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Investigation of the Effectiveness and Tolerability of Colesevelam HCl for Accelerated Elimination of Teriflunomide in Healthy Subjects

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INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS. Four controlled clinical trials in patients with MS have demonstrated consistent efficacy on clinical and MRI endpoints and a manageable safety profile of teriflunomide 14 mg and 7 mg administered once daily[1–4]
- Teriflunomide is contraindicated in pregnancy, as data from animal studies suggest the potential for embryotoxic and teratogenic effects (as observed in rats and rabbits)[5]
  - Teriflunomide has an elimination half-life of 19 days and takes an average of 8 months for plasma concentrations to reach 0.02 µg/mL, a level expected to confer minimal embryo-fetal risk to humans based on animal data[5]
  - Due to individual variations in drug clearance, it may take up to 2 years to reach plasma concentrations <0.02 µg/mL
- For patients taking teriflunomide, the following accelerated elimination procedure (AEP) is recommended for people taking teriflunomide who become pregnant or are planning a pregnancy, and any case where rapid elimination of teriflunomide is medically desirable[5–7]:
  - Cholestyramine 8 g 3 times daily for 11 days (or 4 g, if the 8-g dose is not well tolerated), or
  - Activated charcoal 50 g twice daily for 11 days
- At the end of 11 days, plasma concentrations of teriflunomide in plasma were reduced by >98%.[7] A reduction in plasma concentration of >99% is required to reach 0.02 µg/mL of teriflunomide[5]
- The most frequently reported adverse event (AE) occurring during an AEP is gastrointestinal disorder[5]
- We investigated colesevelam hydrochloride (HCl) as an alternative treatment to cholestyramine for the elimination of teriflunomide
  - Colesevelam HCl, a bile acid sequestrant, has a capacity for lowering cholesterol (primary indication) that is 3 x higher on a per-gram basis than cholestyramine
  - Treatment with colesevelam HCl appears to have less frequent and less severe gastrointestinal side effects than cholestyramine; however, this has not been investigated

OBJECTIVES

Primary Objective

- To investigate if colesevelam HCl was able to accelerate the elimination of teriflunomide

Secondary Objectives

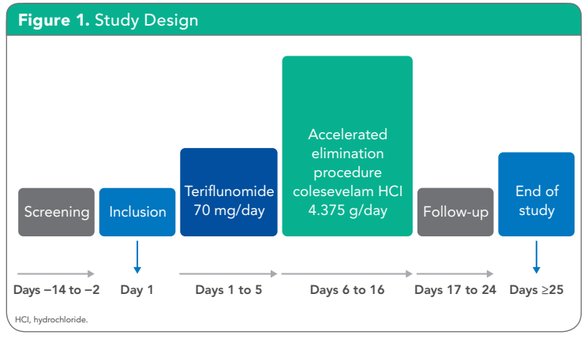
- To investigate the safety and tolerability of colesevelam HCl
- To assess teriflunomide plasma concentrations during and after AEP

METHODS

Study Design

- This was an open-label single-center study in healthy men and women aged 18–45 years
- Subjects received a loading dose of teriflunomide (70 mg). This dosage regimen was chosen to approximate the steady state plasma concentrations observed after repeated 14-mg doses in patients with MS. This was immediately followed by an AEP with colesevelam HCl, as detailed below and in **Figure 1**
- All study medication was to be administered with a meal
  - Days 1–5: Teriflunomide, 5 × 14-mg tablets once daily (70-mg total daily dose)
  - Days 6–16: Colesevelam HCl, 4 × 625-mg tablets in the morning plus 3 × 625-mg tablets in the evening (7 tablets per day; 4.375-g total daily dose)

Figure 1. Study Design



HCl, hydrochloride.

Pharmacokinetic Evaluations

- Blood was sampled throughout the study to determine plasma teriflunomide concentrations using a validated liquid chromatography coupled with tandem mass spectrometry method with a lower limit of quantification of 0.01 µg/mL
- If plasma teriflunomide concentration was >0.02 µg/mL at Day 17 (end of AEP), subjects received cholestyramine 4 g 3 times daily (12-g total daily dose) as a precautionary measure until teriflunomide concentration was ≤0.02 µg/mL

Safety Evaluations

- Subjects were monitored for AEs, including gastrointestinal events, standard clinical laboratory evaluations (biochemistry, hematology, urinalysis, and coagulation), vital signs (heart rate, systolic and diastolic blood pressure), oral body temperature, 12-lead electrocardiogram (automatic readings), physical examination, and body weight

RESULTS

Subjects

- A total of 18 subjects were treated and completed the study. Baseline characteristics are summarized in **Table 1**

Pharmacokinetics

- Mean (standard deviation) plasma teriflunomide concentration was 36.3 (6.42) µg/mL at Day 6 (start of AEP) and 1.33 (0.833) µg/mL at Day 17 (end of 11-day AEP), showing a mean decrease of 96.1% (coefficient of variation 3.51%) (**Figure 2** and **Table 2**)

Table 1. Baseline Characteristics and Subject Demographics

	All (N=18)
Age, mean (SD), y	37.3 (6.1)
Male, n (%)	11 (61.1)
Caucasian/white, n (%)	18 (100)
Body mass index, mean (SD)	23.95 (2.24)

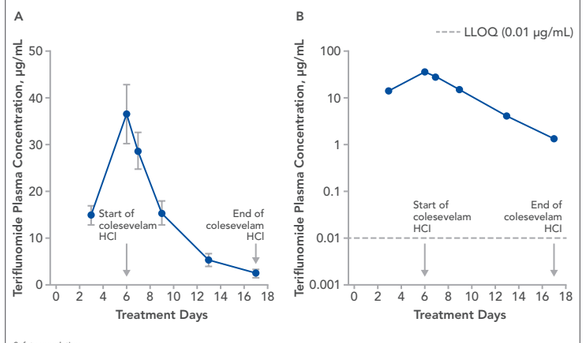
Safety population.
SD, standard deviation.

Table 2. Percent Change in Plasma Concentrations of Teriflunomide During AEP With Colesevelam HCl

Duration of Colesevelam HCl Administration (Study Day)	Mean Percent Change (CV%)
1 day (Day 7)	−21.8 (−28.51)
3 days (Day 9)	−59.3 (−13.6)
7 days (Day 13)	−87.9 (−5.83)
11 days (Day 17)	−96.1 (−3.51)

AEP, accelerated elimination procedure; CV, coefficient of variation; HCl, hydrochloride.

Figure 2. Mean (±SD) Plasma Concentrations of Teriflunomide (Linear [A] and Semi-Log [B] Plots)



Safety population.
HCl, hydrochloride; LLOQ, lower limit of quantification; SD, standard deviation.

- To ensure complete elimination of teriflunomide after the AEP, all subjects received cholestyramine, as follows, to attain plasma concentrations of teriflunomide ≤0.02 µg/mL: 1 subject for 10 days, 16 subjects for 11 days, and 1 subject for 12 days

Safety

- There were no serious or severe AEs, and no AEs led to discontinuation of study treatment
- A summary of AEs related to treatment (teriflunomide or colesevelam HCl) is provided in **Table 3**
- All subjects recovered from AEs

Table 3. Summary of AEs

	Teriflunomide	Colesevelam HCl (After Teriflunomide)
All AEs,[a] n (%)	6 (33.3)	6 (33.3)
Intensity of AEs, n (%)		
Mild	6 (33.3)	3 (16.7)
Moderate	0	3 (16.7)
Severe	0	0
AEs related to treatment, by MedDRA preferred term,[b] n (%)		
Headache	1 (5.6)	2 (11.1)
Constipation	1 (5.6)	0
Diarrhea	1 (5.6)	0
Flatulence	1 (5.6)	0
Fatigue	4 (22.2)	1 (5.6)

Safety population. [a]n=18; [b]subjects may have experienced >1 event and therefore may be captured in >1 category.
AE, adverse event; HCl, hydrochloride; MedDRA, Medical Dictionary for Regulatory Activities.

- One subject receiving cholestyramine experienced moderate gastrointestinal disorder AEs

CONCLUSIONS

- Administration of colesevelam HCl for 11 days was sufficient to reduce plasma teriflunomide concentrations by on average >96%
- Although a direct comparison with cholestyramine has not been conducted, colesevelam HCl may offer an alternative method for accelerated elimination of teriflunomide with improved gastrointestinal tolerability

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Disclosures

CL, ZG, ST, and **AD:** Employees of Sanofi. **NF:** Employee of Biotrial. **TT** and **FB:** Employees of Genzyme.

Disclaimer

Teriflunomide is approved in many countries, including the US and the European Union, for the treatment of relapsing multiple sclerosis or relapsing-remitting multiple sclerosis. This material may contain information that is outside of the approved labeling in some countries.

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