Original Research Paper

Plasma neurofilament light chain in children with relapsing MS receiving teriflunomide or placebo: A post hoc analysis of the randomized TERIKIDS trial

Jens Kuhle, Tanuja Chitnis (iD)**, Brenda Banwell, Marc Tardieu, Douglas L Arnold** (iD)**,
Andreea M Rawlings, Svend S Geertsen, Alex L Lublin, Stephane Saubadu,
Philippe Truffinet and Ludwig Kappos** (iD)

Abstract

Background: The phase 3 TERIKIDS study demonstrated efficacy and manageable safety for teriflunomide versus placebo in children with relapsing multiple sclerosis (RMS).

Objective: Evaluate plasma neurofilament light chain (pNfL) concentrations in TERIKIDS.

Methods: Patients received placebo or teriflunomide (14 mg adult equivalent) for up to 96 weeks in the double-blind (DB) period. In the open-label extension (OLE), all patients received teriflunomide until up to 192 weeks after randomization. pNfL was measured using single-molecule array assay (Simoa® NF-light™).

Results: Baseline mean age was 14.5 years; 69.4% were female. Baseline geometric least square mean pNfL levels were similar for teriflunomide ($n=78$) and placebo ($n=33$) patients (19.83 vs 18.30 pg/mL). Over the combined DB and OLE periods, pNfL values were lower for teriflunomide versus placebo (analysis of variance $p < 0.01$; Week 192: 10.61 vs 17.32 pg/mL). Observed between-group pNfL differences were attenuated upon adjustment for gadolinium (Gd)-enhancing or new/enlarged T2 lesion counts at DB Week 24. Higher baseline pNfL levels were associated with shorter time since first MS symptom onset, higher baseline Gd-enhancing lesion counts and T2 lesion volume, and increased hazard of high magnetic resonance imaging activity or clinical relapse during the DB period.

Conclusion: Teriflunomide treatment was associated with significantly reduced pNfL levels in children with RMS.

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Keywords: Neurofilament light chain, pediatric MS, teriflunomide

Correspondence to:
J Kuhle
MS Center, Neurology and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), Departments of Head, Spine and Neuromedicine, Biomedicine and Clinical Research, University Hospital Basel and University Basel, Petersgraben 4, 4031 Basel, Switzerland.
Jens.Kuhle@usb.ch

**Jens Kuhle
Ludwig Kappos**
MS Center, Neurology and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), Departments of Head, Spine and Neuromedicine, Biomedicine and Clinical Research, University Hospital Basel and University Basel, Basel, Switzerland

Tanuja Chitnis
Massachusetts General Hospital for Children, Boston, MA, USA

Brenda Banwell
Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA

Marc Tardieu
Hôpitaux Universitaires Paris-Sud, Paris, France

Douglas L Arnold
McGill University, Montréal, QC, Canada NeuroRx Research, Montréal, QC, Canada

**Andreea M Rawlings
Svend S Geertsen
Alex L Lublin**
Sanofi, Cambridge, MA, USA

**Stephane Saubadu
Philippe Truffinet**
Sanofi, Chilly-Mazarin, France

Introduction

Pediatric multiple sclerosis (MS) accounts for 2%–5% of MS cases[1] and is typically relapsing-remitting.[2] Children with MS often have higher relapse rates early in the disease course compared with adults with MS.[2] Although disease progression may be slower when MS onset occurs at a younger age, these patients often reach adult disability milestones earlier than patients with later MS onset.[3] Multiple disease-modifying therapies (DMTs) have been used off-label to treat children with MS.[4,5] Fingolimod is now approved for the treatment of children and adolescents aged ⩾10 years with relapsing forms of MS in the United States,[6] European Union,[7] and other geographies. However, the safety and efficacy of most DMTs are yet to be investigated in children with MS.

Teriflunomide is a DMT,[8] taken orally once daily, and is approved in more than 80 countries for the treatment of relapsing MS (RMS) in adults. The phase 3 TERIKIDS trial was a 96 week, multicenter, multinational, randomized, double-blind (DB), placebo-controlled, parallel-group study investigating teriflunomide in pediatric RMS, followed by a

Figure 1. TERIKIDS study design.
[a]Entry to OLE any time after initial PK run-in; a new run-in period (8 weeks) starts after entry to extension.
[b]Criteria for high MRI activity to qualify for switch to the OLE treatment were $\geqslant 9$ new/enlarged T2 lesions at Week 36 or $\geqslant 5$ new/enlarged T2 lesions on each of two consecutive MRI scans at Weeks 36 and 48, or at Weeks 48 and 72.
[c]Determined by body weight category: patients who weighed 20–40 kg received 3.5 mg/day; patients >40 kg received 7 mg/day.
[d]Determined by a combination of body weight category and individually predicted PK parameters based on data collected during the run-in period: patients who weighed 20–40 kg received 7 mg/day if predicted PK parameters were equal to or less than the adult range of predicted parameters for a repeated dose of 7 mg, or received 3.5 mg/day if PK parameters were higher than the adult range; patients > 40 kg received 14 mg/day if PK parameters were equal to or less than the adult range of predicted parameters, or received 7 mg/day if PK parameters were higher than the adult range.
EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; OLE = open-label extension; PK = pharmacokinetic; pNfL = plasma neurofilament light chain; R = randomization.

96-week open-label extension (OLE). Results from the DB period demonstrated efficacy and manageable safety for teriflunomide in children with RMS, with teriflunomide significantly reducing the combined risk of clinical relapse or high magnetic resonance imaging (MRI) activity compared with placebo.[9] Teriflunomide has subsequently been approved for use in the European Union in children aged 10 years or older with relapsing-remitting MS (RRMS).[10]

Several potential biomarkers are currently being explored to detect neuroaxonal injury, which is an important correlate of long-term disability in MS, but is not well captured by routine MRI scans.[11] Blood neurofilament light chain (NfL) concentrations have shown promise as a biomarker of axonal damage in many neurological diseases including MS.[12] Blood NfL is emerging as a measurable, real-time, fluid biomarker of disease evolution and treatment response in patients with MS.[13–15]

This post hoc analysis of the TERIKIDS trial aimed to evaluate changes in plasma NfL (pNfL) levels over time in children with RMS treated with teriflunomide or placebo, determine demographic or clinical characteristics associated with pNfL levels, and examine whether pNfL levels were associated with prospective outcomes.

Methods

Study design and participants
The TERIKIDS (NCT02201108) study design has been described previously.[9] Briefly, patients with RMS aged 10–17 years were randomized 2:1 to teriflunomide or placebo at the start of the DB period, which lasted for up to 96 weeks (Figure 1). The first 8 weeks of the DB period included a run-in period in which teriflunomide patients received a half dose of teriflunomide, determined by body weight category.

For the rest of the DB treatment period, teriflunomide patients received a dose equivalent to 14 mg in adults, determined by body weight category and patient pharmacokinetic parameters. Upon entering the OLE, patients from the DB placebo group received a half dose of teriflunomide during an 8-week run-in followed by the 14 mg adult equivalent teriflunomide dose; patients from the DB teriflunomide group continued through the OLE with the same previously adjusted teriflunomide dose from the DB period. Thus, for the OLE, the DB placebo group is referred to as the placebo/teriflunomide group and the DB teriflunomide group as the teriflunomide/teriflunomide group. Patients could enter the OLE early if they experienced a clinical relapse or high MRI activity ($\geq$9 new or enlarged T2 lesions at Week 36 or $\geq$5 new/enlarged T2 lesions on each of two consecutive MRI scans at Weeks 36 and 48, or at Weeks 48 and 72).

Written informed consent to participate in this substudy, additional to the consent provided for the main TERIKIDS trial, was obtained from the patient and patient's legal representative (parents or guardians) according to local regulations. The study conduct was approved by local institutional ethics review boards or ethics committees, as required by local regulations.

Assessments

Sample collection. This study used ethylenediaminetetraacetic acid (EDTA) plasma samples from blood that had been taken for pharmacokinetic analysis at DB Weeks 2, 12, 24, and 36; OLE Weeks 4, 8, 12, 24, and 36; and Week 192/end of treatment (EOT; Figure 1). DB Week 2 was used as the baseline, since no blood samples were taken at DB Week 0. EDTA plasma samples were stored in accordance with local regulations and processed at Pharmaceutical Product Development bioanalytical lab (Richmond, VA, USA).

pNfL analysis. Plasma NfL was measured using a highly sensitive single-molecule array (Simoa® NF-light™) immunoassay, with a calibration range of 500–0.167 pg/mL. All samples were briefly centrifuged to pellet aggregates and the clear supernatant was diluted at least four-fold in sample diluent and plated into 96 well microtiter plates that were processed in a Quanterix HD-X Analyzer™ (Quanterix, Lexington, MA, USA).

Each analytical run consisted of a set of calibrators and two sets of buffer controls and one matrix quality control for run acceptance per United States Food and Drug Administration (FDA) guidance.[16] Precision was evaluated by replicate analyses of buffer and human plasma quality control pools prepared at three concentrations spanning the calibration range, and was measured as the percent coefficient of variation (CV) of the set of values for each pool.

Sample quality control data acceptance criteria included $\leq$20% CV between duplicate average enzymes per bead (AEB) for calibration standards, quality controls, and unknowns; and $\leq$25% CV between duplicate AEB for upper and lower limits of quantification. The observed intra-assay CV ranged from 2.1% (mean 505 pg/mL) to 6.3% (0.6 pg/mL), and inter-assay CV ranged from 0.3% (mean 6.6 pg/mL) to 10.0% (150 pg/mL). All samples ($N \approx 792$) were analyzed at the Pharmaceutical Product Development bioanalytical lab in Richmond, VA, USA in duplicate. The fluorescence signal emitted from samples was captured with a built-in time-lapse molecular imager. Unknown sample concentrations were determined by interpolation from the standard curve, using a four-parameter logistic regression with $1/y^2$ weighting.

MRI assessment. Brain MRI acquisition in TERIKIDS has been described previously.[9] Briefly, MRI with and without contrast was acquired using a standardized protocol on 1.5 or 3.0 T scanners, and scans were reviewed and interpreted independently by trained neuroradiologists with no access to treatment assignment at a central facility. The time points at which MRI was acquired are shown in Figure 1.

Assessment of disability progression. Expanded Disability Status Scale (EDSS) score was used to quantify disability.[17,18] Disability progression was defined as a $\geq$0.5-point increase from baseline EDSS score if baseline score was >5.5, or a $\geq$1-point increase from baseline EDSS score if baseline score wasn $\leq$5.5, sustained for $\geq$24 weeks.[9]

Relapse assessment. Clinical relapses were defined as new or recurrent neurological symptoms that were not associated with fever or infection, lasted $\geq$24 hours, and were accompanied by new objective neurological findings on examination by a neurologist; relapses were confirmed by an independent adjudication panel.[9]

Statistical analysis

We summarized baseline characteristics by study arm using mean (standard deviation) for continuous variables or *n* (%) for categorical variables.

Differences between pNfL levels by study arm over time were examined using a mixed effects model for repeated measures (MMRM) including treatment arm, study visit (modeled categorically), treatment-arm-by-visit interaction, and baseline age as fixed effects. As pNfL values were skewed and not normally distributed, we log-transformed pNfL (base e) and modeled pNfL on a log scale. Due to the log transformation and exponentiation of the resulting coefficients, values represent the geometric least square means (GLSM). To examine the difference between study treatment arms, we used the GLSM ratio (GLSMR). We used an analysis of variance (ANOVA) global *F*-test to assess the significance of the treatment-arm-by-visit interaction.

We conducted an exploratory analysis to evaluate whether observed differences in pNfL between study arms over time can be partially explained by early changes on MRI. For this analysis, we used the MMRM model described above, additionally adjusting for gadolinium (Gd)-enhancing lesion counts and, in a separate model, for new/enlarged T2 lesion counts; both MRI outcomes were measured at DB Week 24. In these analyses, we excluded pNfL values from DB Weeks 2 and 12.

We conducted two sensitivity analyses to test the robustness of our main findings. First, because of observed differences between treatment arms with respect to sex and region, we ran separate models additionally adjusting for these values. Second, because we observed a small, albeit non-significant, difference in pNfL levels between study arms at baseline, we modeled post-baseline pNfL values with adjustment for baseline pNfL values.

We examined the cross-sectional relationship at baseline between pNfL values and patient characteristics using multivariate linear regression. We examined the following baseline characteristics: age, sex, body mass index, EDSS score, time since first symptoms of MS, time since most recent relapse onset prior to randomization (<120 days vs ≥ 120 days), number of Gd-enhancing lesions, and T2 lesion volume (cube root transformed).

We examined the association between baseline pNfL and the following prospective outcomes using Cox proportional hazards regression adjusted for age: first confirmed clinical relapse during the DB period, high MRI activity or first confirmed clinical relapse during the DB period, and 24-week sustained disability progression during the OLE. In this analysis, we used log base 2 transformation so that the hazard ratio of pNfL

would reflect the hazard of each outcome per doubling of baseline pNfL level. Given the expected association between treatment with teriflunomide and pNfL values over time, we conducted these analyses stratified by treatment arm.

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). We report 95% confidence intervals (CIs) and all statistical tests were two-sided, with *p*-values < 0.05 considered statistically significant. The sample size of this analysis was lower than that of the main trial because participants had to opt into this sub-study, have available blood samples, and pass pNfL sample quality controls.

Results

From the original TERIKIDS trial patient cohort, 111 (67%) patients volunteered to participate in the pNfL sub-study and had available measurements (33 patients from the placebo arm and 78 patients from the teriflunomide arm). At baseline among the patients in this sub-study, mean age was 14.5 years, 69.4% of patients were female, mean number of relapses within the previous year was 1.5, and mean number of Gd-enhancing lesions was 3.7. Treatment groups were well balanced at baseline for demographic and disease characteristics (Table 1). The median (interquartile range) follow-up time among the patients in this analysis was 193.0 (191.1, 196.1) weeks. In general, baseline demographic and disease characteristics were similar to the overall TERIKIDS trial population.[9]

The cross-sectional associations of baseline pNfL with demographic and clinical characteristics are shown in Table 2. Shorter MS disease duration, higher Gd-enhancing lesion counts, and higher T2 lesion volume were associated with higher baseline pNfL levels (Table 2).

Estimated GLSM concentrations of pNfL over time are shown in Figure 2 and Supplemental Table 1. At DB Week 2, GLSM (95% CI) pNfL levels were 18.30 (13.27, 25.25) pg/mL in the placebo arm and 19.83 (16.10, 24.42) pg/mL in the teriflunomide arm. In the DB period, pNfL levels for placebo increased to Week 24 before decreasing at Week 36, by which time 10 of the 33 placebo patients (30.3%), compared with 12 of the 78 teriflunomide patients (15.4%), had transferred early to the OLE after experiencing relapse or high MRI activity (Supplemental Table 2). For teriflunomide, pNfL levels decreased to Week 24 and then remained stable to Week 36. Over the OLE, pNfL levels decreased in both treatment arms from Week 4

Table 1. Baseline demographic and disease characteristics.

Characteristic	Placebo (*n*=33)	Teriflunomide (*n*=78)
Age, years	14.6 (2.0)	14.5 (2.1)
Female, *n* (%)	25 (75.8)	52 (66.7)
Pubertal status, *n* (%)		
Prepubertal (Tanner stage 1)	2 (6.1)	5 (6.4)
Pubertal (Tanner stage > 1)	31 (93.9)	73 (93.6)
Number of relapses within past 1 year	1.4 (0.7)	1.6 (0.7)
Number of relapses within past 2 years	1.9 (1.0)	2.1 (1.0)
MS disease duration, years	2.5 (2.3)	2.3 (2.1)
Patients receiving MS medication in past 2 years, *n* (%)	8 (24.2)	10 (12.8)
Patients with Gd-enhancing lesions, *n* (%)	14 (42.4)	41 (53.9)
Number of Gd-enhancing lesions	2.6 (6.3)	4.1 (8.1)
T2 lesion volume, cm^3	11.1 (11.1)	13.1 (19.0)
Normalized brain volume, cm^3	1556.7 (82.1)	1542.5 (80.0)

Values are mean (standard deviation) unless otherwise indicated. Disease duration was calculated as the difference between date of first MS symptoms and randomization date.
Gd = gadolinium; MS = multiple sclerosis.

Table 2. Associations between demographic and clinical factors and baseline pNfL values.

	Beta (95% CI) (*N*=111)	Percentage change in pNfL[a] (95% CI) (*N*=111)	*p*-value
Age[b]	−0.043 (−0.113, 0.027)	−4.2 (−10.7, 2.7)	0.23
Male sex[c]	−0.036 (−0.354, 0.281)	−3.6 (−29.8, 32.4)	0.82
Body mass index	−0.018 (−0.058, 0.021)	−1.8 (−5.6, 2.1)	0.36
EDSS score	0.109 (−0.057, 0.274)	11.5 (−5.5, 31.5)	0.20
Relapse < 120 days ago[d]	0.091 (−0.218, 0.399)	9.5 (−19.6, 49.1)	0.56
MS disease duration relative to randomization[b]	**−0.068 (−0.135, −0.001)**	**−6.5 (−12.6, −0.1)**	**0.048**
Number of Gd-enhancing lesions	**0.048 (0.025, 0.071)**	**4.9 (2.6, 7.4)**	**<0.01**
T2 lesion volume[e]	**0.347 (0.143, 0.551)**	**41.5 (15.3, 73.6)**	**<0.01**

Multivariable linear regression analysis of log-transformed pNfL concentration values was used to examine association with the variables listed above. Numbers in bold indicate statistical significant association ($p < 0.05$) between the variable and the baseline pNFL value.
[a]Beta coefficients were back-transformed and converted to a percentage for interpretation; values represent percentage increase/decrease in pNfL per unit change of the independent variable for continuous variables or relative to the reference group for categorical variables. Disease duration was calculated as the difference between date of first MS symptoms and randomization date.
[b]Per year.
[c]Reference is female sex.
[d]Reference group is relapsed ⩾120 days ago.
[e]Cubic root.
CI = confidence interval; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MS = multiple sclerosis; pNfL = plasma neurofilament light chain.

(GLSM (95% CI) pNfL at OLE Week 4: placebo/teriflunomide arm, 20.02 (14.30, 28.04) pg/mL; teriflunomide/teriflunomide arm, 12.66 (10.19, 15.72) pg/mL), reaching their lowest levels at OLE Week 36 (placebo/teriflunomide, 13.80 (10.26, 18.57) pg/mL; teriflunomide/teriflunomide, 10.16 (8.38, 12.31) pg/mL).

Over the combined DB and OLE periods, pNfL values were significantly lower for teriflunomide compared with placebo (global ANOVA F-test for interaction: $p < 0.01$). In the DB period, the greatest difference between treatment arms was observed at Week 24, with a GLSMR (95% CI) for teriflunomide versus placebo of 0.74 (0.53, 1.05; $p = 0.09$). At five of the six OLE time points, pNfL values differed significantly between the treatment groups, with GLSMRs for teriflunomide/teriflunomide versus placebo/teriflunomide ranging from 0.61–0.65; at OLE
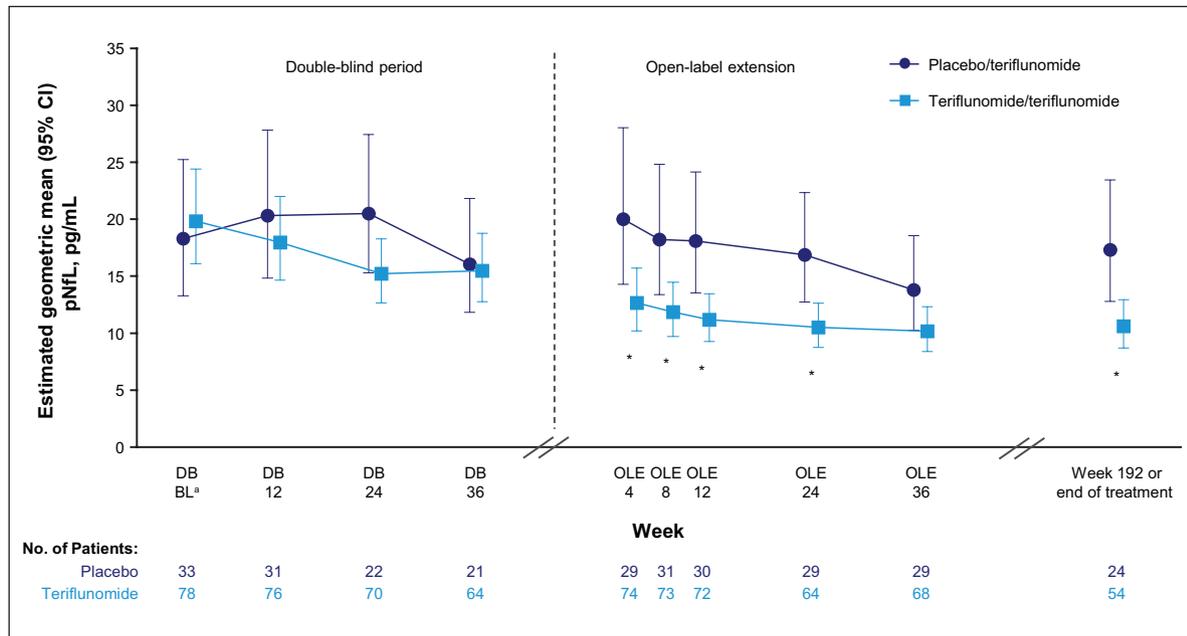
Figure 2. The effect of teriflunomide versus placebo on pNfL levels over time in the TERIKIDS study
*$p < 0.05$ between treatment groups.
Geometric least square means and 95% CIs were obtained by exponentiating estimates from the mixed model for repeated measures analysis, which modeled the log-transformed pNfL concentration as response variable, and had treatment, visit, treatment-by-visit interaction, and age as covariates.
[a]BL is DB Week 2.
BL = baseline; CI = confidence interval; DB = double blind; OLE = open-label extension; pNfL = plasma neurofilament light chain.

Week 36, the reduction with teriflunomide/teriflunomide was not significant (GLSMR (95% CI): 0.74 (0.52, 1.05); $p = 0.09$; Supplemental Table 1).

In exploratory analyses that included adjustment for MRI lesion counts at DB Week 24, the GLSMR at DB Week 24 for teriflunomide versus placebo was attenuated from 0.74 in the main analysis, to 0.98 and 1.00, after including Gd-enhancing lesion and new/enlarged T2 lesion counts as covariates, respectively. During the OLE, GLSMRs were attenuated at each time point, ranging from 0.74–0.94 and 0.76–0.96 after adjustment for DB Week 24 Gd-enhancing lesion and new/enlarged T2 lesion counts, respectively; all p-values for these GLSMRs were not significant (Supplemental Table 3). In sensitivity analyses adjusting the mixed models for sex (Supplemental Table 4) and region (Supplemental Table 5), the results were similar to those from the main analysis. A final sensitivity analysis examining post-baseline pNfL values with adjustment for baseline pNfL yielded slightly more favorable GLSMRs, compared with the main analysis, for teriflunomide versus placebo in the DB period (p-value at DB Week 24: < 0.01) and teriflunomide/teriflunomide versus placebo/teriflunomide in the OLE (significant p-values at all OLE time points; Supplemental Table 6).

In analyses of prospective outcomes, each doubling of baseline pNfL was associated with an increased hazard of high MRI activity or clinical relapse for all patients during the DB period (hazard ratio [HR] = 1.22, 95% CI: 1.01, 1.48; $p = 0.04$); statistical significance was not reached for associations between baseline pNfL level and the other prospective outcomes for the overall study population, nor when any of these prospective outcomes were assessed by treatment arm (Table 3).

Discussion

In this post hoc analysis of the TERIKIDS trial, in the combined DBP and OLE, we found that pNfL levels were lower among children with RMS treated with teriflunomide compared with placebo. We also found that pNfL was prognostic of relapse or MRI activity. Thus, our analysis supports pNfL as a useful biomarker of the risk of acute focal inflammatory activity in pediatric MS.

Previous studies of DMTs for MS have reported similar effects on NfL levels in adults. In an analysis of 246 patients with MS, adjusted for demographic and disease characteristics, use of a DMT was significantly associated with approximately

Table 3. Hazard ratio of the association between baseline pNfL level and prospective outcomes.

	Placebo	Teriflunomide	Overall
First confirmed clinical relapse during DB period			
n/N (%)	15/33 (45%)	27/78 (35%)	42/111 (38%)
Hazard ratio (95% CI)	1.00 (0.66, 1.50)	1.22 (0.91, 1.62)	1.10 (0.88, 1.38)
p value	0.98	0.18	0.41
High MRI activity or first confirmed clinical relapse during DB period			
n/N (%)	23/33 (70%)	35/78 (45%)	58/111 (52%)
Hazard ratio (95% CI)	1.21 (0.90, 1.64)	1.27 (0.99, 1.63)	1.22 (1.01, 1.48)
p value	0.21	0.06	0.04
24-week sustained disability progression in OLE			
n/N (%)	8/32 (25%)	11/74 (15%)	19/106 (18%)
Hazard ratio (95% CI)	1.01 (0.56, 1.80)	1.40 (0.95, 2.06)	1.26 (0.92, 1.73)
p value	0.98	0.09	0.15

Hazard ratios (95% CIs) were estimated using Cox proportional hazards regression with adjustment for age. pNfL was modeled using log base 2 transformation so that the hazard ratio of pNfL would reflect the hazard of each outcome per doubling of baseline pNfL level. Analyses of 24 week sustained disability progression extend to the OLE; the 5 patients who did not enter the OLE were excluded from the disability progression analyses.
CI = confidence interval; DB = double blind; MRI = magnetic resonance imaging; OLE = open-label extension; pNfL = plasma neurofilament light chain.

18% lower serum NfL levels.[15] In another cohort study (*N* = 286) of treatment-naïve patients with MS, there was an 11% reduction in median serum NfL levels upon initiation of a DMT; switching to a higher efficacy therapy resulted in a 30% reduction in NfL levels.[19] These findings have been further supported by studies of patients from clinical trials. In an analysis of patients with RRMS from two phase 3 trials (*N* = 589), fingolimod treatment was associated with significantly reduced blood NfL levels compared with intramuscular interferon beta (IFNB)-1a (ratio of means (95% CI): 0.794 (0.705–0.894) over 1 year and compared with placebo (0.628 (0.552–0.714) over 2 years (*p* < 0.001 for both comparisons).[20] Similarly, over 2 years among treatment-naïve RRMS patients in the phase 3 CARE-MS I study, median serum NfL levels reduced to a significantly greater extent with alemtuzumab treatment (from 31.7 to 13.2 pg/mL) compared with subcutaneous IFNB-1a (from 31.4 to 18.7 pg/mL; *p* < 0.0001 between groups); the lower levels with alemtuzumab also remained stable over longer-term follow-up (12.7 pg/mL at Year 7).[21]

Our study found associations between higher baseline pNfL levels and shorter MS disease duration, higher baseline Gd-enhancing lesion counts, and higher baseline T2 lesion volume, as well as increased hazard of high MRI activity or clinical relapse during the DB period. Several previous studies in adult patients have yielded similar correlations between higher pNfL levels and worsening disability, increased

number of relapses, and increased MRI disease activity.[13,19–23] Of note, recent cohort studies have extended these findings to pediatric MS, with associations reported between higher serum NfL levels and recent relapse,[24] future relapses,[25] increased MRI activity,[24,25] and higher EDSS scores.[24] The previous reports of elevated pNfL levels for up to 3 months after a relapse[19,24] may explain the trajectory of pNfL levels observed in the placebo arm in our study. pNfL levels increased in this placebo arm from DB Week 2 to 24, and decreased at Week 36. These findings likely reflect the higher frequency of relapses in these patients and therefore the higher proportion switching early to the OLE, compared with the DB teriflunomide group. This higher proportion of patients switching to the OLE early due to relapse or high MRI activity may also explain the higher pNfL levels observed at OLE Week 4 in the placebo/teriflunomide arm compared with teriflunomide/teriflunomide.

The present study has some limitations. The statistical power of the study, which is already limited in a post hoc analysis, was further reduced due to many patients in the DB placebo arm experiencing relapses or meeting the high MRI activity criteria and therefore switching early to the OLE. This potentially attenuated the observed differences in pNfL between the teriflunomide and placebo arms. In addition, we had limited power to quantify the associations between baseline pNfL level and prospective outcomes since only a small number of the children experienced those

outcomes. Furthermore, while it was necessary to set the baseline for this analysis at 2 weeks after the start of treatment, previous studies suggest meaningful changes in NfL levels would not be expected within this time frame post-DMT initiation.[26,27] Finally, as the Week 192/EOT time point included a range of treatment exposures, this limited direct comparisons with the OLE Week 36 data. Nonetheless, TERIKIDS was a multinational study conducted in 57 clinical centers in 22 countries, potentially increasing generalizability of the findings. The measurements in this study, including for pNfL, MRI outcomes, and relapses, were performed in a rigorous and standardized manner, to minimize measurement error, and the study arms in this post hoc analysis were well balanced at baseline.

The findings of this post hoc analysis of the TERIKIDS trial suggest that pNfL levels decrease over time among children treated with teriflunomide compared with placebo, in parallel with the impact of treatment on inflammatory activity observed on MRI. Further investigation is warranted on the utility of pNfL as a biomarker for monitoring disease activity and treatment effects in clinical practice.

Authorship Contributions
All authors participated in study design, or data acquisition, analysis or interpretation; drafted or critically revised the manuscript; and approved the final version before submission. AMR performed the statistical analyses.

Data Sharing Statement
Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and data set specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

ORCID iDs

Tanuja Chitnis https://orcid.org/0000-0002-9897-4422

Douglas L Arnold https://orcid.org/0000-0003-4266-0106

Ludwig Kappos https://orcid.org/0000-0003-4175-5509

Supplemental Material

Supplemental material for this article is available online.

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