SUPPLEMENTARY MATERIAL

Additional Methodological Details – Secondary Analysis

For the secondary outcome of time to a confirmed and sustained EDSS score of 6.0, subjects were required to have at least one year of residency in BC following initiation of treatment ('Year 1'). There were additional residency and EDSS related requirements. Subjects were required to have at least two EDSS scores; one recorded during Year 1 (the baseline EDSS) and one after Year 1. For this time-to-event analysis, subjects were followed from the start of Year 2 until either the outcome was reached or the study end (Figure S1b). Adherence was estimated using the proportion of days covered (PDC) during Year 1. If the outcome was not reached, subjects were censored at their last recorded EDSS score, or at the preceding EDSS measurement if the last score was ≥6.0 and could not be confirmed as sustained.

Potential confounders for the multivariable Cox proportional hazards models included sex, age, EDSS, SES quintile, number of distinct prescription drug classes (fourth level of ATC classification), and Deyo's adaption of the Charlson comorbidity index, all measured during Year 1. Covariates were categorized, and selected for inclusion in the adjusted model, using the same approach as for the primary analyses.

Results from the secondary analysis

The secondary analysis, examining the association between IMD adherence and time to sustained EDSS 6.0, included 673 MS subjects. Similar to results from the primary analysis,

SES, prescription drug exposure and the comorbidity index were not significantly associated with time to sustained EDSS 6. After adjustment for sex, age, and baseline EDSS, optimal adherence was not found to be associated with the hazard of reaching sustained EDSS 6.0 (adjusted hazard ratio (adjHR) 0.91; 95% CI 0.57 – 1.44) (Table S1). A shorter time to the disability outcome was associated with increased age [adjHR 1.02; 95% CI 1.00 – 1.05] and with higher baseline EDSS [adjHR 1.49; 95% CI 1.33 – 1.68].

Results from the sensitivity analyses

A total of 634 subjects were included in the sensitivity analysis, in which the effects of IMD adherence on disability accumulation were examined only over the period that the subject was still 'on drug'. Optimal adherence was not associated with disability accumulation (adjusted odds ratio (adjOR) 1.06; 95% CI 0.81 – 1.39) (Table S2).

A total of 801 subjects were included in the sensitivity analysis where the lowest, rather than highest, score was used as the outcome EDSS when multiple EDSS scores were recorded in a single one-year interval. Consistent with the primary analysis, optimal adherence was not associated with disability accumulation (adjOR 1.03; 95% CI 0.84 – 1.26), (Table S2).

When we examined the association between first year adherence and disability accumulation in only those subjects with both reference and outcome EDSS scores available for every year between the index date and study end date, a total of 703 were included in this analysis.

Consistent with previous findings, optimal adherence was not associated with disability accumulation (adjOR 1.12; 95% CI 0.87 – 1.44).

Table S1. Association between IMD adherence anD disability accumulation: findings based on Cox Proportional Regression analysis of time to sustained EDSS 6 (n=673)

Factors	**Hazard Ratios [a] (95% Confidence Intervals)**	
	Univariate Analysis	**Multivariable Analysis[b]**
Level of adherence (PDC)		
'Suboptimal' (<80%)	1	1
'Optimal' (≥80%)	0.84 (0.53 – 1.33)	0.91 (0.57 – 1.44)
Sex		
Female	1	1
Male	1.49 (0.97 – 2.31)	1.20 (0.77 – 1.88)
Baseline age, years	1.03 (1.01 – 1.06)	1.02 (1.00 – 1.05)
Baseline EDSS	1.53 (1.37 – 1.71)	1.49 (1.33 – 1.68)

Abbreviations: EDSS, Expanded Disability Status Scale; PDC, proportion of days covered.

[a]Hazard ratio > 1 indicated an increased hazard of disability accumulation.

[b]Model adjusted for age, sex, and baseline EDSS

Table S2. Association between IMD adherence and disability accumulation: findings from the three sensitivity analyses

Factors	**Odds Ratios [a] (95% Confidence Intervals)**	
	Univariate Analysis	**Multivariable Analysis**
[b]*Analysis 1: Follow-up continued only during exposure to first-line injectable IMDs (n=634)*		
Level of adherence (PDC)		
'Suboptimal' (<80%)	1	1
'Optimal' (≥80%)	1.04 (0.80 – 1.34)	1.06 (0.81 – 1.39)
Analysis 2: When multiple EDSS scores were available in a given year, the lowest (rather than highest) was selected (n=801)		
Level of adherence (PDC)		
'Suboptimal' (<80%)	1	1
'Optimal' (≥80%)	1.02 (0.84 – 1.23)	1.03 (0.84 – 1.26)
[c]*Analysis 3: EDSS scores were not carried forward (only patients with both reference and outcome EDSS scores for every year between the index date and study end were included, n= 703)*		
Level of adherence (PDC)		
Suboptimal (<80%)	1	1
Optimal (≥80%)	1.16 (0.91 - 1.48)	1.12 (0.87 – 1.44)

Abbreviations: EDSS, Expanded Disability Status Scale; PDC, proportion of days covered; IMD, immunomodulatory drug.

Each model was adjusted for sex, baseline age, baseline EDSS, and time between the reference and outcome EDSS.

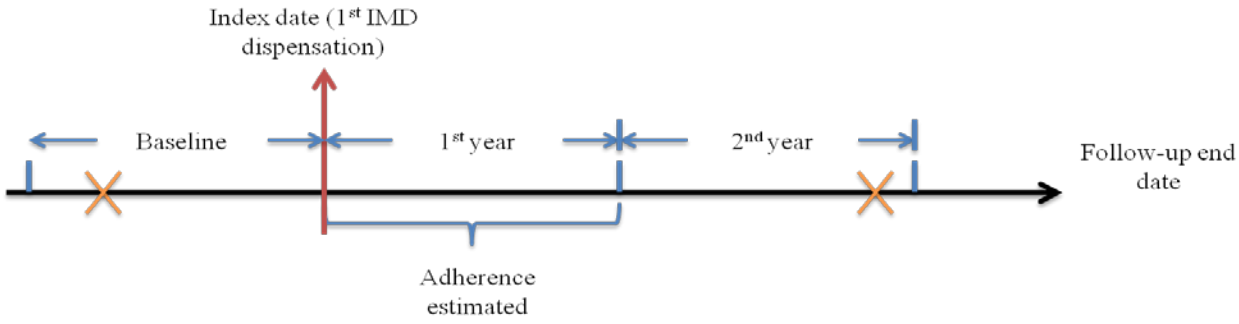
[a]OR>1 indicated an increased likelihood of disability accumulation; hazard ratio >1 indicated an increased hazard of disability accumulation.

[b]Analysis 1: Subjects were followed until the last available EDSS before: first-line IMD discontinuation, initiation of a non-first line IMD, MS drug clinical trial registration, or December 31, 2008. There were 167 fewer subjects included in this sensitivity analysis compared to the primary analysis because these individuals discontinued their first-line injectable IMD before the start of Year 2 (i.e. no follow-up EDSS assessments were available prior to drug discontinuation).

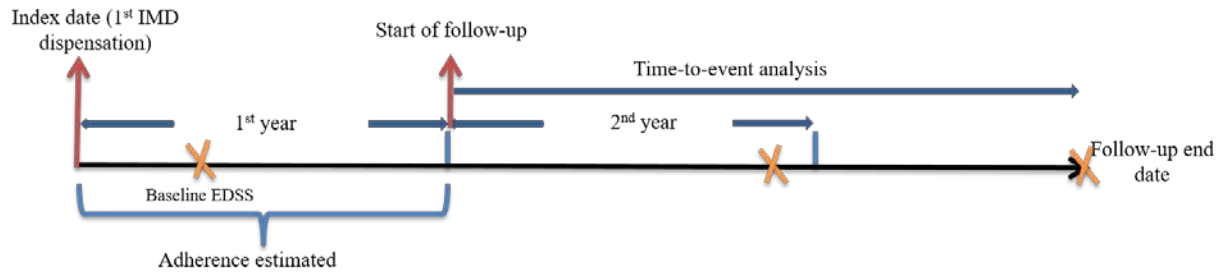
[c]Analysis 3: There were 98 fewer subjects included compared to the primary analysis because these individuals did not have at least one EDSS score available in each one year interval between the index date and the study end date.

Figure S1. Measurement of the study exposure (adherence) and outcomes (disability accumulation and the sustained disability milestone, EDSS 6.0)

a. Primary analysis:



b. Secondary analysis:



Notes:

X indicates a recorded EDSS score.

Subjects were followed from their index date (date of the first IMD dispensation) until the last available EDSS score recorded prior to the study end.

a. For the primary analysis, adherence was measured during Year 1. EDSS scores were examined during each one-year interval from Year 2 onwards to determine if disability accumulation had occurred (yes/no) relative to the previous year (the reference interval). The effects of IMD adherence on subsequent disability accumulation were examined using generalized estimating equations.

If no EDSS score was available during the reference interval, the EDSS score from the most recent interval (including the baseline year) with a recorded EDSS score was used as the reference. In Figure 1a, for example, as an EDSS score was not available during Year 1, the baseline EDSS served as the reference for the EDSS score during Year 2.

b. For the secondary analysis, adherence was measured during Year 1. Time from the beginning of Year 2 (start of follow-up) to a confirmed and sustained EDSS score of 6.0 was modeled using multivariable Cox proportional hazards regression models, which were adjusted for sex and age at the start of Year 2, and Year 1 (baseline) EDSS. In the situation where a patient reached EDSS 6.0 at their last assessment, but this was not confirmed by another score of EDSS >= 6.0 after at least 180 days, the patient was censored at the preceding EDSS assessment.