**Web-only files**

**Appendix 1:** BENEFIT Study Group
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Szczudlik (Krakow), K Selmaj (Lodz), Z Stelmasiak (Lublin), R Podemski (Wroclaw), Z Maciejek (Bydgoszcz); *Portugal* L Cunha (Coimbra); *Slovenia* S Sega-Jazhee (Ljubljana); *Spain* X Montalbán, T Arbizu, A Saiz (Barcelona), J Barcena (Barakaldo), R Arroyo (Madrid), O Fernandez (Malaga), G Izquierdo (Seville), B Casanova (Valencia); *Sweden* J Lycke, (Mölndal); *Switzerland* L Kappos (Basel), H Mattle (Bern), K Beer (St. Gallen); *United Kingdom* R Coleman (Aberdeen), J Chataway (London), J O'Riordan (Dundee), S Howell (Sheffield).

Steering committee: G Edan, M Freedman, H-P Hartung, L Kappos, DH Miller, X Montalbán, CH Polman, L Bauer, M Ghazi, C Pohl, R Sandbrink.

Eligibility review committee: CH Polman, F Barkhof, B Uitdehaag.

CDMS confirmation committee: L Kappos, A de Vera, S Wu.

Central MRI analysis: F Barkhof, E-W Radue.

Independent advisory board: HF McFarland, J Kesselring, AJ Petkau, KV Toyka.

**Appendix 2:** statistical modeling procedures

Statistical modeling procedures were used to estimate treatment effects and explore the relationships of target variables to treatment and prognostic covariates that were determined at the start of the study. Analyses that used covariates that were part of the minimization process for assigning study treatment in BENEFIT were based on the covariate information in case report forms (CRFs). Efficacy analyses were performed in the full analysis set, which included all subjects with at least one administration of study drug during the BENEFIT study. Treatment groups were considered as randomized according to the minimization procedure regardless of the kind of study treatment received. Generally, efficacy analyses, including time to CDMS, were also performed for the subset of subjects with informed consent in the BENEFIT Extension study. The safety analysis set included all patients who had at least one administration of study drug during BENEFIT.

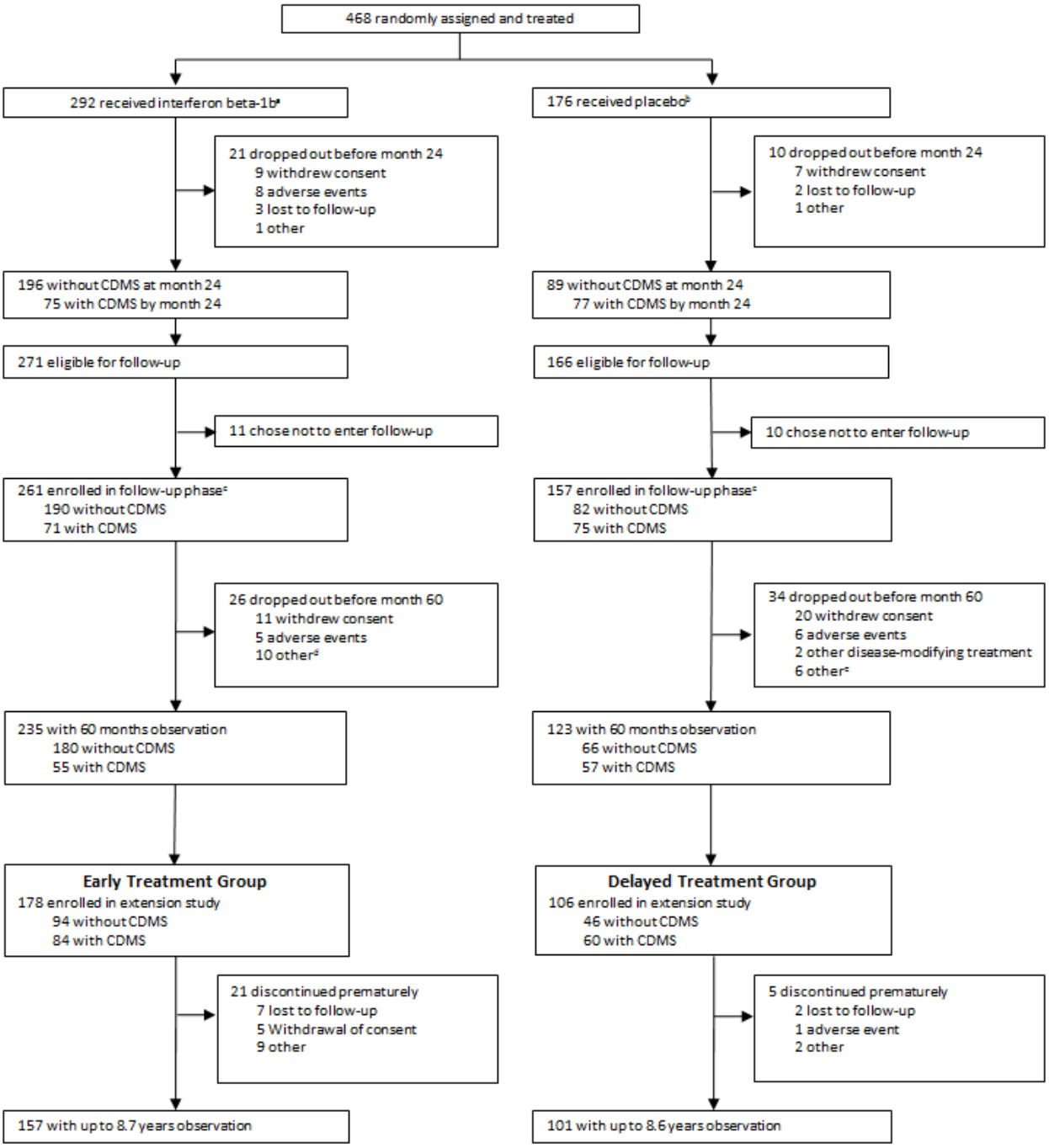
The following statistical methods were used in the data analysis:

- Time to CDMS, and first escalation therapy: Long-rank test (nonparametric method) and proportional hazards model (semi-parametric method) (covariates: randomized treatment in BENEFIT, steroid use during first event, type of disease onset, categorized number of T2 lesions on BENEFIT screening MRI)
- Annualized relapse rate: Generalized linear Poisson model (covariates: randomized treatment in BENEFIT, steroid use during first event, type of

disease onset, categorized number of T2 lesions on BENEFIT screening MRI)

- Recurrent relapses: Andersen-Gill model (covariates: randomized treatment in BENEFIT, steroid use during first event, type of disease onset, categorized number of T2 lesions on BENEFIT screening MRI)
- EDSS: Nonparametric longitudinal model (covariate: randomized treatment in BENEFIT, categorized BENEFIT baseline EDSS)
- MSFC: MSFC subtests, FAMS-TOI: Non-parametric longitudinal model (covariate: randomized treatment in BENEFIT), parametric longitudinal linear mixed model (covariates: randomized treatment in BENEFIT, BENEFIT baseline MSFC subtest)
- EQ-5D: Nonparametric longitudinal model (covariate: randomized treatment in BENEFIT)

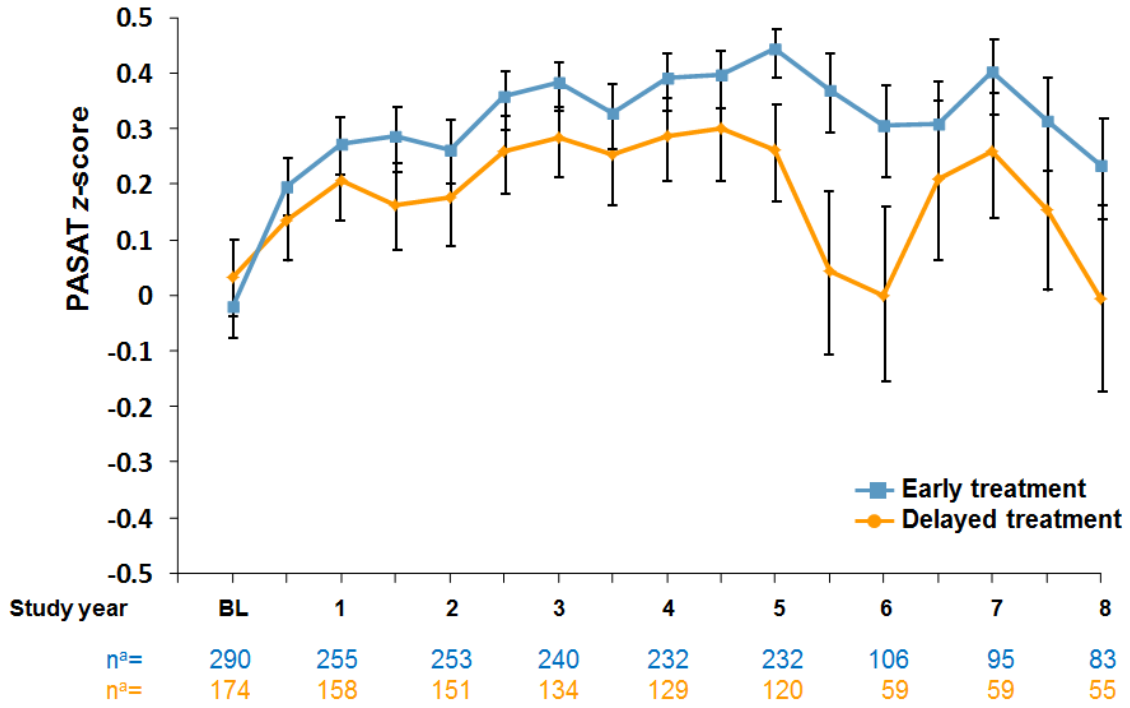
**Supplemental Figure 1:** Patient disposition in the placebo-controlled and extension phases of the BENEFIT study




CDMS, clinically definite multiple sclerosis.

[a]Includes 1 patient randomized to receive interferon beta-1b but treated with placebo. [b]Includes 1 patient randomized to receive placebo but treated with interferon beta-1b. [c]Includes 1 patient entered BENEFIT follow-up study after premature discontinuation of the BENEFIT study. [d]Four lost to follow-up, 2 missing data, 1 non-compliance, 1 treatment failure, 2 refused final visit. [e]3 lost to follow-up, 1 relocated away from site, 1 pregnancy, 1 unable to attend visit because of job.

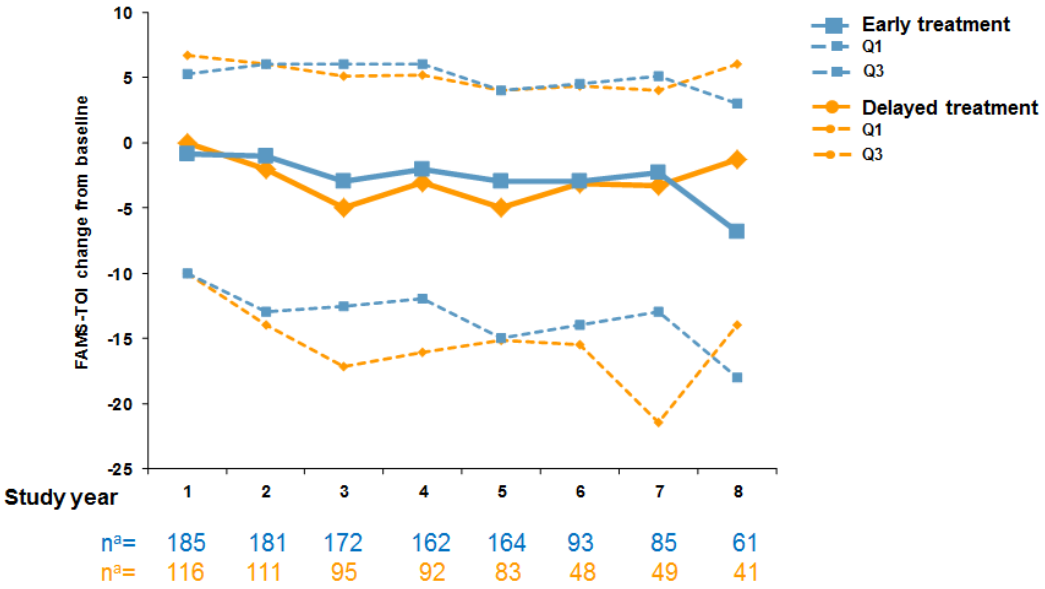
**Supplemental Figure 2:** Mean (SEM) PASAT *z* scores over the 8-year observational period in the total number of patients observed during each study year




PASAT, Paced Auditory Serial Addition Test; SEM, standard error of the mean.

[a]Number of patients providing data at the respective visit.

**Supplemental Figure 3:** Median FAMS-TOI change from baseline score in the total number of patients observed during each study year




FAMS-TOI, Functional Assessment of Multiple Sclerosis-Trial Outcome Index.

[a]Number of patients providing data at the respective visit.