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Study Design of a Phase 3 Trial Evaluating Teriflunomide in Children and Adolescents With Relapsing Multiple Sclerosis

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INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing–remitting MS
- In phase 3 clinical studies in adult patients, teriflunomide 14 mg showed consistent and significant clinical benefits compared with placebo[1,2]
  - TEMSO (**TE**riflunomide **M**ultiple **S**clerosis **O**ral, NCT00134563): 31.5% reduction in annualized relapse rate (ARR; *P*<0.001) and 29.8% decrease in sustained disability progression (confirmed for 12 weeks) (*P*=0.028)[1]
  - TOWER (**T**eriflunomide **O**ral in people **W**ith relapsing multipl**E** scle**R**osis, NCT00751881): 36.3% reduction in ARR (*P*<0.001) and 31.5% decrease in risk of disability progression (*P*=0.044)[2]
- Teriflunomide 7 mg also showed significant benefits on ARR and, although not significant, showed a reduction in risk of disability progression[1,2]
- Both teriflunomide doses showed similar and manageable safety and tolerability profiles across the two studies[1,2]
- Pediatric patients represent approximately 5% of MS cases,[3] and many children with MS experience substantial cognitive impairment[4]
  - However, none of the currently approved treatments for adult relapsing MS have been formally evaluated in pediatric clinical trials and none are approved for pediatric use by the US Food and Drug Administration[5]
  - Teriflunomide is the active metabolite of leflunomide, approved for the treatment of rheumatoid arthritis since 1998.[6] Leflunomide has been evaluated in children with juvenile arthritis, and the safety profile was similar to that observed in adults
- Here we report the design of the TERIKIDS study, which will evaluate teriflunomide treatment in pediatric patients with relapsing MS

OBJECTIVES

Primary Objective

- To assess the effect of teriflunomide compared with placebo on time to first clinical relapse after randomization

Key Secondary Objectives

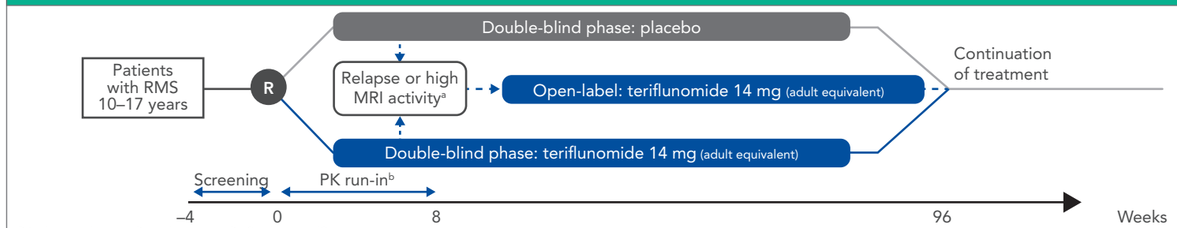
- To assess the effects of teriflunomide compared with placebo on brain magnetic resonance imaging (MRI) parameters and cognitive function
- To evaluate the safety and tolerability of teriflunomide compared with placebo
- To measure the pharmacokinetics (PK) of teriflunomide

METHODS

Study Design

- TERIKIDS is a 2-year, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study (**Figure 1**)

Figure 1. TERIKIDS Study Design



PK, pharmacokinetics; R, randomization; RMS, relapsing MS.
In case of at least five new/enlarged T2 lesions at the MRI of Week 24, an additional MRI will be performed at Week 36; relapse or high disease activity defined as: [a]A cumulative number ≥9 new/enlarged T2 lesions at Week 36 or ≥5 new/enlarged T2 lesions at both Week 36 and Week 48. [b]Blinded 8-week PK run-in phase following randomization, consisting of 4 weeks with PK sample collection plus 4 weeks of analysis. During the 4-week PK run-in, patients weighing 30±10 kg will receive 3.5 mg teriflunomide once daily, and patients weighing >40 kg will receive teriflunomide 7 mg once daily. Patients entering the open-label teriflunomide arm will be required to repeat the 8-week PK run-in, which includes additional PK samples corresponding to Weeks 2, 3, and 4 of open-label treatment.

Table 1. Inclusion and Key Exclusion Criteria for the TERIKIDS Study

Inclusion criteria	• Pediatric patients (aged 10–17 years) who satisfy McDonald criteria for MS (2010)[6] and International Pediatric Multiple Sclerosis Study Group criteria for pediatric MS (2013)[7] • ≥1 relapse (attack) in the 12 months preceding randomization, or ≥2 relapses (attacks) in the 24 months preceding randomization • Signed informed consent/assent obtained from patient and patient's legal representative (parents or guardians) according to local regulations
Key exclusion criteria	• EDSS score >5.5 at screening or randomization • Relapse within 30 days prior to randomization • Treatment with other disease-modifying therapies or immunomodulatory agents within the previous 3 months or five half-lives, whichever is greater

EDSS, Expanded Disability Status Scale.

Table 2. Primary and Secondary Efficacy Endpoints in the TERIKIDS Study

Primary efficacy endpoint	• Time to first clinical relapse[a] after randomization
Secondary efficacy endpoints	• Proportion of relapse-free patients • MRI endpoints – Number of new/newly enlarged T2 lesions – Number of T1 Gd-enhancing T1 lesions – Number of new T1-hypointense lesions – Change in volume of T2 lesions – Change in volume of T1-hypointense lesions – Brain atrophy – Proportion of patients with new or enlarged T2 lesions at Weeks 48 and 96 • Cognitive function endpoints – SDMT[4] – Cognitive Battery Test (when available)

Gd, gadolinium; MRI, magnetic resonance imaging; SDMT, Symbol Digit Modalities Test.
[a]A relapse is defined as new or recurrent neurological symptoms lasting at least 24 hours without fever and accompanied by new neurological findings documented using the Functional System Score.

Table 3. Timing of Efficacy and Safety Assessments in the TERIKIDS Study (Double-Blind Phase)

	Screening		Treatment Period																	Post Drug Elimination Follow-up		Unscheduled
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	
W	W –4	R	4	8	12	16	20	24	30	36	42	48	54	60	66	72	78	84	90	EOT	EOT +2 W	EOT +4 W	Relapse visit
Efficacy																							
EDSS	✓	✓						✓				✓				✓				✓			✓
SDMT		✓						✓				✓				✓				✓			
Cognitive Battery Test		✓																		✓			
Brain MRI		✓						✓				✓				✓				✓			✓
Safety[a]																							
ECG 12-leads		✓																		✓	✓	✓	
Clinical routine and safety laboratories	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Teriflunomide PK sampling			✓	✓	✓			✓		✓										✓	✓	✓	

ECG, electrocardiogram; EDSS, Expanded Disability Status Scale; EOT, end of treatment; MRI, magnetic resonance imaging; PK, pharmacokinetics; R, randomization; SDMT, Symbol Digit Modalities Test; W, week.
[a]Adverse events reporting and vital signs assessment took place at each visit. [b]Samples will be taken at Weeks 2, 3, and 4 for dose adjustment.

- A total of 165 pediatric patients will be randomized (2:1) to once-daily oral teriflunomide or placebo for 96 weeks
  - After an 8-week titration and adaptation process, the pediatric teriflunomide dose will correspond to the adult 14-mg dose
- Open-label period
  - Patients will switch to open-label teriflunomide treatment in the event of a confirmed relapse following the 8-week titration and adaption process, or high MRI activity (≥9 new/enlarged T2 lesions at Week 36 or ≥5 new/enlarged T2 lesions at both Week 36 and Week 48)

Entry Criteria

- Key study eligibility criteria are shown in **Table 1**[7,8]

Assessments

- The primary and secondary efficacy endpoints are presented in **Table 2**[4]
- Efficacy measures and PK parameters will be assessed during the double-blind treatment phase, as shown in **Table 3**
  - PK parameters will also be assessed at the same time points in patients entering the open-label period
- Assessments of adverse events, vital signs, clinical laboratory parameters, and electrocardiogram will be made throughout both double-blind (**Table 3**) and open-label period

RESULTS

- Results will be reported on completion of the study

CONCLUSIONS

- The TERIKIDS study will provide data on the use of teriflunomide in children and adolescent patients with relapsing forms of MS

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