


## ORIGINAL ARTICLE

# Baseline characteristics and effects of fingolimod on cognitive performance in patients with relapsing-remitting multiple sclerosis

Dawn W. Langdon<sup>1</sup>  | Davorka Tomic<sup>2</sup> | Iris-Katharina Penner<sup>3,4</sup> |  
Pasquale Calabrese<sup>5</sup> | Gary Cutter<sup>6</sup> | Dieter A. Häring<sup>2</sup> | Frank Dahlke<sup>2</sup> |  
Ludwig Kappos<sup>7</sup>

<sup>1</sup>Department of Psychology, Royal Holloway, University of London, Egham, UK

<sup>2</sup>Novartis Pharma AG, Basel, Switzerland

<sup>3</sup>Medical Faculty, Department of Neurology, Heinrich Heine University, Düsseldorf, Germany

<sup>4</sup>COGITO Center for Applied Neurocognition and Neuropsychological Research, Düsseldorf, Germany

<sup>5</sup>Neuropsychology and Behavioral Neurology Unit, Division of Cognitive and Molecular Neuroscience, University of Basel, Switzerland

<sup>6</sup>Department of Biostatistics, University of Alabama, Birmingham, AL, USA

<sup>7</sup>Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB) and MS Center, Neurology, Departments of Head, Spine and Neuromedicine and Clinical Research, University Hospital and University of Basel, Spitalstrasse 2, Basel, Schweiz 4031, Switzerland

## Correspondence

Dawn W. Langdon, Royal Holloway, University of London, Egham, Surrey TW20 0EX, UK.  
Email: d.langdon@rhul.ac.uk

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## Abstract

**Background and purpose:** Studies reporting the baseline determinants of cognitive performance and treatment effect on cognition in patients with multiple sclerosis (MS) are limited. We investigated the baseline correlates of cognition and the long-term treatment effects of fingolimod 0.5 mg once daily on cognitive processing speed and attention in patients with relapsing-remitting MS.

**Methods:** This post hoc analysis pooled data from the phase 3 FREEDOMS and FREEDOMS II trials ( $N = 1556$ ). We assessed the correlation between baseline patient demographic and disease characteristics and baseline 3-second Paced Auditory Serial Addition Test (PASAT-3) scores (Spearman's rank test) and the changes from baseline in PASAT-3 (mixed model repeated measures model) in the fingolimod and placebo (up to 24 months) or placebo-fingolimod switched (from Month 24 up to 120 months) groups. Additionally, the predictive value of PASAT-3 score for future disease outcomes was assessed (Cox or logistic regression models).

**Results:** Among the variables assessed, lower PASAT-3 score at baseline correlated with higher disease burden (total brain volume, T2 lesion volume, and Expanded Disability Status Scale score), longer disease duration and older age ( $p < 0.0001$  for all). Fingolimod significantly improved PASAT-3 scores from baseline versus placebo at 6 (1.3;  $p = 0.0007$ ), 12 (1.1;  $p = 0.0044$ ) and 24 months (1.1;  $p = 0.0028$ ), with a sustained effect (overall treatment effect  $p = 0.0012$ ) up to 120 months. Improvements were seen regardless of baseline cognitive status (PASAT quartile). Baseline PASAT-3 score was predictive of both clinical and magnetic resonance imaging measures of disease activity at Month 24 ( $p < 0.001$  for all).

**Conclusion:** Early fingolimod treatment may offer long-term cognitive benefit in patients with relapsing-remitting MS.

## KEYWORDS

cognitive processing speed, correlation, disability progression, fingolimod, MRI, multiple sclerosis, PASAT

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## INTRODUCTION

Cognitive impairment affects 35%–60% of people with multiple sclerosis (MS), is most marked in the domains of information processing speed and memory, and has a negative impact on many aspects of quality of life [1]. Cognition is significantly linked to current and future employment status [2] and is an independent predictor of income among patients with MS [3].

Evidence from cross-sectional and longitudinal studies suggests that both clinical and magnetic resonance imaging (MRI) variables of disease worsening and progression (e.g., Expanded Disability Status Scale [EDSS] score, brain volume loss and MRI lesion load) are closely linked to cognitive measures, in both the short and long term [4–7]. Recently, the concept of ‘cognitive relapses’ has also been advocated [8,9], and retrospective studies have found early cognitive impairment to be an important predictor of disease progression [4,10]. The functional domains that are most severely impaired in MS are information processing speed, attention-executive function, and memory [11]. The 3-second Paced Auditory Serial Addition Test 3 (PASAT-3) is an auditory test that is often used to assess cognitive processing speed (CPS), attention and working memory functions in clinical trials [12]. Despite cognition being so intricately coupled with disease pathology and progression, studies reporting the long-term effects of disease-modifying therapies (DMTs) on cognition are limited [13]. It is therefore of interest to investigate the predictive value of cognitive measures for disease worsening in MS in large long-term, high-quality studies.

The present analysis pooled PASAT-3 data from two fingolimod phase 3 trials [14,15] to: (1) explore correlations between baseline characteristics of patients with relapsing-remitting MS and PASAT-3 scores at baseline; (2) evaluate the effect of fingolimod 0.5 mg once daily on domains of CPS, attention, and working memory over 10 years; and (3) assess the predictive value of PASAT-3 for future disease outcome in patients with relapsing-remitting MS.

## METHODS

### Study design and patients

This study is a post hoc analysis of the pooled data from the core (24 months) and extension (up to 120 months) phases of two phase 3, placebo-controlled, randomized clinical trials: FREEDOMS and FREEDOMS II. These studies compared the efficacy and safety of once-daily fingolimod (0.5-mg and 1.25-mg doses) with placebo. The random allocation was in a 1:1:1 ratio. Key eligibility criteria were patients aged 18–55 years, a diagnosis of relapsing-remitting MS according to the 2005 McDonald criteria, one or more documented relapses in the previous year (or two or more in the previous 2 years) and an EDSS score of 0–5.5. Details of the study design and patient population of the two FREEDOMS trials have been reported elsewhere and the primary results of these trials have been published in accordance with CONSORT guidelines [14,15]. In the present paper,

we report data from patients who were in the fingolimod 0.5-mg arm from randomization until the end of the extension phase (Month 120) and from patients who were in the placebo group during the core phase of the study and switched to fingolimod 0.5 mg at the end of the core study (i.e. after 24 months).

### Assessments and data analysis

In the FREEDOMS and FREEDOMS II studies, clinical assessments were performed at screening and at randomization. Study visits were scheduled at baseline and 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 months after randomization. The EDSS score was determined every 3 months and the individual components of the Multiple Sclerosis Functional Composite were measured every 6 months. Standardized MRI scans were obtained at the screening visit and at 6, 12 and 24 months. Two pretreatment PASAT-3 measurements were taken 14 days before baseline, and a further PASAT-3 measurement was taken at baseline, to reduce learning effect over subsequent repeated measures. All analyses at baseline were performed on the single baseline PASAT-3 score at the start of the study.

The associations between baseline PASAT-3 score and various patient demographics and baseline disease activity parameters were evaluated by (1) patient category and (2) quartiles based on baseline PASAT-3 score. The changes in PASAT-3 score on treatment from baseline to 6, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 months were assessed. The predictive value of baseline PASAT-3 score for disease outcomes at Month 24, such as annualized relapse rate, confirmed disability worsening, number of gadolinium-enhancing (Gd+) T1 lesions and new/newly enlarged T2 lesions, brain volume loss (as measured by annual rate of brain atrophy [ARBA]), no evidence of disease activity (NEDA-4; no confirmed relapses, no 6-month confirmed disability worsening, no new or enlarging T2 lesions and an ARBA of  $\leq 0.4\%$ ) were evaluated for patients overall and by baseline PASAT-3 quartile (Q).

### Statistical analysis

The present study reports post hoc analysis of pooled data from the FREEDOMS and FREEDOMS II studies. All analyses were based on the full analysis set, which includes patients who were randomized and received at least one dose of study medication during the core study phase, following the intention-to-treat principle. Data were summarized using descriptive statistics. The patients were categorized into groups based on their baseline disease burden or severity. The differences in mean PASAT-3 scores within the patient categories were compared using the Wilcoxon rank-sum (for two categories) and the Jonckheere-Terpstra (for three or more categories) tests. Quartiles of distribution of baseline PASAT-3 score were considered to classify patients into three categories:  $\leq Q1$  (0–42; subgroup of patients with a low baseline PASAT-3 score);  $> Q1, < Q3$  (43–56); and  $\geq Q3$  (57–60; subgroup of patients with a high baseline

PASAT-3 score). Furthermore, a multiple linear regression analysis was performed with variables found to be significantly associated with baseline PASAT-3 score. Spearman's rank correlation coefficients and the associated 95% confidence intervals (CIs) were calculated to investigate the relationship of baseline PASAT-3 scores to baseline clinical and MRI characteristics. The within-group changes (mean, unadjusted) in PASAT-3 scores for the fingolimod treatment group and the placebo group from baseline to 6, 12 and 24 months were assessed using the Wilcoxon rank-sum test. Change in PASAT-3 score in the two treatment groups over time was assessed using a mixed model for repeated measures (MMRM) and reported as adjusted mean. A sensitivity analysis (using data from the FREEDOMS trial), adjusting the MMRM model for change in PASAT-3 score from pre-baseline value, was performed to account for potential learning effect. Cox proportional hazard models (relapse, disability and NEDA-4 outcomes) and logistic regression models (MRI lesions and ARBA) were used to determine the associations among baseline PASAT-3 score, treatment status, disease worsening and related measures (details of covariates presented in the corresponding figure footnote).

## RESULTS

### Study population

The analysis compared 783 patients in the fingolimod groups (425 from FREEDOMS and 358 from FREEDOMS II) with 773 patients in the placebo groups (418 from FREEDOMS and 355 from FREEDOMS II). Although patients from the FREEDOMS II study were older and had longer disease duration compared with those in FREEDOMS, the baseline characteristics of our analysis cohort were similar (Table S1).

### PASAT-3 and baseline characteristics

The mean (standard deviation [SD]) PASAT-3 score at baseline was 48.3 (10.7) for the fingolimod group and 47.5 (11.1) for the placebo group ( $p =$  nonsignificant). PASAT-3 scores at baseline were significantly related to a number of clinical and MRI variables (Table 1). There was a significant ( $p < 0.0001$ , Wilcoxon rank-sum test) difference between pretreatment PASAT-3 scores for high ( $>1500 \text{ cm}^3$ ) and low ( $\leq 1500 \text{ cm}^3$ ) brain volume groups, and high ( $>3.5$ ) and low ( $0-3.5$ ) EDSS groups. Patients with high brain volume and lower EDSS at baseline also had better PASAT performance. There was also a significant ( $p < 0.0001$ , Jonckheere-Terpstra test) step function relating T2 lesion volume, duration of MS, and age to pretreatment PASAT-3 scores, with a decline in baseline PASAT performance with increasing severity of each disease activity variable. However, multiple regression confirmed baseline brain volume, EDSS score, T2 lesion volume and age as significant correlates of baseline PASAT-3 score; duration of MS no longer showed significant

**TABLE 1** Baseline PASAT-3 score by patient category

Patient category	n	PASAT-3 score Mean (SD)	p value*
<b>Age</b>			
$\leq 30$ years	308	50.1 (9.8)	$<0.0001$
31–40 years	557	48.9 (10.5)	
$\geq 41$ years	665	46.1 (11.4)	
<b>Sex</b>			
Male	392	48.6 (11.3)	0.0395
Female	1138	47.7 (10.8)	
<b>Duration of MS since first symptom</b>			
0–5 years	520	49.5 (9.9)	$<0.0001$
$>5-10$ years	452	48.1 (11.3)	
$>10$ years	558	46.3 (11.2)	
<b>Number of relapses in the year prior to baseline</b>			
0 or 1	996	47.7 (10.9)	0.1264
$>1$	534	48.4 (11.0)	
<b>Previous treatment for MS</b>			
No	674	48.8 (10.4)	0.0074
Yes	856	47.2 (11.3)	
<b>EDSS score</b>			
0–3.5	1279	48.9 (10.3)	$<0.0001$
$>3.5$	251	42.8 (12.4)	
<b>Number of Gd+ T1 lesions</b>			
0	953	48.1 (10.9)	0.1071
1–2	353	48.1 (10.8)	
$\geq 3$	217	46.9 (10.8)	
<b>T2 lesion volume, <math>\text{cm}^3</math></b>			
$<800$	294	50.4 (9.2)	$<0.0001$
800–3,500	534	49.5 (9.7)	
$>3,500-12,000$	484	47.8 (10.8)	
$>12,000$	210	40.9 (13.1)	
<b>Total brain volume</b>			
$\leq 1,500 \text{ cm}^3$	588	44.6 (11.9)	$<0.0001$
$>1,500 \text{ cm}^3$	932	50.0 (9.6)	

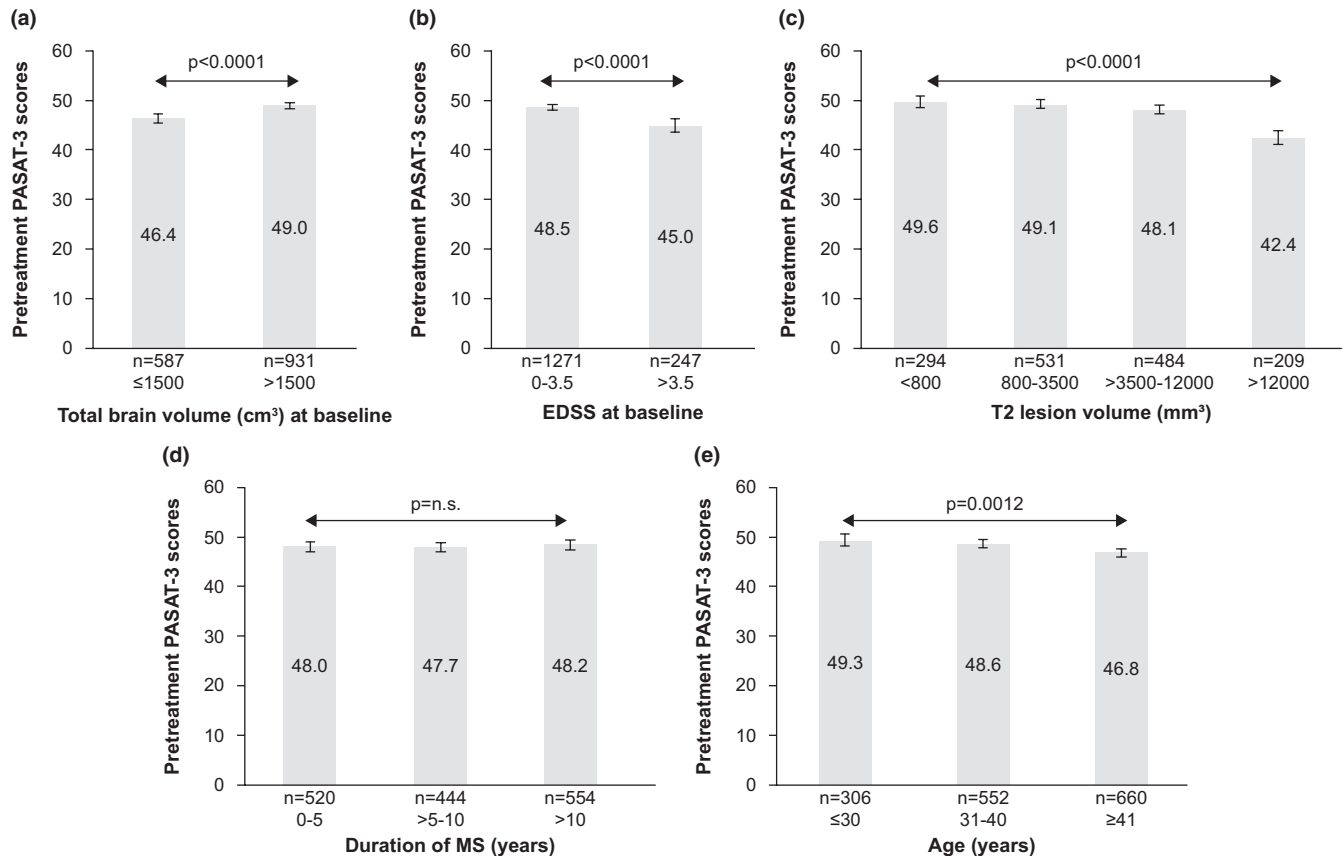
Abbreviations: EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; PASAT-3, 3-second Paced Auditory Serial Addition Test.

SD, standard deviation.

\*p values are from Wilcoxon rank-sum tests for trend (for two groups) and from the Jonckheere-Terpstra test (for three or more groups).

correlation with baseline PASAT-3 score (Figure 1). The PASAT-3 score quartile analysis showed a similar association; patients in the high-score PASAT-3 quartile ( $\geq Q3$ ) were younger and had less severe disease than patients in the low-score PASAT-3 quartile ( $\leq Q1$ ; Table 2).

These associations were further confirmed by Spearman's correlations with the continuous variables and PASAT-3 (Spearman's  $r$ : total brain volume 0.278, 95% CI 0.224 to 0.331,  $p < 0.0001$ ;



**FIGURE 1** 3-second Paced Auditory Serial Addition Test (PASAT-3) scores at baseline as a function of baseline characteristics: (a) total brain volume; (b) Expanded Disability Status Scale (EDSS) score; (c) T2 lesion volume; (d) duration of disease; and (e) age. The single baseline scores at the start of each study were used to calculate pretreatment PASAT-3 scores of the pooled study. Data presented as mean (95% confidence interval). *p* values are from linear regression analysis. Only patients with non-missing values for all baseline characteristics are included in the analysis. *n* = patients who performed two PASAT-3 assessments on Day -14 and one PASAT-3 assessment on Day 1

EDSS  $-0.274$ , 95% CI  $-0.328$  to  $-0.220$ ,  $p < 0.0001$ ; T2 lesion volume  $-0.238$ , 95% CI  $-0.293$  to  $-0.183$ ,  $p < 0.0001$ ; duration of MS  $-0.153$ , 95% CI  $-0.210$  to  $-0.097$ ,  $p < 0.0001$ ; age  $-0.189$ , 95% CI  $-0.245$  to  $-0.132$ ,  $p < 0.0001$ ). There were no significant correlations between relapses, or Gd+ lesions at baseline, and PASAT-3 scores (data not shown).

### PASAT-3 and treatment effect of fingolimod

A statistically significant improvement (Wilcoxon rank-sum test) in PASAT-3 scores from baseline was observed in fingolimod-treated (49.2 vs. 48.6 at baseline, mean change 0.6;  $p = 0.0352$ ) compared with placebo-treated (47.2 vs. 47.5, mean change  $-0.3$ ) patients early at 6 months, and this was maintained at Month 12 (fingolimod, 49.6 vs. 48.5; mean change of 1.1 as compared with placebo, 47.7 vs. 47.4; mean change 0.3,  $p = 0.0152$ ) and Month 24 (fingolimod, 50.8 vs. 48.7; mean change 2.1 as compared with placebo, 48.9 vs. 47.7; mean change 1.2,  $p = 0.0157$ ). In the MMRM analysis of change in PASAT-3 score between the two treatment groups, a statistically significant improvement was noted during the core phase of the studies.

A numerical difference was still observed after the switch of the placebo group at 24 months to fingolimod at most time points during the study, with a statistically significant difference observed at certain time points over the 120-month follow-up period (Figure 2). The overall treatment effect of fingolimod in improving PASAT-3 performance was statistically significant (fingolimod vs. placebo-fingolimod mean change, baseline to M120 1.5;  $p = 0.0012$ ). The results of the sensitivity analysis are presented in Figure S1. To check for the influence of study discontinuations on the overall results, we performed a 'completer analysis' in the subgroup of patients who had available data up to week 108; this comprised 465 (32.9%) out of the total of 1413 patients. The effect sizes in the completer analysis were qualitatively similar and in the same direction as the main results. The overall treatment effect was statistically significant (fingolimod vs. placebo-fingolimod mean change, baseline to M108 1.2;  $p = 0.0427$ ), although not always significant, probably due to the lower sample size (data not shown).

Treatment with fingolimod resulted in improved PASAT-3 scores in patient categories as well, with a significant difference observed until Month 24 (end of core study phase). However, no difference between fingolimod and placebo was observed from Month 36

TABLE 2 Patient demographic and disease characteristics by PASAT-3 baseline quartile

Characteristic	Fingolimod 0.5 mg, N = 783				Placebo, N = 773			
	PASAT quartile		p value for trend	≥57	PASAT quartile		p value for trend	≥57
	≤42	>42, <57			≤42	>42, <57		
Age, years	40.2	38.6	<0.0001	36.3	40.9	<0.0001	36.6	<0.0001
Duration of MS since first symptom, years	10.8	9.2	<0.0001	7.6	10.3	<0.0001	8.1	0.0105
Number of relapses in the year prior to baseline	1.4	1.5	0.5802	1.5	1.4	0.5802	1.5	0.1134
Number of relapses in the 2 years prior to baseline	2.1	2.2	0.4117	2.1	2.1	0.4117	2.3	0.2844
EDSS score	2.9	2.3	<0.0001	2.0	2.9	<0.0001	2.2	<0.0001
Number of Gd+ T1 lesions	2.4	1.1	0.4983	1.3	1.4	0.4983	1.0	0.6852
T2 lesion volume, cm <sup>3</sup>	9.0	5.3	<0.0001	3.9	8.5	<0.0001	4.0	<0.0001
Total brain volume, cm <sup>3</sup>	1487.5	1524.3	<0.0001	1549.4	1486.5	<0.0001	1548.1	<0.0001

Note: Quartiles are based on the baseline PASAT of the pooled study. p values are from the Mantel-Haenszel chi-squared test for trend (categorical baseline characteristics) and from the Jonckheere-Terpstra test (quantitative baseline characteristics).

Abbreviations: EDSS, Expanded Disability Status Scale, Gd+, gadolinium-enhancing; PASAT-3, 3-second Paced Auditory Serial Addition Test.

onwards, when patients on placebo switched to active treatment (Figure 3; data beyond Month 36 not shown).

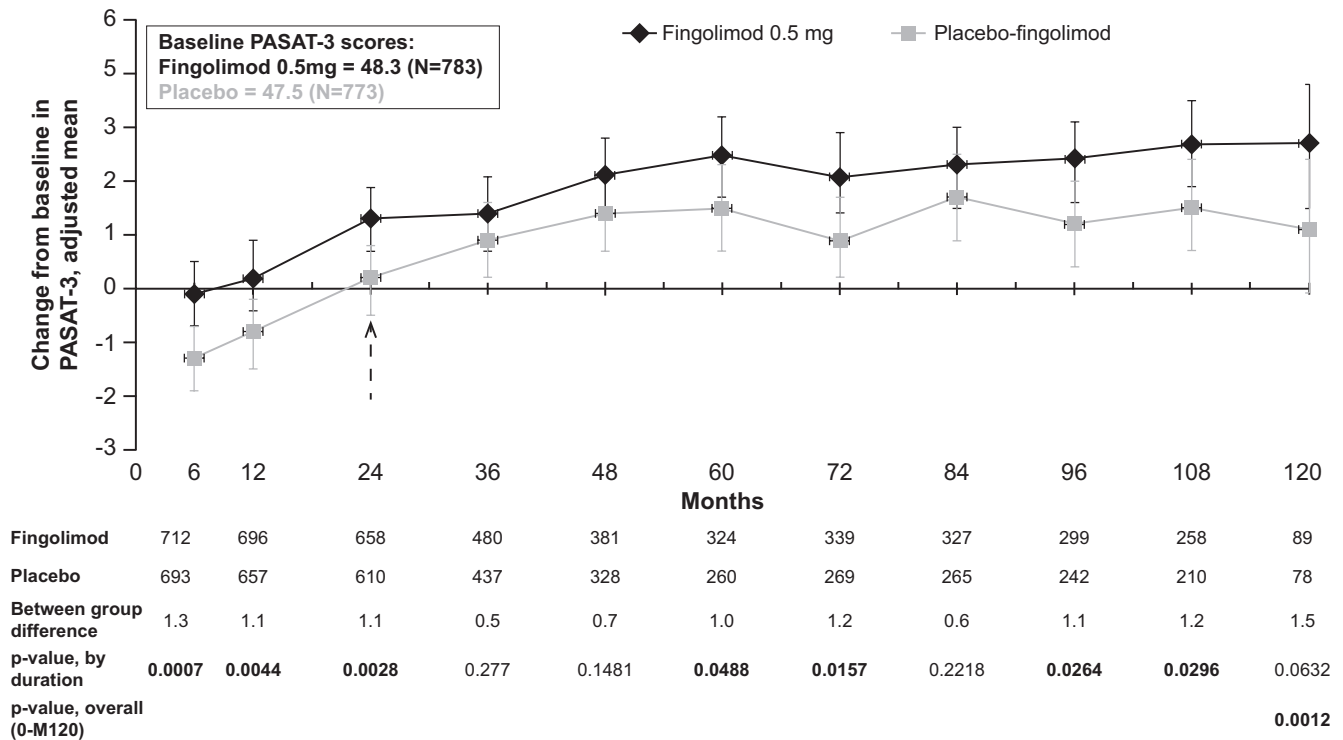
## Predictive value of PASAT-3 for future disease outcomes

Baseline PASAT-3 scores were found to be predictive of time to first confirmed relapse, time to confirmed disability worsening, freedom from Gd+ lesions and new T2 lesions, brain atrophy and disease activity status at Month 24 (Figure 4). Across the PASAT-3 quartiles, patients treated with fingolimod had significantly better outcomes compared to placebo-treated patients for both clinical (relapses, and disability worsening; Figure 4a) and MRI-related (Gd+ lesions, new or enlarging T2 lesions, brain volume loss; Figure 4b,c) measures of disease activity. Treatment with fingolimod significantly reduced time to first disease activity on the composite NEDA-4 endpoint in all PASAT-3 quartiles (Figure 4d). The fingolimod treatment was beneficial across disease variables, irrespective of baseline PASAT-3 score, with the most pronounced effect noted in patients who had higher baseline PASAT-3 score.

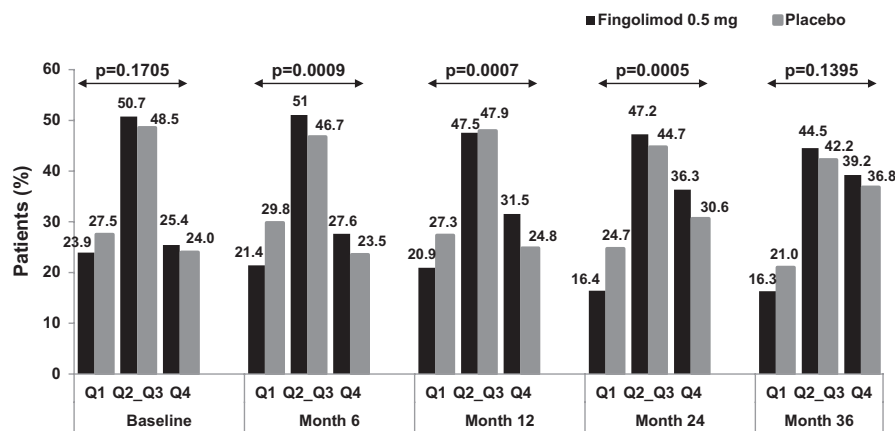
## DISCUSSION

Cognitive impairment is evident in all stages of MS. Cognitive rehabilitation has progressed, but is currently far from being a universal, feasible therapeutic option [16,17]. Symptomatic medication and phytomedicines are ineffective, and there is some evidence for the efficacy of DMTs for cognition in MS [18]. Observational, often uncontrolled, studies provide evidence supporting the treatment effect on cognitive dysfunction for interferon-beta [19] and natalizumab [20,21]. There are several other, open-label studies with varying findings [22–24]. Recently, more randomized clinical trials have been evaluating cognitive performance; however, very limited data are available. Longer cognitive batteries would be more informative [25]. We have presented a post hoc analysis of data pooled from two large phase 3 clinical trials, totalling 1556 patients with relapsing-remitting MS, evaluating the efficacy of fingolimod in improving cognitive performance, mainly CPS, attention and working memory, as measured by PASAT-3. This large dataset also gave us the opportunity to explore the value of baseline cognition (represented by PASAT-3 score) as a correlate of disease variables and a predictor of disease progression.

Our findings linking PASAT-3 performance to disease and other patient variables are largely consistent with previous work. We have demonstrated a clear relationship between PASAT-3 score, brain volume and EDSS, which is consistent with findings from smaller studies [6,26]. The correlation we reported between PASAT-3 score and T2 lesion volume,  $-0.238$ , is close to that derived in a recent meta-analysis between cognition and T2 lesion volume in MS ( $-0.30$ ) [27]. Disease duration and age have been linked extensively to cognitive function in MS [26,28], as we found in the present study. We



**FIGURE 2** Mean change from baseline in 3-second Paced Auditory Serial Addition Test (PASAT-3) scores – pooled FREEDOMS studies\*. \*Mixed model for repeated measures model included the covariates visit, treatment, baseline PASAT-3 score, age ( $\leq 30$ , 31–40,  $> 40$  years), duration of multiple sclerosis (MS) since first symptom ( $\leq 5$ , 5–10,  $> 10$  years), baseline Expanded Disability Status Scale (EDSS) score ( $\leq 3.5$ ,  $> 3.5$ ), baseline normalized brain volume ( $\leq 1,500$ ,  $> 1,500$  cm<sup>3</sup>), T2 lesion volume at baseline ( $< 800$ , 800–3,500,  $> 3,500$ –12,000,  $> 12,000$  mm<sup>3</sup>), and a visit\*treatment interaction. *p* values are for comparisons between fingolimod and placebo-fingolimod groups [Correction added on 03 November 2021, after first online publication: The interval of Months and the alignment of the overall *p*-value have been corrected in the Figure 2 image.]



**FIGURE 3** Effect of fingolimod across 3-second Paced Auditory Serial Addition Test (PASAT-3) quartiles. Quartiles (Q) are based on the baseline PASAT-3 score of the pooled study (Q1 = 42, Q3 = 57). *p* values are from chi-squared test for trend to test for differences between fingolimod and placebo

did not find a significant correlation between PASAT-3 score and Gd+ lesions, which contradicts a previous study [29]. Bellman-Strobl et al. [29] collected data on cognition and MRI in MS patients with frequent retesting, and it may be that our 6-monthly data sampling was not sufficiently fine-grained to demonstrate this association.

Taken together, these correlations sit comfortably with previous work, confirming the interrelations between cognition and disease and other variables in our larger dataset.

Baseline PASAT-3 scores were good predictors of future disease worsening and other pathologies in the short term (24-month study



duration). There are several convincing smaller studies of cognition predicting disease outcomes and MRI pathology in the medium and long term. Cognition at diagnosis of clinically isolated syndrome predicts time to clinically definite MS [30], cognition at MS diagnosis predicts disability progression [31], and cognition predicts disability accumulation and cortical thinning [10]. Learning ability on the PASAT also predicts disease progression [32]. Our larger dataset and more frequent assessments have enabled us to demonstrate this predictive power in a shorter time frame.

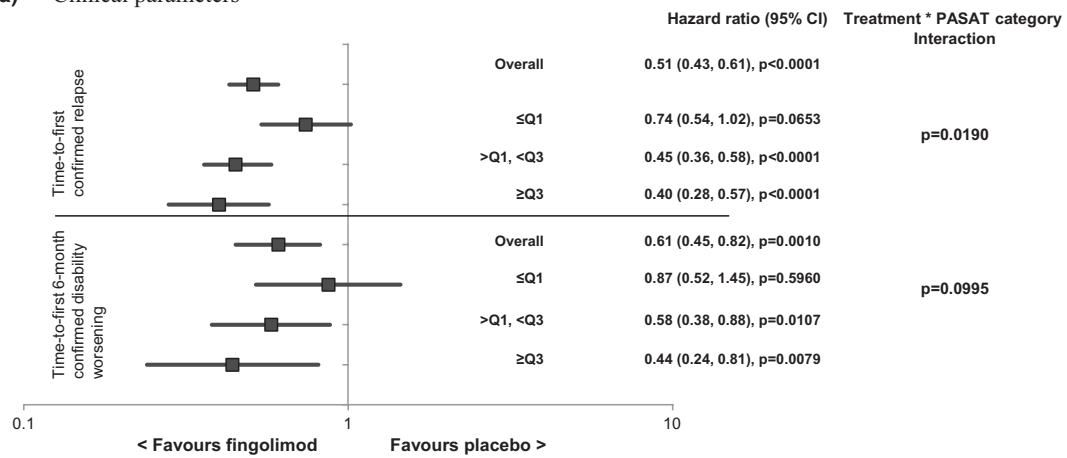
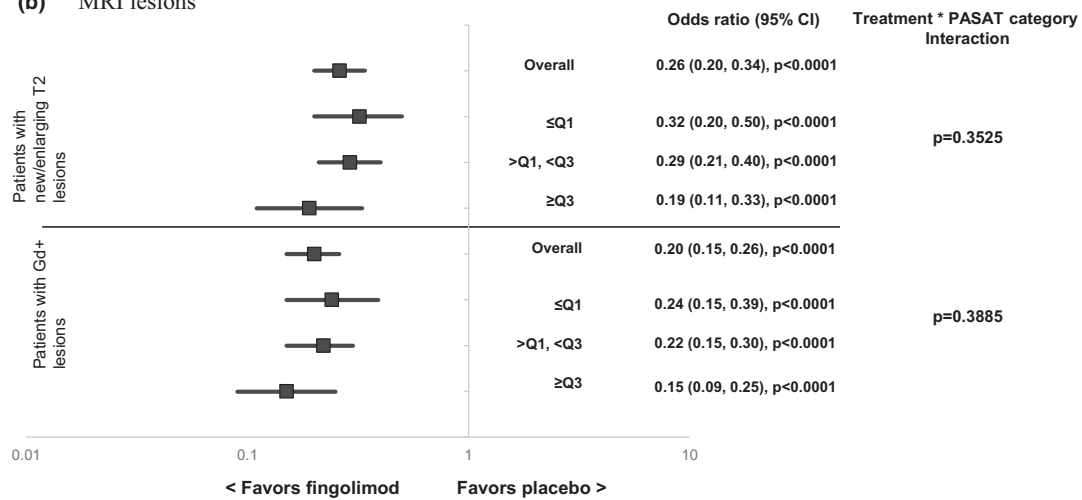
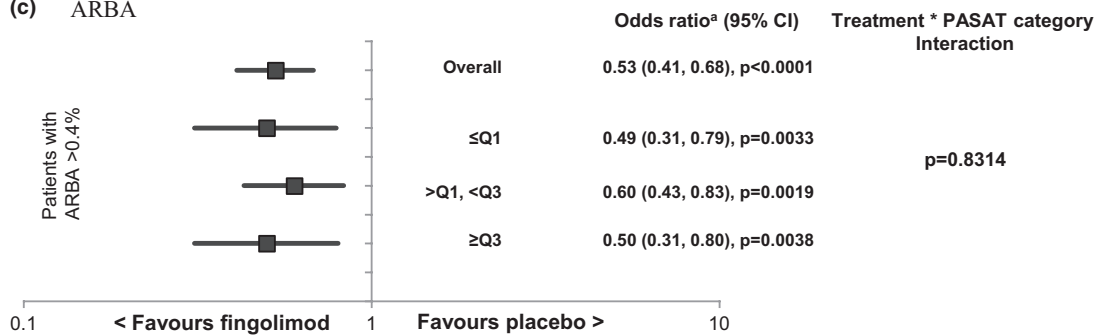
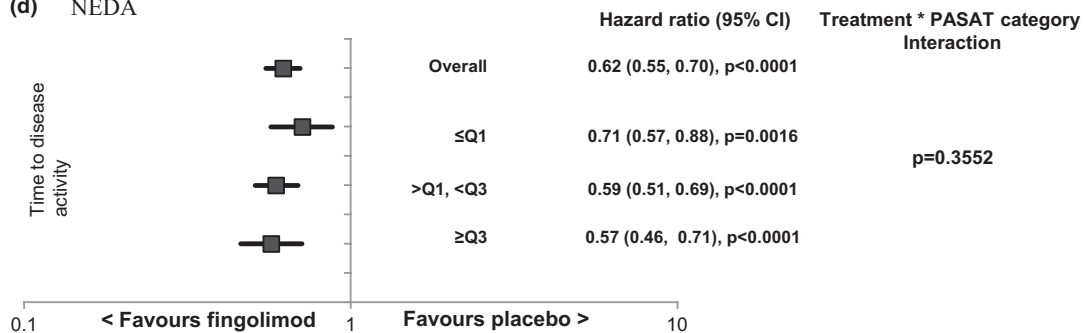
Fingolimod acts by modulating S1P receptors expressed on the neural cells which are relevant for the MS pathology [33]. Fingolimod crosses the blood-brain barrier, and preclinical and *in vitro* studies suggest that fingolimod reduces neurodegenerative processes and promotes myelin preservation, repair and normalization of neurological function [34]. The clinical efficacy demonstrated in the phase 3 studies of fingolimod [14,15] give credence to direct central nervous system effects of fingolimod. A recent small observational trial has reported reduced functional connectivity in the posterior (parieto/occipital) cortex and cerebellum after fingolimod treatment [35]. There was a correlation with an increase in PASAT scores. The reduction in functional connectivity, correlating with PASAT performance, after fingolimod treatment could possibly be explained by the drug allowing adaptive neuroplastic changes which reduce functional overload and hence support network efficiency, in addition to having anti-inflammatory effects [36].

We observed a clear cognitive advantage in the fingolimod-treated patients compared with placebo. The fact that a significant difference in mean PASAT-3 score emerges at 6 months and remains for the 24 months of double-blind phases of the trials, and that a clear difference is maintained till the end of the study, indicates that early treatment with fingolimod was effective in preserving cognitive function in the long term. The 2.1-point difference in mean PASAT-3 score at 24 months is close to the reported 2.5 mean difference between MS patients with stable and deteriorated work status after 40 months [37], and is therefore arguably clinically meaningful [22]. PASAT mean scores also significantly differentiate work-stable, work-challenged and work-disabled MS patient groups [38], clearly linking PASAT performance to real-world function. It has also been noted that early effective treatments are associated with better socioeconomic outcomes [39]. The present study reports an early effect of fingolimod on cognitive functioning as measured by PASAT, in accordance with the long-term benefits seen on the clinical and MRI outcomes over a decade of fingolimod treatment [40]. The early treatment effect observed in the present study occurs much sooner than the treatment advantage with interferon-beta observed in the BENEFIT trial in clinically isolated syndrome [41]. The different trial design and target patient population may explain this difference. A clear treatment benefit was observed in patients receiving placebo who switched to fingolimod after 24 months, highlighting the importance of early treatment with an effective DMT, such as fingolimod, for preserving future cognitive function. Furthermore, treatment with fingolimod improved PASAT-3 scores regardless of the patient's

baseline cognitive status; all patients benefitted from fingolimod treatment, from the most impaired patients who had a lower baseline PASAT-3 score (<Q1, 0-42) to the best performers with a baseline PASAT-3 score of 57 or higher. In our analysis, patients with low cognitive performance at baseline had worse outcomes in the follow-up. Based on the MMRM analysis (overall dataset and the M108 completer set), the treatment-by-time interaction effect was insignificant in both analyses; however, baseline PASAT-3 score was a significant covariate in both the models (Table S2). This supports low baseline cognitive performance as a risk factor for worse clinical and cognitive disability in the long term [4,42]. These improvements are of clinical relevance and even more so for patients with lower PASAT scores than those patients with high scores at baseline, considering the ceiling effect associated with this tool, which limits the sensitivity to performance changes over time. Our results were further corroborated by the findings in a recent open-label, rater-blinded, randomized study wherein fingolimod treatment resulted in significant improvement from baseline in cognitive performance as assessed by Rao's Brief Repeatable Battery and the Delis-Kaplan Executive Function System test [43]. It is important to note that the PASAT-3 score is less influenced by cultural differences and therefore appropriate for multinational trials [44].

The present results, together with the current evidence, suggest that early treatment with high-efficacy DMTs is likely to be most beneficial [45] and that cognitive status should be routinely evaluated in MS clinics [25]. In the future, it may be possible to use cognitive status as formal evidence of breakthrough disease and as an indicator for treatment escalation. Currently, cognitive decline can alert clinicians to assess other variables that can define high-risk scenarios [46].

There are a number of limitations of the present study that need to be borne in mind. Firstly, we have analysed pooled data from two studies from a post hoc perspective. We cannot rule out that knowledge of the results affected the analysis plan. Secondly, the trials were not designed specifically to investigate cognition as a primary outcome measure and the participants were not selected for cognitive status [13]. Thirdly, we only have data on the PASAT-3 scores, not a cognitive battery, and hence accessed only a limited sample of the cognitive function of the recruited patients [47]. Fourthly, the PASAT-3 score is less stringent than the PASAT-2 [48], and so may have failed to differentiate within patients in the severe cognitive impairment quartiles and may have been more susceptible to practice effects [49]. Learning effects on the PASAT have been reported in a separate paper [32]. It should also be noted that, for PASAT, a clinically meaningful threshold has not been established as yet, unlike the symbol digit modality test, for which a difference in four points approximating a magnitude of 10% change is considered clinically relevant [50]. Finally, the patients were within major phase 3 trials and there is an acknowledged selection bias among trial participants. Also, as with all longitudinal studies, a significant drop-out rate was noted and may have influenced the results. The present results, therefore, may not be generalizable to the broader relapsing-remitting MS patient community.

**(a) Clinical parameters****(b) MRI lesions****(c) ARBA****(d) NEDA**



**FIGURE 4** Relation of 3-second Paced Auditory Serial Addition Test (PASAT-3) baseline scores to measures of disease progression at Month 24, by treatment group: (a) clinical variables; (b) magnetic resonance imaging lesions; (c) annual rate of brain atrophy (ARBA); (d) no evidence of disease activity (NEDA). Quartiles (Q) are based on the baseline PASAT-3 score of the pooled study (Q1 = 42, Q3 = 57). *x*-axis is in logarithmic scale. NEDA was defined as the absence of confirmed relapses, new or enlarging T2 lesions, 6-month confirmed disability worsening, and ARBA  $\leq -0.4\%$ . Hazard ratios (or odds ratios) and the corresponding *p* values are derived from a Cox regression model (or logistic regression model) on treatment, baseline PASAT-3 category, the corresponding parameter at baseline, study, and treatment  $\times$  baseline PASAT-3 category interaction. A hazard ratio  $<1$  implies a lower risk of the event compared to reference category (i.e., favours fingolimod). <sup>a</sup>An odds ratio  $<1$  implies a lower risk of the ARBA compared to reference category (i.e., favours fingolimod). Treatment  $\times$  PASAT-3 category interaction *p* value: time to first confirmed relapse, *p* = 0.0190; time to first 6-month confirmed disability worsening, *p* = 0.0995; patients free of gadolinium-enhancing (Gd+) lesions, *p* = 0.3885; patients free of new/enlarging T2 lesions, *p* = 0.3525, patients with ARBA, *p* = 0.8314; time to NEDA, *p* = 0.3552. CI, confidence interval

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## CONFLICT OF INTEREST

The study sponsor was responsible for the study design and conduct, data collection, data management and data analysis. All authors had access to the data, and were involved in the manuscript preparation, including those employed by Novartis, for which they take full responsibility and have given final approval for submission before publication. **D.W.L.** has participated in speaker bureau panels for Bayer, Merck, Ammirall, Excemed, TEVA, Roche, Novartis, Biogen, Sanofi and Celgene, has had consultancy from Novartis, Bayer, Merck, Biogen, TEVA and Sanofi, and has received research grants from Bayer, Merck and Novartis, Biogen. **I.K.P.** has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Adamas Pharma, Ammirall, Bayer Pharma, Biogen, Celgene, Desitin, Sanofi-Genzyme, Janssen, Merck, Novartis, Roche and Teva, and has received research support from the German MS Society, Celgene, Novartis, Roche and Teva. **P.C.** has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Abbvie, Actelion, Ammirall, Bayer-Schering, Biogen, Eisai, Lundbeck, Merck Serono, Novartis, Sanofi-Aventis and Teva. He also receives research grants from the Swiss Multiple Sclerosis Society (SMSG), and the Swiss National Research Foundation. **G.C.** has received honoraria for serving on Data and Safety Monitoring Boards of Astra-Zeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Meyers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Mapi Pharmaceuticals Ltd, Merck, Merck/Pfizer, Opko Biologics, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata Pharmaceuticals, Teva Pharmaceuticals, VielaBio Inc., National Heart, Lung, and Blood Institute (Protocol Review Committee), (OPRU oversight committee), and for consulting or serving on advisory boards for Alexion, Antisense Therapeutics, Biodelivery Sciences International, Biogen, Genzyme, Genentech, GW Pharmaceuticals, Immunic, Klein-Buendel Incorporated, Medimmune/Viela Bio, Medday, Merck/Serono, Neurogenesis Ltd, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Recursion/Cerexis Pharmaceuticals, Regeneron, Reckover Pharmaceuticals, Roche, SAB Blotherapeutics and TG Therapeutics.

He is employed by the University of Alabama at Birmingham and is President of Pythagoras, Inc. a private consulting company located in Birmingham, AL. **L.K.'s institution** (University Hospital Basel) has received the following exclusively for research support: steering committee, advisory board and consultancy fees (Actelion, Bayer HealthCare, Biogen, BMS, Genzyme, Janssen, Merck, Novartis, Roche, Sanofi, Santhera, TG Therapeutics); speaker fees (Bayer HealthCare, Biogen, Merck, Novartis, Roche, Sanofi); support of educational activities (Allergan, Bayer HealthCare, Biogen, CSL Behring, Desitin, Genzyme, Merck, Novartis, Roche, Pfizer, Sanofi, Shire, Teva); licence fees for Neurostatus products; and grants (Bayer HealthCare, Biogen, European Union, InnoSwiss, Merck, Novartis, Roche, Swiss MS Society, Swiss National Research Foundation). **D.A.H.** is an employee of Novartis Pharma AG. **F.D.** and **D.T.** were employees of Novartis Pharma AG during the study and preparation of manuscript.

## AUTHOR CONTRIBUTIONS

**Dawn Langdon:** Conceptualization (equal); Methodology (equal); Writing – original draft (lead); Writing – review and editing (supporting). **Davorka Tomic:** Conceptualization (equal); Methodology (equal); Writing – review and editing (equal). **Iris-Katharina Penner:** Conceptualization (equal); Methodology (equal); Writing – review and editing (equal). **Pasquale Calabrese:** Conceptualization (equal); Methodology (equal); Writing-review and editing (equal). **Gary Cutter:** Conceptualization (equal); Methodology (equal); Writing – review and editing (equal). **Dieter A. Häring:** Conceptualization (equal); Formal analysis (lead); Methodology (lead); Writing – review and editing (equal). **Frank Dahlke:** Conceptualization (equal); Methodology (equal); Writing-review and editing (equal). **Ludwig Kappos:** Conceptualization (equal); Supervision (lead); Writing – review and editing (equal).

## DATA AVAILABILITY STATEMENT

Anonymized clinical data from the individual studies are available on reasonable request provided that it is in line with current ethical and intellectual property requirements surrounding the use of data. Requests should be directed through ClinicalStudyDataRequest.com.

## ORCID

Dawn W. Langdon  <https://orcid.org/0000-0003-1128-7417>

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

App S1

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