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Original Research Paper

Improved cognitive outcomes in patients with relapsing–remitting multiple sclerosis treated with daclizumab beta: Results from the DECIDE study

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Abstract

Background: Cognitive impairment is common in multiple sclerosis (MS), with cognitive processing speed being the most frequently affected domain.

Objective: Examine the effects of daclizumab beta versus intramuscular (IM) interferon (IFN) beta-1a on cognitive processing speed as assessed by Symbol Digit Modalities Test (SDMT).

Methods: In DECIDE, patients with relapsing–remitting multiple sclerosis (RRMS) (age: 18–55 years; Expanded Disability Status Scale (EDSS) score 0–5.0) were randomized to daclizumab beta ($n=919$) or IM IFN beta-1a ($n=922$) for 96–144 weeks. SDMT was administered at baseline and at 24-week intervals.

Results: At week 96, significantly greater mean improvement from baseline in SDMT was observed with daclizumab beta versus IM IFN beta-1a ($p=0.0274$). Significantly more patients treated with daclizumab beta showed clinically meaningful improvement in SDMT (increase from baseline of ⩾3 points ($p=0.0153$) or ⩾4 points ($p=0.0366$)), and significantly fewer patients showed clinically meaningful worsening (decrease from baseline of ⩾3 points ($p=0.0103$)). Odds representing risk of worsening versus stability or improvement on SDMT were significantly smaller for daclizumab beta ($p=0.0088$ (3-point threshold); $p=0.0267$ (4-point threshold)). In patients completing 144 weeks of treatment, the effects of daclizumab beta were generally sustained.

Conclusion: These results provide evidence for a benefit of daclizumab beta versus IM IFN beta-1a on cognitive processing speed in RRMS.

Trial registration: ClinicalTrials.gov identifier NCT01064401 (Efficacy and Safety of BIIB019 (Daclizumab High Yield Process) Versus Interferon β 1a in Participants With Relapsing-Remitting Multiple Sclerosis (DECIDE)): https://clinicaltrials.gov/ct2/show/NCT01064401.

Keywords: Clinical trial, phase III, cognitive impairments, daclizumab, interferon beta-1a, multiple sclerosis, randomized controlled trial

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Introduction

Cognitive impairment impacts roughly 50% of the patients with multiple sclerosis (MS), and cognitive processing speed is the most frequently affected domain.[1] Cognitive impairment in MS correlates strongly with magnetic resonance imaging (MRI) measures of lesion burden[2] and brain atrophy[3] and affects occupational, social, and psychological functioning.[4] Thus, prevention of the development or worsening of cognitive decline is a therapeutic goal in MS.

Several studies examined the effect of MS disease-modifying therapies on neuropsychological tests.[5–11] Some of these studies were observational, such as Cognitive Impairment in Multiple Sclerosis, in which patients with relapsing–remitting multiple sclerosis (RRMS) initiating treatment with interferon (IFN)

beta were administered a battery of neuropsychological tests once yearly.[8] In patients treated with subcutaneous (SC) IFN beta-1a, risk of cognitive impairment was significantly reduced following 3 years of treatment with 44 µg compared with 22 µg dosing.[8] Only a few randomized, placebo-controlled phase III trials included neuropsychological tests.[5,12–15] In the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. Natalizumab significantly reduced the risk of confirmed progression of cognitive deficits compared with placebo, based on 0.5 standard deviation (SD) change on the 3-Second Paced Auditory Serial Addition Test (PASAT-3) sustained for 12 weeks.[11] In SENTINEL, there was no significant PASAT-3 effect of natalizumab co-administered with intramuscular (IM) IFN beta-1a compared with placebo co-administered with IM IFN beta-1a.[11] In a pooled analysis of FREEDOMS and FREEDOMS II, fingolimod (0.5 mg) demonstrated a significant benefit compared with placebo on change from baseline in PASAT scores after 6 months of treatment.[16] Finally, in the Multiple Sclerosis Collaborative Research Group trial, IM IFN beta-1a demonstrated a significant benefit compared with placebo over 2 years on a composite multi-domain neuropsychological test battery.[5]

Daclizumab beta (formerly daclizumab high-yield process, approved as ZINBRYTA®, which has a different form and structure than an earlier form of daclizumab) is a humanized monoclonal antibody against the interleukin 2 (IL-2) receptor alpha subunit (CD25).[17] In the randomized, double-blind, active-controlled, phase III DECIDE study, daclizumab beta 150 mg SC every 4 weeks showed superior efficacy on relapses, MRI outcomes, and 24-week confirmed disability progression compared with IFN beta-1a 30 µg IM once weekly over 96–144 weeks of treatment in patients with RRMS.[18] Cognitive outcomes were assessed using PASAT-3 as well as the Symbol Digit Modalities Test (SDMT),[19] a less frequently used but highly sensitive[20] and promising measure of cognitive processing speed in the visual modality. On both instruments, there was evidence for a benefit of daclizumab beta versus IM IFN beta-1a at week 96. As reported previously,[18] the increase from baseline in the PASAT-3 composite *z*-score was significantly different in daclizumab beta–treated patients (median (interquartile range), 0.177 (0.088, 0.530)) compared with IM IFN beta-1a–treated patients (0.177 (0.088, 0.442); $p = 0.04$) using an analysis of covariance model based on ranks, a non-parametric test that tests on a difference in the distribution and not solely on a difference in the means or medians.[21] Similarly, mean (SD) improvement from baseline in SDMT scores was significantly greater in daclizumab beta–treated patients (4.1 (12.4)) compared with IM IFN beta-1a–treated patients (2.9 [12.7]; $p = 0.0274$).[18]

Cutoffs to evaluate clinically meaningful change on the PASAT have not been established,[22] although 0.5 SD change on the PASAT-3 has been used as a non-clinically validated endpoint in some studies.[11] The SDMT does have proposed benchmarks for clinically meaningful change that are anchored to functional points of reference in the real-world setting, allowing for a richer analysis of responders and deteriorating cognitive status. A decline of 3–4 points in mean SDMT scores has been tied to mental status change during MS relapse as observed by patients, caregivers, or clinicians,[23] as well as decline in vocational status as defined by reduction in work responsibilities, early retirement, and/or receipt of disability benefits.[22]

Herein, we report an expanded analysis of the effects of daclizumab beta on cognitive processing speed as measured by the SDMT, examining the time course of improvement from baseline in SDMT scores—including effects at week 144—as well as odds of clinically meaningful change (3-point or 4-point change in SDMT score).

Method

Patients and study design

As described previously,[18] DECIDE (ClinicalTrials.gov identifier NCT01064401) enrolled patients with RRMS[24] 18–55 years of age, with Expanded Disability Status Scale (EDSS) score[25] 0–5.0, and one of the following: two or more clinical relapses within the previous 3 years, including at least one clinical relapse within 1 year prior to randomization, or one or more clinical relapse and one or more new lesion on MRI that was not associated with the clinical relapse within the previous 2 years, with at least one of these events occurring within 1 year prior to randomization. Exclusion criteria included MS relapse within 50 days prior to randomization; treatment with mitoxantrone, cyclophosphamide, fingolimod, or natalizumab within 1 year prior to randomization; or treatment with intravenous or oral corticosteroids or glatiramer acetate within 30 days prior to randomization.

Patients were randomized 1:1 to receive daclizumab beta 150 mg SC every 4 weeks and IM placebo once weekly or IM IFN beta-1a 30 µg once weekly and SC

placebo every 4 weeks for at least 96 weeks and no more than 144 weeks. The study was designed to end when the last enrolled patient completed the week 96 visit. Study visits occurred every 4 weeks and included clinical and safety assessments. Patients who permanently discontinued study treatment before week 140 had the option to initiate treatment with an approved open-label alternative MS medication. Changes from baseline to weeks 48 and 96 in SDMT and PASAT-3 scores were tertiary endpoints in the study.

All patients provided written informed consent. The study was approved by relevant central and local ethics committees and was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki.

SDMT

The oral response version of the SDMT was administered at baseline and at 24-week intervals thereafter. As described in prior MS studies,[20,26,27] the SDMT[19] presents a key consisting of nine abstract symbols paired with numbers ranging from 1 to 9 and a test consisting of a 120-item sequence (10 for learning) of abstract symbols presented in random order. Patients are asked to associate the symbols with the corresponding numbers as shown in the key, responding orally as quickly as possible. The number of correct responses (out of a maximum of 110) in 90 seconds was recorded, with higher scores indicating better performance.

Statistical analysis

The analyses were performed on data from the intention-to-treat (ITT) population, defined as all randomized patients who received at least one dose of study treatment. Patients with missing data for baseline covariates and observed data after patients switched to alternative MS medications were excluded.

Two approaches were used to analyze change from baseline on the SDMT. The statistical analysis plan specified that the data would be analyzed using an analysis of covariance model on the change from baseline after imputing missing data using a last observation carried forward (LOCF) approach. However, because the dropout rate in the IM IFN beta-1a group was higher earlier in the treatment period, the imputation method using LOCF was susceptible to bias; therefore, a post hoc analysis using a linear mixed model also was used and is presented here.[28] In this model, a likelihood-based method was used to estimate the treatment effect, and no explicit imputation on the missing data was performed. The analysis included observed data up to either the end of the study or use of alternative MS medication. Treatment was included as the fixed effect and individual specific time (visit) and intercept were included as random effects. Interaction terms were treatment and time, adjusting for baseline SDMT score, prior IFN beta use (yes, no) and baseline age ($\leqslant$35, >35 years). Treatment differences at each study visit were estimated from this model.

Patients were classified into three groups (worsened, stable, or improved) at week 96 based on validated thresholds for clinically meaningful change on the SDMT (3-point or 4-point changes from baseline).[22,23] For the 3-point threshold, worsening was defined as a change of $\leqslant -3$ points, stability was defined as a change of >-3 points and <3 points, and improvement was defined as a change of $\geqslant 3$ points. For the 4-point threshold, worsening was defined as a change of $\leqslant -4$ points, stability was defined as a change of >-4 points and <4 points, and improvement was defined as a change of $\geqslant 4$ points).

Treatment differences in the proportion of patients with SDMT worsening (yes vs no) were evaluated post hoc based on a generalized estimating equations (GEE) approach with a logistic model. The analysis was repeated to evaluate treatment differences in the proportion of patients with SDMT improvement. In addition, a repeated measures ordinal regression model using the GEE approach was also evaluated to compare changes in SDMT when categorized as worsened, stable, or improved. Models included treatment group, time, and treatment by time interaction, adjusting for baseline SDMT score, prior IFN beta use (yes, no), and baseline age ($\leqslant$35, >35 years). An unstructured working correlation matrix was used.

Results

Descriptive data

A total of 1841 patients were randomized (daclizumab beta, $n=919$; IM IFN beta-1a, $n=922$). All were included in the ITT population. Demographic and baseline MS disease characteristics were well balanced across treatment groups, as reported previously.[18] At baseline, in the daclizumab beta and IM IFN beta-1a groups, mean (SD) SDMT score was 48.5 (15.9) and 47.7 (16.1), respectively, and median (range) SDMT score was 49 (0–110) and 49 (3–110), respectively.

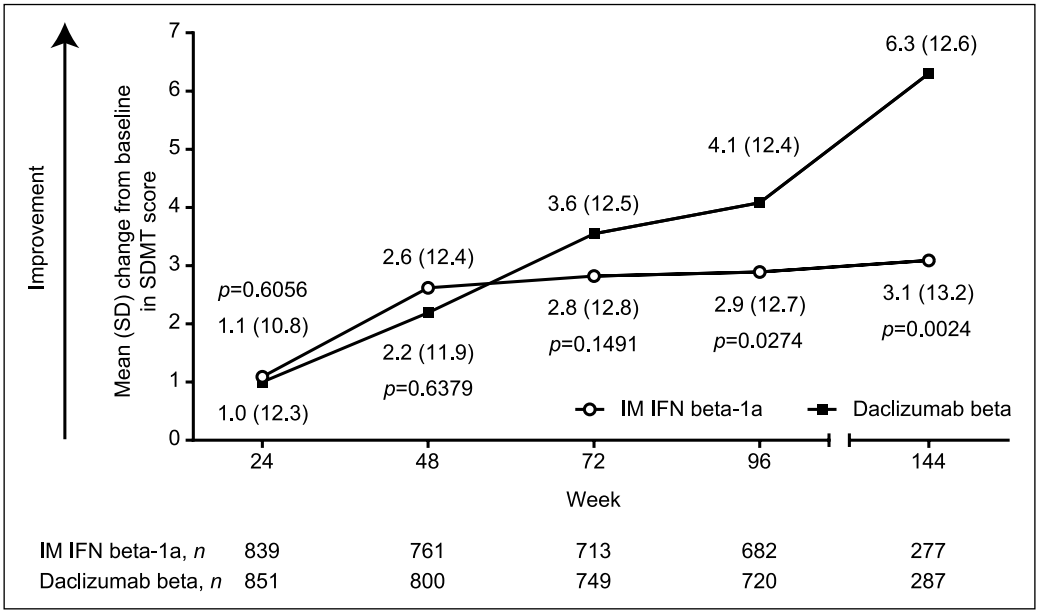

Figure 1. Mean change from baseline in Symbol Digit Modalities Test (SDMT) score at weeks 24, 48, 72, 96, and 144. Patients with available data for baseline covariates were included. Analyses were based on observed data with no imputation for missing data. IFN: interferon; IM: intramuscular; SD: standard deviation.

Group effects on SDMT

Based on the linear mixed model analysis approach, there was a significant group × time interaction ($p=0.0004$). Significantly greater mean improvement from baseline in SDMT scores was observed with daclizumab beta compared with IM IFN beta-1a at week 96 (mean (SD) change from baseline: 4.1 (12.4) vs 2.9 (12.7); $p=0.0274$), as reported previously (Figure 1).[18] This effect was sustained at week 144 (6.3 (12.6) vs 3.1 (13.2); $p=0.0024$) in a limited number of patients completing 144 weeks of treatment with available SDMT scores (daclizumab beta, $n=287$; IM IFN beta-1a, $n=277$).

Clinically meaningful change and responder analyses

In the GEE analysis, significantly more patients treated with daclizumab beta compared with IM IFN beta-1a showed clinically meaningful improvement, defined as a ⩾3-point increase on the SDMT, at week 96 (60.0% vs 54.1%; odds ratio (OR; 95% confidence interval, CI): 1.30 (1.05–1.62); $p=0.0153$) and week 144 (65.5% vs 52.0%; OR (95% CI): 1.60 (1.18–2.19); $p=0.0028$; Figure 2(a)). Similarly, significantly more patients treated with daclizumab beta showed a ⩾4-point increase at week 96 (55.4% vs 50.1%; OR (95% CI): 1.26 (1.01–1.56); $p=0.0366$) and week 144 (61.7% vs 48.4%; OR (95% CI): 1.53 (1.12–2.07); $p=0.0067$; Figure 2(b)).

Significantly fewer patients treated with daclizumab beta versus IM IFN beta-1a showed clinically meaningful worsening, defined as a ⩾3-point decrease on the SDMT at week 96 (19.4% vs 24.8%; OR (95% CI): 0.72 (0.56–0.92); $p=0.0103$; Figure 3(a)). There was a trend for significance at week 144 (18.8% vs 26.4%; OR (95% CI): 0.72 (0.50–1.03); $p=0.0754$). When clinically meaningful worsening was defined as a ⩾4-point decrease, there was a trend for significance at week 96 (17.5% vs 21.1%; OR: 0.78 (95% CI: 0.60–1.02); $p=0.0645$) and no significant difference between daclizumab beta and IM IFN beta-1a at week 144 (17.1% vs 23.5%; OR: 0.77 (95% CI: 0.53–1.12); $p=0.1719$; Figure 3(b)).

Based on the 3-point threshold, the percentage of patients exhibiting worsening, stability, and improvement at week 96 was 19.4%, 20.6%, and 60.0%, respectively, in the daclizumab beta group and 24.8%, 21.1%, and 54.1%, respectively, in the IM IFN beta-1a group (Figure 4(a)). Based on the 4-point threshold, the percentage of patients exhibiting worsening, stability, and improvement at week 96 was 17.5%, 27.1%, and 55.4%, respectively, in the daclizumab beta group and 21.1%, 28.7%, and 50.1%, respectively, in the IM IFN beta-1a group (Figure 4(b)). The OR (95% CI) for worsening and worsening or stable SDMT scores for daclizumab beta compared with IM IFN beta-1a was 0.75 (0.61–0.93; $p=0.0088$) for the 3-point threshold and 0.79 (0.64–0.97; $p=0.0267$) for the 4-point threshold.

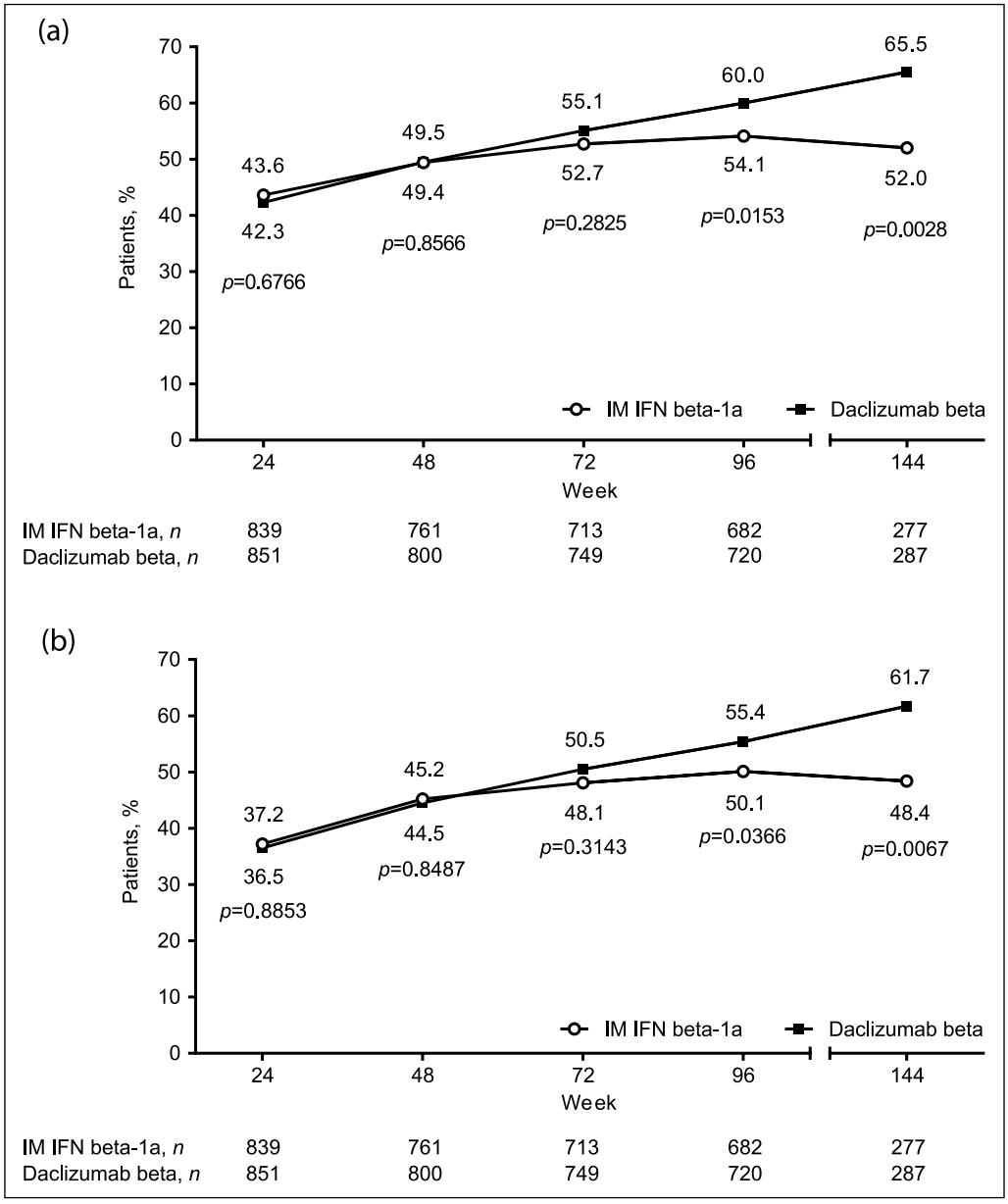

Figure 2. Percentage of patients with (a) ⩾3-point improvement or (b) ⩾4-point improvement in Symbol Digit Modalities Test score at weeks 24, 48, 72, 96, and 144. Patients with available data for baseline covariates were included. Analyses were based on observed data with no imputation for missing data. IFN: interferon; IM: intramuscular.

Discussion

Although cognitive deficits associated with MS are well-documented and contribute to functional disability and diminished quality of life,[4] relatively little is known about the effect of MS therapeutics on cognitive function. Even less is understood about treatment effects on the SDMT, a promising and increasingly touted[1] measure of cognitive processing speed that is accepted by patients and could be easily applied in a large phase III trial. The SDMT also has the advantage of proposed benchmarks for clinically meaningful change in test performance, most notably a 3-point to 4-point or greater change in scores.[22,23] Here, we report that daclizumab beta showed significantly greater benefits on the SDMT compared with IM IFN beta-1a over 96–144 weeks in a large cohort of patients with RRMS in the randomized double-blind phase III DECIDE study.[18]

As reported previously, mean improvement from baseline in SDMT scores was significantly greater in daclizumab beta–treated patients compared with IM

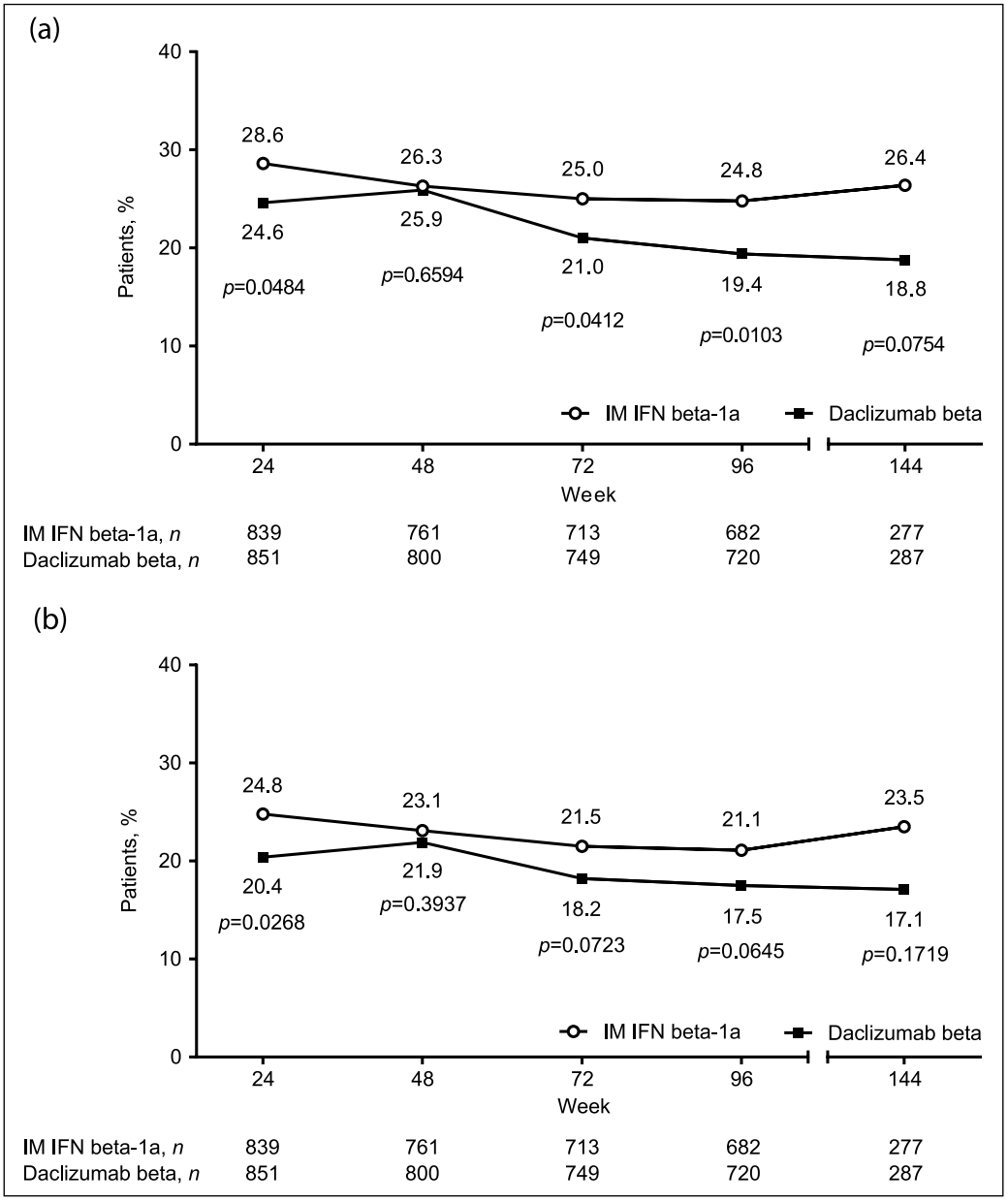

Figure 3. Percentage of patients with (a) ⩾3-point decline or (b) ⩾4-point decline in Symbol Digit Modalities Test score at weeks 24, 48, 72, 96, and 144. Patients with available data for baseline covariates were included. Analyses were based on observed data with no imputation for missing data. IFN: interferon; IM: intramuscular.

IFN beta-1a–treated patients at week 96.[18] Although not part of our primary discussion because of the much smaller number of patients at week 144 and concerns for selection bias, the superiority of daclizumab beta over IM IFN beta-1a appeared to persist at week 144. Using the 3-point responder definition, the odds of clinically meaningful improvement on the SDMT were significantly higher with daclizumab beta compared with IM IFN beta-1a at weeks 96 and 144, and the odds of clinically meaningful worsening were significantly lower at weeks 24, 72, and 96. Using the 4-point responder definition, the odds of clinically meaningful improvement on the SDMT were significantly higher with daclizumab beta compared with IM IFN beta-1a at weeks 96 and 144, and the odds of clinically meaningful worsening were significantly lower at week 24. These results provide evidence of not only a statistically significant benefit of daclizumab beta compared with IM IFN beta-1a in raw SDMT scores but also a clinically meaningful benefit in performance tied to a measurable functional deficit, highlighting the

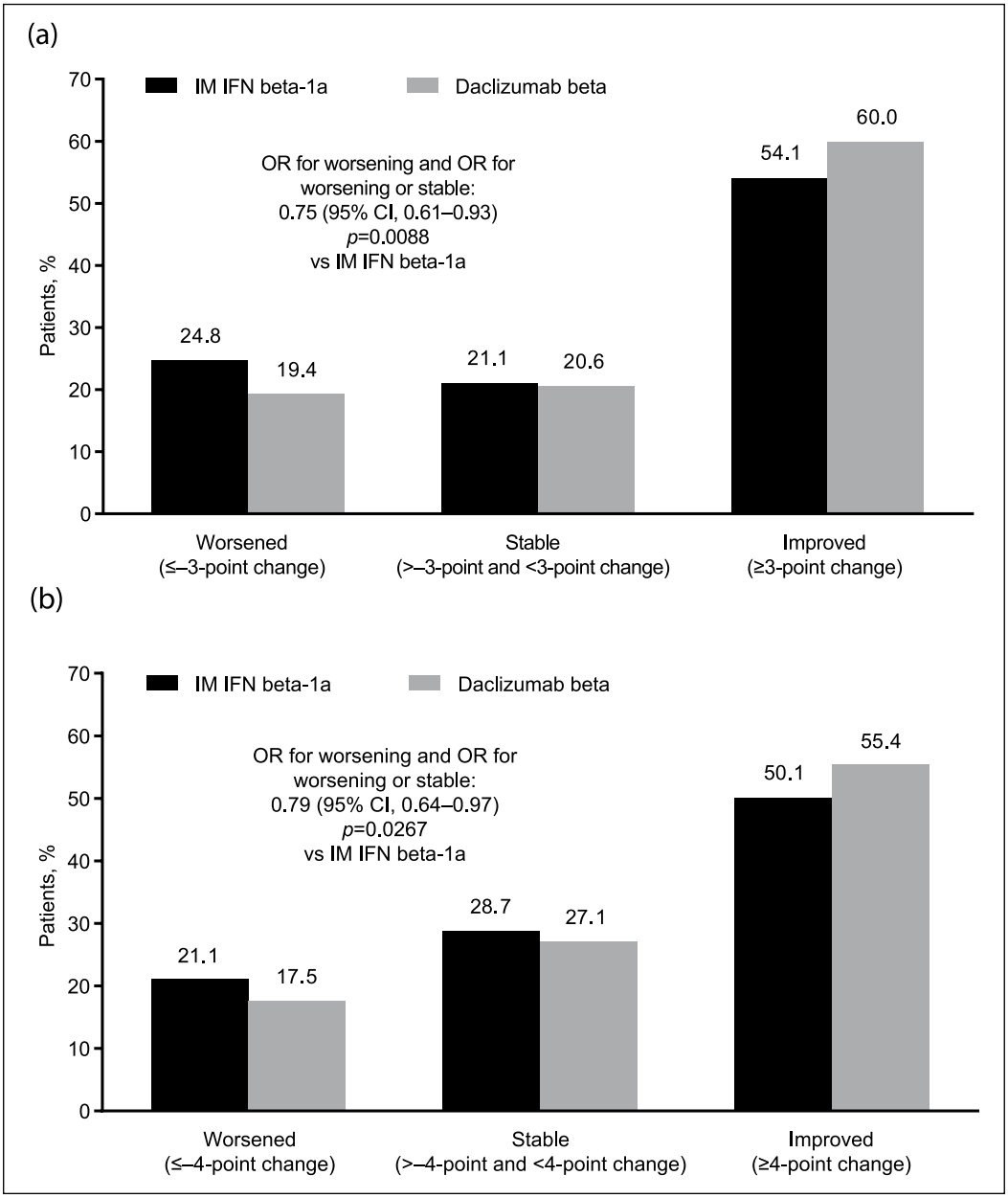

Figure 4. Percentage of patients with worsened, stable, or improved Symbol Digit Modalities Test score at week 96 using (a) a 3-point threshold or (b) a 4-point threshold. Patients with available data for baseline covariates were included. Analyses were based on observed data with no imputation for missing data. CI: confidence interval; IFN: interferon; IM: intramuscular; OR: odds ratio.

importance of these findings from a clinical perspective.[22,23]

It is interesting that there was greater observed reduction in relapses in the daclizumab beta group compared with the IM IFN beta-1a group by 12 weeks in DECIDE,[18] while the statistically significant effect on the SDMT occurred much later, at the 96-week time point. A delay between reduced inflammatory activity and benefits as measured on a neuroperformance scale such as the SDMT may be related to the time necessary for tissue repair, possibly including partial remyelination, neuronal functional recovery, synaptic reconstitution, and so on. Furthermore, the time course of these functional reparative events might reflect the volume of inflamed brain tissue and the locations of the active area of inflammation responding to daclizumab therapy. Over the course of 2–3 years, these anti-inflammatory and remyelination effects could conceivably protect against neurodegeneration. SDMT

is robustly correlated with deep gray matter volume in MS,[29,30] and recently, changes in SDMT over 3 years were found to be correlated with preserved morphology of the anterior and dorsal aspects of the thalamus.[31] It remains to be seen how changes in SDMT correlate with MRI variables in this phase III study.

The positive changes in SDMT scores seen in our study represent small, if statistically significant effects. By comparison, the magnitude of improvement was much larger in a retrospective analysis of SDMT when used to screen for progressive multifocal leukoencephalopathy during the reintroduction of natalizumab (STRATA).[32] The studies differ in many respects, not the least of which is that herein SDMT was administered every 24 weeks, whereas in STRATA, patients took the test every 4 weeks. STRATA was also an uncontrolled open-label extension study in which patients had been receiving therapy for a duration longer than 96 weeks. Furthermore, the primary purpose of the retrospective analysis of the STRATA neuropsychology data was to assess the reliability of monthly administrations of SDMT and the MS Neuropsychological Questionnaire[33] over a 48-week period. Frequent administrations of the SDMT are suitable to assess reliability but may not be suitable to evaluate treatment effects, as practice and training effects would be magnified with monthly administrations of the SDMT.[34] The difference in practice effect between monthly versus 24-week intervals is unknown and may explain this difference.[18,32] Moreover, practice and training effects were controlled for in DECIDE through the use of a two-arm design to answer the question of relative effects between two treatments.

There are several limitations of this analysis that must be taken into consideration when interpreting the results. First, DECIDE was not powered to study the effects of daclizumab beta on cognitive function; the primary and secondary objectives of the study were to examine the effect of daclizumab beta on clinical endpoints (relapse and disability progression) and MRI endpoints (number of new or newly enlarging T2-hyperintense lesions).[18] That said, the large sample size was more than adequate to determine a small but reliable effect. Second, the linear mixed-model approach used to analyze change from baseline in SDMT score[28] was not pre-planned and was used because it is less sensitive to bias related to unequal dropout rates in the treatment groups. Third, although the result at week 144 appears to substantiate the findings of the pre-planned 96-week tertiary outcome analysis, only a small subset of patients completed 144 weeks of treatment due to study design (i.e. because the end of study visit occurred for each patient either at week 144 or when the last patient enrolled had completed the week 96 visit, whichever was sooner), thereby introducing the potential for selection bias. Finally, the SDMT does not provide an exhaustive assessment of cognitive function; rather, it is used to assess a relatively narrow range of cognitive ability, even if processing speed impairment is known to be very relevant to disability in MS. The effects of daclizumab beta on SDMT scores at week 96 are complemented by a similar effect on the PASAT-3,[18] but a fuller understanding of the impact of daclizumab beta treatment on cognitive function in patients with RRMS requires a more comprehensive test battery.

In summary, daclizumab beta demonstrated a benefit on one sphere of cognitive function as measured by the SDMT. In addition to improvements in traditional MS clinical and MRI outcomes,[18] these findings suggest that daclizumab beta provides superior benefits over IM IFN beta-1a on cognitive outcomes, which may increase over time. These benefits may have implications for patients' psychological, social, and occupational functioning and may contribute to improved quality of life.

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Declaration of Conflicting Interests

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References

1. Costa SL, Genova HM, DeLuca J, et al. Information processing speed in multiple sclerosis: Past, present, and future. *Mult Scler* 2017; 23: 772–789.
2. Rao SM, Leo GJ, Haughton VM, et al. Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. *Neurology* 1989; 39: 161–166.
3. Zivadinov R, Sepcic J, Nasuelli D, et al. A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2001; 70: 773–780.
4. Rao SM, Leo GJ, Ellington L, et al. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology* 1991; 41: 692–696.
5. Fischer JS, Priore RL, Jacobs LD, et al. Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group. *Ann Neurol* 2000; 48: 885–892.
6. Mattioli F, Stampatori C and Capra R. The effect of natalizumab on cognitive function in patients with relapsing-remitting multiple sclerosis: Preliminary results of a 1-year follow-up study. *Neurol Sci* 2011; 32: 83–88.
7. Mokhber N, Azarpazhooh A, Orouji E, et al. Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: A randomized clinical trial. *J Neurol Sci* 2014; 342: 16–20.
8. Patti F, Amato MP, Bastianello S, et al. Effects of immunomodulatory treatment with subcutaneous interferon beta-1a on cognitive decline in mildly disabled patients with relapsing-remitting multiple sclerosis. *Mult Scler* 2010; 16: 68–77.
9. Patti F, Morra VB, Amato MP, et al. Subcutaneous interferon beta-1a may protect against cognitive impairment in patients with relapsing-remitting multiple sclerosis: 5-year follow-up of the COGIMUS study. *PLoS ONE* 2013; 8: e74111.
10. Weinstein A, Schwid SR, Schiffer RB, et al. Neuropsychologic status in multiple sclerosis after treatment with glatiramer. *Arch Neurol* 1999; 56: 319–324.
11. Weinstock-Guttman B, Galetta SL, Giovannoni G, et al. Additional efficacy endpoints from pivotal natalizumab trials in relapsing-remitting MS. *J Neurol* 2012; 259: 898–905.
12. Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): A double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; 13: 545–556.
13. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 387–401.
14. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; 354: 899–910.
15. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006; 354: 911–923.
16. Kappos L, Radue EW, Chin P, et al. Onset of clinical and MRI efficacy occurs early after fingolimod treatment initiation in relapsing multiple sclerosis. *J Neurol* 2016; 263: 354–360.
17. Wiendl H and Gross CC. Modulation of IL-2Rα with daclizumab for treatment of multiple sclerosis. *Nat Rev Neurol* 2013; 9: 394–404.
18. Kappos L, Wiendl H, Selmaj K, et al. Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2015; 373: 1418–1428.
19. Smith A. *Symbol digit modalities test: Manual*. Los Angeles, CA: Western Psychological Services, 1982.
20. Parmenter BA, Weinstock-Guttman B, Garg N, et al. Screening for cognitive impairment in multiple sclerosis using the Symbol Digit Modalities Test. *Mult Scler* 2007; 13: 52–57.
21. Conover WJ and Iman RL. Analysis of covariance using the rank transformation. *Biometrics* 1982; 38: 715–724.

22. Morrow SA, Drake A, Zivadinov R, et al. Predicting loss of employment over three years in multiple sclerosis: Clinically meaningful cognitive decline. *Clin Neuropsychol* 2010; 24: 1131–1145.

23. Benedict RH, Morrow S, Rodgers J, et al. Characterizing cognitive function during relapse in multiple sclerosis. *Mult Scler* 2014; 20: 1745–1752.

24. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005; 58: 840–846.

25. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444–1452.

26. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a brief international cognitive assessment for multiple sclerosis (BICAMS). *Mult Scler* 2012; 18: 891–898.

27. Benedict RH, Smerbeck A, Parikh R, et al. Reliability and equivalence of alternate forms for the Symbol Digit Modalities Test: Implications for multiple sclerosis clinical trials. *Mult Scler* 2012; 18: 1320–1325.

28. Molenberghs G, Thijs H, Jansen I, et al. Analyzing incomplete longitudinal clinical trial data. *Biostatistics* 2004; 5: 445–464.

29. Houtchens MK, Benedict RH, Killiany R, et al. Thalamic atrophy and cognition in multiple sclerosis. *Neurology* 2007; 69: 1213–1223.

30. Minagar A, Barnett MH, Benedict RH, et al. The thalamus and multiple sclerosis: Modern views on pathologic, imaging, and clinical aspects. *Neurology* 2013; 80: 210–219.

31. Bergsland N, Zivadinov R, Dwyer MG, et al. Localized atrophy of the thalamus and slowed cognitive processing speed in MS patients. *Mult Scler* 2016; 22: 1327–1336.

32. Morrow SA, O'Connor PW, Polman CH, et al. Evaluation of the symbol digit modalities test (SDMT) and MS neuropsychological screening questionnaire (MSNQ) in natalizumab-treated MS patients over 48 weeks. *Mult Scler* 2010; 16: 1385–1392.

33. Benedict RH, Cox D, Thompson LL, et al. Reliable screening for neuropsychological impairment in multiple sclerosis. *Mult Scler* 2004; 10: 675–678.

34. Roar M, Illes Z and Sejbaek T. Practice effect in Symbol Digit Modalities Test in multiple sclerosis patients treated with natalizumab. *Mult Scler Relat Disord* 2016; 10: 116–122.