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Effectiveness and Tolerability of Colesevelam HCl for Accelerated Elimination of Teriflunomide in Healthy Participants

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Keywords

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Teriflunomide, a once-daily oral immunomodulator approved for the treatment of relapsing-remitting multiple sclerosis, demonstrated efficacy on clinical and magnetic resonance imaging measures of disease activity and a consistent and manageable safety profile in clinical trials.[1–5] Teriflunomide is contraindicated in pregnancy because data from animal studies (observed in rats and rabbits) suggest the potential for embryotoxic and teratogenic effects[5]; however, to date, there has been no human signal of teratogenticity.[6]

Teriflunomide undergoes enterohepatic recycling in which it is excreted into bile and transported to the small intestine, where it is reabsorbed.[7,8] Because the mean elimination half-life of teriflunomide is approximately 19 days, it may take an average of 8 months (up to 2 years owing to individual variation in substance clearance) once dosing is halted for plasma concentrations to decrease to <0.02 μg/mL, a concentration expected to confer minimal embryo-fetal risk to humans based on animal data.[5]

The following accelerated elimination procedure (AEP) is available for patients taking teriflunomide who become pregnant or who are planning a pregnancy, or in any case in which it is medically desirable to rapidly reduce the plasma concentrations of teriflunomide[5]:

- 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.

Both cholestyramine and activated charcoal sequester teriflunomide within the lumen of the small intestine and prevent reabsorption.[8]

Gastrointestinal disorders are the most frequently reported adverse events (AEs) associated with the AEP; therefore, it is desirable to identify an alternative procedure that will minimize these effects.[9] Colesevelam hydrochloride (HCl), a bile acid sequestrant indicated as an adjunct therapy for the treatment of primary hyperlipidemia,[10] has a 3-fold higher capacity on a per-gram basis than cholestyramine to lower cholesterol and appears to have less frequent and less severe gastrointestinal AEs than cholestyramine[9]; however, no direct comparisons have been made.

The primary objective of this study was to investigate whether colesevelam HCl was able to accelerate elimination of teriflunomide. The secondary objectives were to investigate the safety and tolerability of colesevelam HCl and to assess the pharmacokinetic (PK) parameters of teriflunomide during the AEP.

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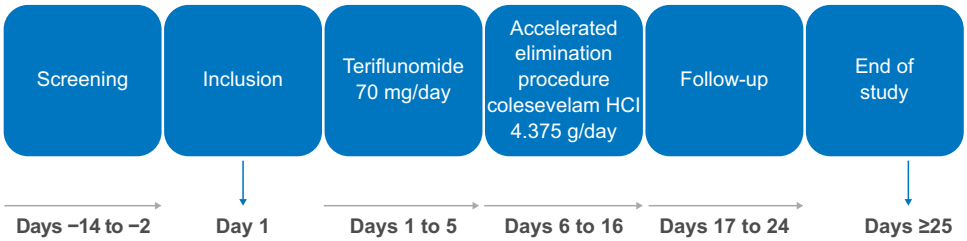

Figure 1. Study design. HCl, hydrochloride.

Methods

Study Design

The study protocol was reviewed and approved by an independent ethics committee. Before any study procedures, participants provided written informed consent after having been informed of the procedure and possible hazards and risks of the study. The study was an open-label, phase 1, single-center study in healthy men and women aged 18–45 years, conducted at Biotrial (Rennes, France) in accordance with the ethical principles set forth in the Declaration of Helsinki and in compliance with local regulations.

Participants received teriflunomide (AUBAGIO, Sanofi Genzyme, Cambridge, Massachusetts) 70 mg per day for 5 days to allow the rapid approach to steady-state concentrations, which would normally take several weeks with the once-daily 14-mg dose of teriflunomide. This was immediately followed on day 6 by an AEP with colesevelam HCl (Figure 1). The dose of colesevelam HCl selected was based on the prescribing information.[10] A study-specific requirement was the administration of all study medication with a meal:

- Days 1–5: teriflunomide, five 14-mg tablets once daily at approximately 8 AM (70-mg total daily dose)
- Days 6–16: colesevelam HCl, four 625-mg tablets in the morning at approximately 8 AM plus three 625-mg tablets in the evening at approximately 8 PM (7 tablets per day; 4.375-g total daily dose), which is the recommended maximum dose.

If at the end of the AEP (day 17) the plasma teriflunomide concentration was >0.02 μg/mL, participants were given cholestyramine 4 g 3 times daily (12-g total daily dose) to ensure plasma teriflunomide concentrations were ≤0.02 μg/mL at study completion.[6] The lowest recommended dose of cholestyramine was used to reduce the risk of gastrointestinal AEs.[9]

Pharmacokinetic Evaluations

Blood was sampled on days 1, 3, 6 (before the start of the AEP with colesevelam HCl), 7, 9, 13, and 17 (before the end of the AEP with colesevelam HCl) to determine teriflunomide concentrations in plasma using validated liquid chromatography coupled with a tandem mass spectrometry method, with a lower limit of quantification of ≤0.01 μg/mL. This assay is highly selective for teriflunomide; no interference from other drugs was expected. The method (performed by Eurofins Medinet, Breda, the Netherlands) was validated for the quantitation of teriflunomide in 50 μL of human ethylenediaminetetraacetic acid plasma following solid-phase extraction (SPE), using deuterated (D4)-teriflunomide as the internal standard and a calibration curve range of 0.1 (lower limit of quantification) to 10 μg/mL for teriflunomide. After the addition of methanol, an internal standard, and a buffer solution (pH 4), samples were homogenized and then injected in activated SPE Oasis 1-mL HLb columns. A mixture of ammonia solution (2%), ultrapure water, and methanol 20% in 2% acetic acid solution was used as the mobile phase. Teriflunomide was eluted using methanol, transferred to vials, and injected on a Sciex API-4000 mass spectrometer. Separation was performed on a Zorbax Eclipse XDB-CB 3.5-μm (4.6 × 50 mm) column with acetonitrile/water (50/50) containing 0.1% acetic acid used as the mobile phase. Teriflunomide was monitored after positive electrospray ionization at a mass-to-charge ratio of 269. Tested at different concentrations, the accuracy was <11% of nominal values, the within-run precision <9.1%, the between-run precision <7.4%, and the total precision <11%. There was no indication of any analytical interference with the internal standard. The lower limit of quantification for the plasma assay is below the threshold of 0.02 μg/mL, at which there is minimal risk of teratogenicity in humans based on animal data.[1]

The percentage changes in teriflunomide concentrations for PK samples taken during the AEP from the day 6 teriflunomide concentration (pre-AEP) were summarized with descriptive statistics, and the mean ±

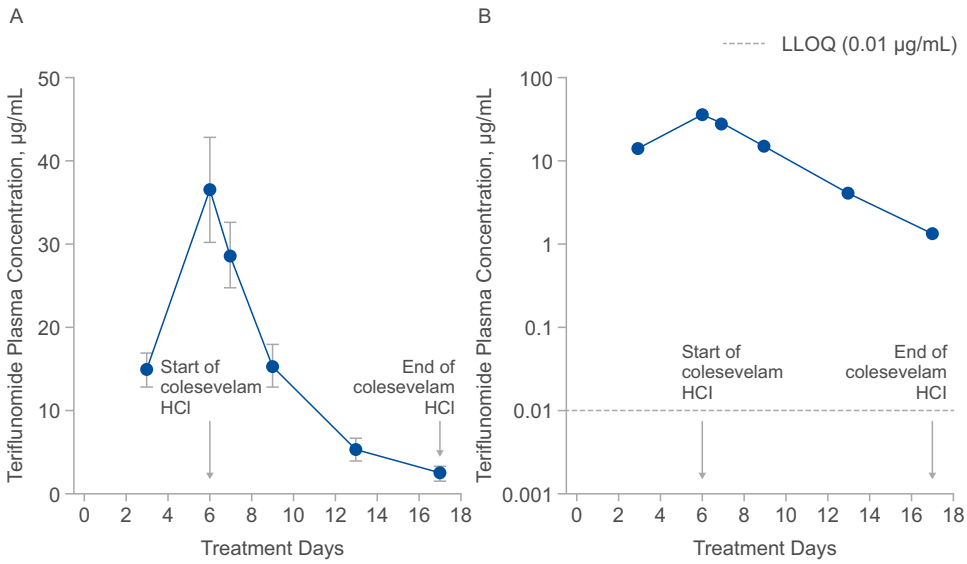

Figure 2. Mean ± SD plasma concentration of teriflunomide (linear [A] and semilog [B] plots.) HCl, hydrochloride; LLOQ, lower limit of quantification; SD, standard deviation.

standard deviation (SD) half-life during the AEP was calculated using noncompartmental analysis (WinNonLin; Pharsight).

Safety Evaluations

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

Table 1. Percentage Change in Plasma Concentrations of Teriflunomide During AEP With Colesevelam HCl

Duration of Colesevelam HCl Administration (Study Day)	Mean Percentage Decrease (CV%)
1 day (day 7)	21.8 (28.5)
3 days (day 9)	59.3 (13.6)
7 days (day 13)	87.9 (5.8)
11 days (day 17)	96.1 (3.5)

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

Results

Participants

A total of 18 participants were treated and completed the study. All participants were white, with a mean ± SD age of 37.3 ± 6.1 years and a mean ± SD body mass index of 24.0 ± 2.2 kg/m^2; the majority were male (61%). The mean ± SD half-life of teriflunomide during the AEP was 54.6 ± 12.5 hours. All participants were included in PK and safety evaluations.

Pharmacokinetics

On day 5, teriflunomide plasma concentrations reached a level that approximated the measured steady state achieved after > 13 weeks of administration of teriflunomide 14 mg once daily in a clinical setting (Figure 2). On day 6 (start of the AEP) the mean ± SD plasma teriflunomide concentration was 36.3 ± 6.4 μg/mL. The plasma concentration was 1.3 ± 0.8 μg/mL on day 17 (end of the 11-day AEP), corresponding to a mean decrease of 96.1% (coefficient of variation, 3.5%; Figure 2A and Table 1). There was no significant difference in the rate of teriflunomide elimination between men and women (data not shown). A semilogarithmic plot of log concentration versus time was linear, demonstrating first-order elimination kinetics (Figure 2B). To ensure complete elimination of teriflunomide, all 18 participants received cholestyramine: 16 participants received cholestyramine for 11 days, 1 participant received cholestyramine for 10 days, and 1 participant received cholestyramine for 12 days (up to a maximum of a 12-g total daily dose). All plasma concentrations were below the threshold of 0.02 μg/mL after administration of cholestyramine.

Safety

A total of 11 participants experienced at least 1 AE (Table 2), all of which were mild or moderate in nature. The most frequently reported AEs were fatigue (4 participants in the teriflunomide group and 1 participant following colesevelam HCl) and headache (4

Table 2. Summary of AEs

	Teriflunomide	Colesevelam HCl (After Teriflunomide)	Cholestyramine (After Colesevelam HCl)
All AEs,[a] n (%)	6 (33.3)	6 (33.3)	1 (5.6)
AEs by MedDRA preferred term,[b] n (%)			
Nasopharyngitis	0	1 (5.6)	0
Syphilis	0	0	1 (5.6)
Headache	1 (5.6)	4 (22.2)	0
Constipation	1 (5.6)	1 (5.6)	0
Diarrhea	1 (5.6)	1 (5.6)	0
Flatulence	1 (5.6)	0	1 (5.6)
Abdominal pain	0	1 (5.6)	1 (5.6)
Nausea	0	1 (5.6)	1 (5.6)
Fatigue	4 (22.2)	1 (5.6)	0

Safety population. AE, adverse event; HCl, hydrochloride; MedDRA, Medical Dictionary for Regulatory Activities.

[a]n = 18.

[b]Participants may have experienced >1 event and therefore may be captured in >1 category.

participants following colesevelam HCl and 1 participant following teriflunomide). No serious AEs were reported, and no AEs led to discontinuation of study treatment. There were no clinically relevant changes in the laboratory parameters assessed.

Discussion

After 11 days of treatment with colesevelam HCl, plasma concentrations of teriflunomide were, on average, reduced by > 96%. To achieve concentrations below 0.02 μg/mL, colesevelam HCl would likely need to be administered for more than 11 days. This is also the case for cholestyramine; teriflunomide plasma concentrations decreased by >98% following 11 days of administration and would therefore require additional days of treatment to decrease to <0.02 μg/mL, a concentration expected to confer minimal embryo-fetal risk in patients.[5] It is important to note that a reduction in teriflunomide plasma concentrations to <0.02 μg/mL is relevant to pregnancy planning, and there is no evidence to support the need to reduce concentrations to <0.02 μg/mL for other AEs.

During the 11-day treatment period, colesevelam HCl was well tolerated, and there were no particular safety concerns identified. The improved safety and tolerability profile of colesevelam HCl may increase patient satisfaction with AEP procedures.

Conclusions

Colesevelam HCl may offer an additional effective and well-tolerated AEP methodology to cholestyramine and activated charcoal when rapid elimination of teriflunomide is required.

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Declaration of Conflicting Interests

Catherine Lunven and Astrid Delfolie are employees of Sanofi R&D, France. Zuyu Guo and Sandrine Turpault are employees of Sanofi R&D, USA. Nicolas Fauchoux is an employee of Biotrial; Timothy Turner is an employee of Sanofi Genzyme, USA; and Francesca Baldinetti was an employee of Sanofi Genzyme, USA, at the time of the study.

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