Effect of Teriflunomide on Neurofilament Light Chain Levels in Children with RMS

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OBJECTIVE

- **To summarize changes in plasma levels of neurofilament light chain (pNfL) in children with relapsing MS (RMS) treated with teriflunomide or placebo**

INTRODUCTION

- For patients with MS, pNfL is a validated biomarker of disease activity and a predictor of disease worsening[1]
- About 2–10% of MS cases worldwide occur in children, most of whom have RMS, with more frequent and severe relapses compared with adults[2]
- Few clinical trials of disease-modifying therapies (DMTs) have been conducted in paediatric patients with MS[3]
  - Despite the lack of evidence, DMTs are commonly used for paediatric patients with MS[3]
- Teriflunomide, a once-daily oral immunomodulator, is approved in more than 80 countries for the treatment of RMS
- The phase 3 TERIKIDS study (NCT02201108) demonstrated efficacy and manageable safety for teriflunomide in children and adolescents with RMS[4]
  - The effects of teriflunomide on pNfL were also evaluated in the TERIKIDS study, and findings are reported here

METHODS

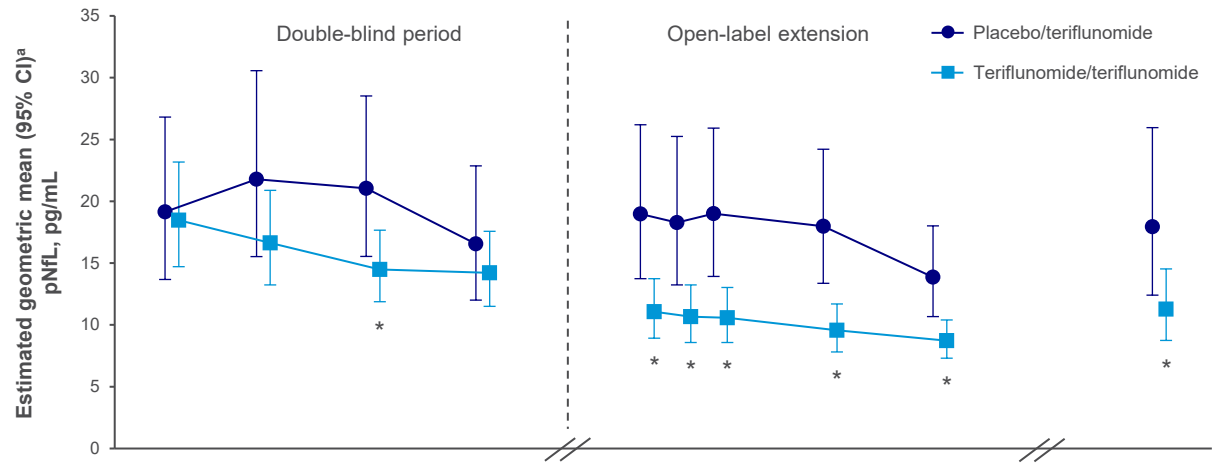
- TERIKIDS is a 96-week, placebo-controlled, multinational phase 3 study of patients with RMS aged 10–17 years, randomized 2:1 to receive teriflunomide (equivalent to 14 mg in adults; n=109) or placebo (n=57), with a 96-week open-label extension (OLE) (**Figure 1**)
- Patients could enter the OLE early if they had clinical relapse or high MRI activity, defined as ≥9 new/enlarging T2 lesions at Week 36 or ≥5 new/enlarging T2 lesions on 2 consecutive MRI scans at Weeks 36/48 or 48/72
- pNfL data were measured and analysed using the NF-light® assay at Weeks 2, 12, 24, and 36 of the core study and during the OLE
  - Core study Week 2 was used as a surrogate for baseline; pNfL data were not available at Week 0, as pNfL levels were measured in leftover blood from samples taken for pharmacokinetic (PK) analysis
- pNfL data were evaluated using descriptive statistics and a mixed-effects model with repeated measures (MMRM)

CONCLUSION

- **This preliminary analysis suggests that teriflunomide treatment is associated with a decrease in pNfL levels in children with RMS**

RESULTS

Figure 2. The Effect of Teriflunomide Versus Placebo on pNfL Levels Over Time in the TERIKIDS Study

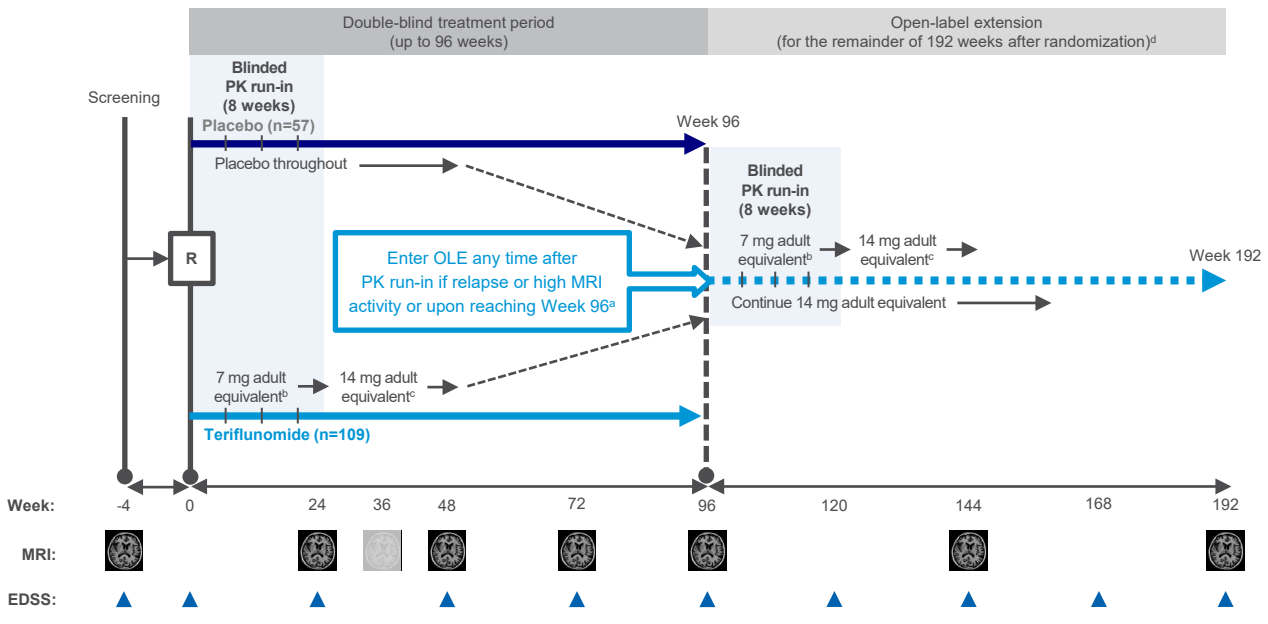


No. of Patients:										
Placebo	25	24	17	17	21	23	22	22	21	16
Teriflunomide	54	54	51	46	51	50	49	45	46	32

BL=baseline; DB=double blind; OL=open label.
*P<0.05 between treatment groups.
[a]Obtained by exponentiating the estimate of the least squares mean (with corresponding CI) from the model, which was an MMRM analysis for log-transformed pNfL concentration as response variable, and treatment, visit, treatment-by-visit interaction and age as covariates.
[b]BL is core study Week 2.

- For this preliminary assessment (OLE cut-off date: 9 April 2021), data were available for 79 patients at baseline, 72 patients at OLE Week 4, and 67 patients at OLE Week 36
- At baseline, treatment groups were well matched for mean age, sex, mean number of relapses within the previous year, and mean number of gadolinium (Gd)-enhancing lesions (**Table 1**)
- At baseline, estimated mean (95% confidence interval [CI]) pNfL values were similar between the treatment groups (teriflunomide, 18.5 [14.7–23.2] pg/mL; placebo, 19.2 [13.7–26.8] pg/mL; P=0.86) (**Figure 2**)
- By core study Week 24, pNfL levels had decreased with teriflunomide (14.5 [11.9–17.7] pg/mL) and increased with placebo (21.1 [15.5–28.5] pg/mL; P=0.04)
- By core study Week 36, pNfL levels had decreased in both groups (teriflunomide, 14.2 [11.5–17.6] pg/mL; placebo, 16.6 [12.0–22.9] pg/mL), possibly because patients receiving placebo who experienced relapse or high MRI activity were transferred to the OLE
  - This interpretation is supported by higher pNfL levels in the placebo/teriflunomide group at OLE Week 4 versus core study Week 36 (+8.4 pg/mL), whereas the teriflunomide/teriflunomide group had lower pNfL levels at OLE Week 4 versus core study Week 36 (−1.8 pg/mL)
- At all OLE timepoints, mean pNfL levels were significantly lower in the teriflunomide/teriflunomide group than the placebo/teriflunomide group
  - In both groups, the lowest mean pNfL level was at OLE Week 36 (teriflunomide/teriflunomide, 8.7 [7.3–10.4] pg/mL; placebo/teriflunomide, 13.9 [10.7–18.0] pg/mL)

Figure 1. TERIKIDS Study Design



EDSS=Expanded Disability Status Scale; R=randomization.
[a]Entry to OLE any time after initial PK run-in; a new run-in period (8 weeks) starts after entry to extension; [b]Determined by body weight (above or below 40 kg); [c]Determined by a combination of body weight (above or below 40 kg) and individually predicted PK parameters based on data collected during the run-in period; [d]An optional additional extension period with teriflunomide was offered to patients when they completed the study, to provide treatment until they were 18 years old and/or could switch to teriflunomide commercial product, whichever came first.

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	Placebo (n=25)	Teriflunomide (n=54)
Age, years	15.0 (1.5)	15.1 (1.7)
Female, n (%)	18 (72.0)	38 (70.4)
Pubertal status, n (%)		
Prepubertal (Tanner stage 1)	1 (4.0)	1 (1.9)
Pubertal (Tanner stage >1)	24 (96.0)	53 (98.1)
No. of relapses within past 1 year	1.3 (0.6)	1.6 (0.7)
No. of relapses within past 2 years	1.8 (0.8)	2.1 (1.0)
Years from first MS symptoms to randomization	2.47 (2.43)	1.88 (1.89)
Patients receiving MS medication in past 2 years, n (%)	8 (32.0)	8 (14.8)
Patients with Gd-enhancing lesions, n (%)	12 (48.0)	30 (57.7)
No. of Gd-enhancing lesions	3.2 (7.1)	3.4 (6.4)
T2 lesion volume	11.2 (12.0)	10.3 (13.0)

Values are mean (SD) unless otherwise indicated.

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