.9 years from disease onset.
- At 30 years from disease onset, there was a 51.7% relative reduction in the proportion of natalizumab-treated patients who met definition 1 of non-active SPMS compared with natural history observations of SPMS (Figure 3).

Figure 3. Extrapolated proportion of patients who attained non-active SPMS<sup>a</sup> in TOP compared with natural history data<sup>b</sup>



<sup>a</sup>Non-active SPMS was assessed based on definition 1.

<sup>b</sup>Natural history data are from Tremlett et al.<sup>1</sup> SPMS was defined as an initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, or plateaus.<sup>2</sup>

1. Tremlett H, et al. *Mult Scler*. 2008;14:314-324; 2. Lublin FD, Reingold SC. *Neurology*. 1996;46:907-911.

