CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202992Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

PRODUCT (Generic Name):	Teriflunomide
PRODUCT (Brand Name):	(b) (4)
NDA:	202-992
DOSAGE FORM:	Film coated Tablets
DOSAGE STRENGTH:	14 mg
INDICATION:	Treatment of relapsing forms of multiple sclerosis
NDA TYPE:	1S
SUBMISSION DATE:	8/12/11
SPONSOR:	Sanofi-Aventis
OCP REVIEWER: PHARMACOMETRICS REVIEWER PHARMACOGENOMICS REVIEWER	Veneeta Tandon, Ph.D. Joo-Yeon Lee, Ph.D. Jeffrey Kraft, Ph.D.
OCP TEAM LEADER: PHARMACOMETRICS TEAM LEADER PHARMACOGENOMICS TEAM LEADER	Angela Men, MD, Ph.D. Yaning Wang, Ph.D. Michael Pacanowski, Ph.D.
OCPB DIVISION:	DPE I, HFD 860
OND DIVISION:	HFD 120

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Teriflunomide ((b) (4) ®, also named as HMR1726 and A771726) tablets, are proposed for the treatment of patients with relapsing forms of multiple sclerosis (b) (4)

The proposed recommended dose is 14 mg administered orally once daily, with or without food.

Teriflunomide is a novel immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the de novo pyrimidine synthesis. Teriflunomide is the active, predominant metabolite of leflunomide (Arava®) and the major circulating moiety. It has been approved in the US and worldwide at the recommended dose of 20 mg for oral treatment of rheumatoid arthritis (RA) since 1998. The relative bioavailability of the active moiety when given as Arava® is 70% that of (b) (4) . Therefore, the exposure after 14 mg teriflunomide tablet is equivalent to that of a 20 mg Arava® tablet.

The clinical development program five Clinical Studies (one completed Phase 2 and Phase 3 study, three ongoing studies) and 18 Clinical Pharmacology Studies. The Clinical Pharmacology Studies included evaluation of single and multiple dose pharmacokinetics in healthy volunteers, multiple dose pharmacokinetics in patients, thorough QTc and drug interaction assessments and pharmacokinetics in special populations.

The Overall Clinical Pharmacology Summary is given in Section 1.2 on page 5 and Questioned Based Review on page 8. For additional details of the Clinical Pharmacology Studies, please refer to the Individual Study Reviews of this NDA.

1.1 RECOMMENDATION

Clinical Pharmacology aspects of the NDA are acceptable. Labeling recommendations on page 49 and Phase 4 Requirements on page 4 should be conveyed to the sponsor.

COMMENTS TO THE MEDICAL OFFICER

1. Teriflunomide appears to block renal tubular reabsorption of urate and is likely to be a uricosuric agent that increases urinary excretion of uric acid and decreases serum uric

acid levels. In addition, multiple sclerosis patients also have low uric acid levels. Please consider labeling implications of this for multiple sclerosis patients due to the possible additive effects (additional discussion on page 29).

2. Including information regarding the potential increase in toxicity with the coadministration of immunosuppressants, particularly methotrexate and mitoxantrone may be considered for the label as these drugs could be used for multiple sclerosis. Teriflunomide is an inhibitor of BCRP and OAT3. Methotrexate is a substrate of both the transporters. A drug interaction study with leflunomide and methotrexate did not show any PK differences but co-administration led to increased hepatoxicity (as per Arava® label). Mitoxantrone is associated with cardiac toxicity and is also a substrate of BCRP. There could be increased exposure of mitoxantrone when co-administered with teriflunomide. Although methotrexate did not show a pharmacokinetic interaction, the theoretical possibility for a interaction with mitoxantrone cannot be ruled out as the relative potencies of these drugs to inhibit the transported is unknown (for additional information, please refer to page 38).

PHASE 4 REQUIREMENT

The following PMR is requested:

1. An in vivo drug-drug interaction study with a substrate of OATP1B1 and BCRP: Rosuvastatin
   Rationale: Teriflunomide is an inhibitor of OATP1B1 and BCRP. Rosuvastatin is a substrate of OATP1B1 and BCRP. Inhibition of both transporters could results in an increase in systemic exposure of the substrates of these transporters. Statins are widely used, hence there is a potential of an increase in statin related adverse events with the increase in exposure of these statins. Rosuvastatin was chosen as it is a substrate of these two transporters and would give an estimate of the worst case by inhibiting the two together, although it will not be able to differentiate the inhibition potential between the two transporters. Depending on the magnitude of interaction observed, additional studies may need to be considered.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The findings from overall clinical pharmacology and biopharmaceutics section are as follows. Additional details on each can be found in Section 2 of this review.

Exposure-Response for Effectiveness:

In the Phase 3 study, teriflunomide doses evaluated in the treatment of MS were 7 and 14 mg once daily. There is an exposure response relationship between the primary endpoint, annualized relapse rate (ARR) and teriflunomide concentrations. The model predicts similar ARR at the median concentrations of each dose (0.38 at 16 ng/ml (7mg/day) and 0.37 at 37 ng/ml (14mg/day). However, more patients who are on the low end of exposure of 7mg may lose efficacy that that on 14 mg as it does not reach a plateau. –

Exposure-Response for Safety:

Teriflunomide shows higher risk in ALT increase compared to placebo but there is little difference between the 7 and 14 mg dose groups.

General Pharmacokinetics (ADME characteristics) of Teriflunomide:

Absorption: Following oral administration, plasma teriflunomide concentrations peaked at a median time of 1 to 4 hours. In a cross study comparison (IV and oral) after normalizing for dose, the bioavailability of teriflunomide seemed complete.

Distribution: In vitro, teriflunomide exhibited a high plasma protein binding in human (99.5% to 99.7%). Protein binding was linear in human plasma in the concentration range 0.75 to 570 μg/mL [this is more than 10 times the mean steady-state teriflunomide plasma concentration (45 μg/mL) observed after repeated doses of 14 mg]. Consistent with the in vitro results, the ex vivo binding was also high (99.7%) with mean unbound fractions being 0.25% to 0.27%. Teriflunomide had a limited Vss (11 liters compared to a volume of human plasma fluid of ~3 liters).

Metabolism: Unchanged teriflunomide was the only major component detected in systemic circulation. 4-TFMA was detected in very small amount after repeated dosing in clinical trials. 4-TFMA plasma concentrations were measurable at relatively low concentrations after repeated teriflunomide doses of 7 mg (≤1.7 ng/mL) and 14 mg (≤5.31 ng/mL) for 468 weeks. In the urine, 18.1% (13.7-22.5%) of the dose was the metabolite 4-TFMA oxanillic acid. In the feces, 35.7% ±12.7 (17.8-52.5%) of the dose was unchanged teriflunomide. Human cytochrome P450 (CYP) enzymes (CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 and 3A5) or flavine monoxidase (FMO) enzymes (FMOs 3 and 5) were not involved in the metabolism of teriflunomide.

Elimination: There was no assessment of teriflunomide $t_{1/2z}$ in healthy volunteers after repeated doses. Based on post-hoc individual prediction of pharmacokinetic parameters using the PopPK model of teriflunomide in healthy volunteers and MS patients, median terminal half-life was 17.8 and 19.4 days for the 7 mg and the 14 mg doses, respectively.

Rapid Elimination Procedure: The elimination of teriflunomide from the circulation can be accelerated by administration of cholestyramine or activated charcoal. Administration of cholestyramine (8 g tid for 7 days) increased the overall mean recovery of radioactivity from 60.1% to 83.2% of the administered dose over 28 days. There was increased excretion of radioactivity in feces particularly (37.5% to 61.3%) following cholestyramine treatment in the radiolabeled study. The apparent terminal half-life is reduced from ~20 days to 2-3 days.

Dose proportionality: Dose proportionality was established between a 7 and 14 mg dose. The pharmacokinetics are linear from 7-20 mg after single doses in healthy volunteers.

Pharmacokinetics in patients: The pharmacokinetics in patients was evaluated by population analysis of Phase 2/3 studies. Data to make direct steady state comparisons (14 mg QD to SS) were not available, but the attainment of steady state via loading dose (70 mg QD for 4 days followed by 14 mg QD for 11 days) in healthy subjects was not appreciably different.

Special Populations:

Renal Impairment: Pharmacokinetic parameters were similar between severe renal impaired subjects (creatinine clearance <30mL/min) and matched subjects with normal renal function (creatinine clearance >80mL/min) after a single oral dose of teriflunomide at 14 mg. No dose adjustment is needed.

Hepatic Impairment: Teriflunomide exposure (total and unbound) in the subjects with mild (Child-Pugh total score from 5 to 6) and moderate hepatic impairment (Child-Pugh total score from 7 to 9) was not appreciably different from those observed in healthy subjects after a single oral dose of 14 mg. No dose adjustment is needed. A study in severe hepatic impairment is not conducted and is not recommended in patients with severe hepatic impairment.

Age:

Elderly: There were no subjects greater than 64 years in the Phase 2/3 studies.
Pediatrics: The pharmacokinetics, safety and effectiveness of [redacted] (b) (4) in pediatric patients with MS below the age of 18 years have not yet been established.

Gender: There was a 31% (7 mg) and 17% (14 mg) increase in the $AUC_{0\text{-}24ss}$ for women versus men. No dose adjustment is needed.

Race: The majority of the patients were Caucasians. No meaningful differences related to race can be established.

Drug-drug Interactions:

Drug interactions that recommend monitoring/caution are given in the Table below. For Confidence intervals, please see page 38.

Concomitant Medication	AUC (% change)	Cmax (% change)
Teriflunomide on Other Drugs		
Repaglinide	2.3-fold ↑	64% ↑
S and R-Warfarin	↔	↔
	25% ↓ in peak INR	
Oral Contraceptives	EE 54% ↑	58% ↑
	LE 41% ↑	33% ↑
Caffiene/Paraxanthine	CAF 55% ↓	18% ↓
	PARA 42% ↓	↔

Concomitant drugs that did not show any changes in exposure when coadministered with teriflunomide are:
Effect of teriflunomide on other drugs: Bupropion, Midazolam, Omeprazole, Metaprolol
Effect of other drugs on teriflunomide exposure: Rifampin

Biopharmaceutics:

Relative Bioequivalence:

- Comparison of Teriflunomide exposure when given as [redacted] vs. ARAVA: The pharmacokinetics of leflunomide are primarily examined as the active metabolite (teriflunomide or HMR1726). The relative bioavailability of leflunomide was approximately 70% that of HMRI726. Thus, a tablet containing 14 mg HMRI726 is expected to produce an exposure to HMRI726 that is comparable to a tablet containing 20 mg leflunomide.

- The following formulations were bioequivalent:
  - Formulation made with [redacted] drug substance
  - Formulation made with and without [redacted]

- The commercial formulation was used in the Phase 3 studies.

Food Effect: No significant food effect. Dosing during clinical trials were conducted without regard to food.

Veneeta Tandon, Ph.D.
Clinical Pharmacology
Division of Clinical Pharmacology I

Joo-Yeon Lee, Ph.D
Pharmacometrics

Jeffery Kraft, Ph.D
Pharmacogenomics

Yaning Wang, Ph.D
Pharmacometrics Team Leader

Michael Pacanowski, Ph.D.
Pharmacogenomics Team Leader

Team Leader: Angela Men, M.D, Ph.D.
Clinical Pharmacology Team Leader

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

Drug/Drug Product Information: Teriflunomide (HMR1726, A771726)
Teriflunomide is the active, predominant metabolite (HWA486) of leflunomide (Arava®), which has been approved in the US and worldwide for oral treatment of rheumatoid arthritis (RA) since 1998.

Dosage Form/Strengths: Film coated immediate release 14 mg Tablets

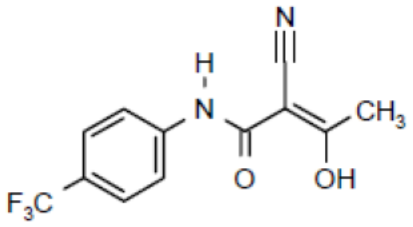
Indication: For the treatment of patients with relapsing forms of multiple sclerosis (b) (4)

Dosage and administration (Sponsor's Proposed): To be taken once daily with or without food.

Pharmacologic Class: Immunomodulatory agent with both anti-inflammatory and anti-poliferative properties.

Mechanism of action: Teriflunomide selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the de novo pyrimidine synthesis. The net result is a blockade of the de novo pyrimidine synthesis and subsequent cytostatic effect on proliferating T- and B-lymphocytes in the periphery, with no apparent cytotoxicity. Teriflunomide does not affect pyrimidine synthesis that occurs via salvage pathway that is used predominantly by resting or slowly dividing cells. Teriflunomide may reduce number of activated lymphocytes in central nervous system by diminishing in periphery the numbers of activated lymphocytes available to migrate into the CNS.

Chemical Name: (Z)-2-Cyano-3-hydroxy-but-2-enoic acid-(4- trifluoromethyl-phenyl)amide, Relative molecular mass: 270.21



Physical Characteristics:
pH: (under saturation conditions) 4.2
pKa: 3.1 at room temperature (+ 21°C to + 23°C)

Partition coefficient (flask shaking method, pH 3): Log Po/w = 2.7

Formulation: Only the 14 mg strength tablet is proposed, but chemistry information on the 7 mg strength is also submitted. The qualitative composition of both dosage strengths is the same, with exception of the colorant ferric oxide, which is not contained in the 14 mg strength. The manufacturing process is the same for both strengths.

Components	Composition		Function
	Percentage [%]	Per unit (1 film-coated tablet) [mg]	
Tablet core			
Teriflunomide	(b) (4)	14.0	Drug substance
Lactose monohydrate		(b) (4)	(b) (4)
Maize starch [Corn starch]			
Hydroxypropylcellulose			
Microcrystalline cellulose			
Sodium starch glycolate (b) (4) [Sodium starch glycolate]			
Magnesium stearate			
(b) (4)			
Film-coating			
Hypromellose		(b) (4)	
Titanium dioxide (b) (4)			
(b) (4)			
Talc			
Macrogol [Polyethylene glycol]			
Indigo carmine aluminum lake (b) (4) [FD&C Blue #2], (b) (4)]			
(b) (4)			
Mass of film-coated tablet	100	155.0	

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

The clinical development program included 5 studies to support the dosing regimen and the indication (as monotherapy).

Studies providing evidence of the efficacy of teriflunomide in the proposed indication

Study	Phase	Main objective	Comparator	Treatment	Number	Status
Monotherapy						
Core studies						
2001	2	Assess the effect on MRI activity, clinical efficacy, and safety of teriflunomide 7 and 14 mg	Placebo-controlled	36 weeks	179	Completed
EFC6049/TEMSO	3	Evaluate the efficacy and safety of teriflunomide 7 and 14 mg in reducing the frequency of relapses in patients with relapsing MS	Placebo-controlled	108 weeks	1088	Completed
EFC10531/TOWER	3	Evaluate the efficacy and safety of teriflunomide 7 and 14 mg in reducing the frequency of relapses in patients with relapsing MS	Placebo-controlle	Fixed end for all 48 weeks for last patient randomized	1096	Ongoing Interim analysis
Extension studies						
LTS6048 (extension of 2001)	2	Assess the long-term safety and efficacy of teriflunomide in patients who had completed Study 2001	Uncontrolled	Open-ended	147	Ongoing, Interim analysis
LTS6050 (extension of EFC6049)	3	Assess the long-term safety and efficacy of teriflunomide in patients who had completed Study EFC6049	Uncontrolled	Open-ended	742	Ongoing, Interim analysis

Two Phase 2 studies assessing the efficacy of teriflunomide as adjunct therapy to either IFN-β ([Study PDY6045]) or glatiramer acetate (GA) ([Study PDY6046]) for 24 weeks, as well as an extension for an additional 24 weeks of treatment ([Study LTS6047]), provide indirect supportive data to the monotherapy program. Results of the combined initial plus extension studies (PDY6045+LTS6047 and PDY6046+LTS6047) were also included in the submission.

The program also included 18 clinical pharmacology studies to determine the pharmacokinetics of teriflunomide in healthy subjects and in special patient populations, to document potential interactions and to evaluate specific pharmacodynamic activities in healthy subjects.

2.3.2 What are the clinical end points and how are they measured in clinical studies?

For the efficacy and safety studies in patients with relapse of MS, the main clinical endpoints are listed in the following Table.

Efficacy Endpoints:

Efficacy variables	2001	EFC6049 TEMSO
Relapses		
Annualized relapse rate (ARR)	X	X (primary endpoint)
Proportion of patients free of relapses		X
Time to relapse	X	X
Disability progression		
Time to disability progression, no confirmation required	X	
Time to disability progression confirmed for at least 12 weeks		X (key secondary endpoint)
Time to disability progression confirmed for at least 24 weeks		X
Proportion of patients free of disability progression		X
MRI variables		
Change from baseline in burden of disease	X	X (main MRI variable)
Number of unique active lesions per scan	X (primary endpoint)	
Number and volume of Gd-enhancing T1	X (only number of Gd-enhancing T1lesions)	X

lesions per scan		
Volume of hypo intense T1 lesions per scan		X
Volume of T2 lesions per scan		X
Change from baseline in atrophy and volume of white and grey matter		X
Fatigue		
Change from baseline in FIS	X	X
Other efficacy variables		
Change from baseline in MSFC	X	X
Change from baseline in SF-36		X
Change from baseline in EQ-5D		X
Change from baseline in MSQOL-54	X	

For the pivotal efficacy study (TEMSO), the main primary and secondary variable were measured as: ARR is measured by counting the number of relapses (new clinical sign of worsening that persisted for 24 hours) per patient year. The total number of confirmed relapses and patient years was calculated for each patient as follows:

- Total number of confirmed relapses was defined as number of confirmed relapses with onset between randomization date and treatment discontinuation/completion date.
- Patient years was calculated as (last dose intake date – randomization date + 1) / 365.25.

Disability progression was defined as at least a 1-point increase in the EDSS from baseline if baseline was EDSS ≤5.5 or at least a 0.5-point increase from baseline in the EDSS if baseline was EDSS >5.5 that was persistent for at least 12 weeks.

Burden of disease (BOD) was assessed by cerebral MRI and was defined as the total volume of all abnormal brain tissue (calculated as the sum of the total volume of T2 lesion component and T1 hypointense lesion component).

2.3.3 What are the characteristics of exposure/effectiveness relationships?

Yes, there was a clear exposure-response relationship for efficacy. The 7 and 14 mg doses were tested in the Phase 3 studies. The sponsor's proposed dose seems to be reasonable based on both the reviewer and sponsor's analyses.

The efficacy of the 2 doses was confirmed in the Study EFC6049/TEMSO. Sponsor's primary analysis showed that teriflunomide significantly reduced annualized relapse rate (ARR) after a 2-year treatment: 0.539, 0.370, and 0.369 for placebo, 7 mg/day and 14 mg/day, respectively, corresponding to statistically significant risk reductions of 31.2% (p=0.0002) in the 7 mg group and 31.5% (p=0.0005) in the 14 mg group relative to placebo.

Analysis of annualized relapse rate – intent-to-treat population - Study EFC6049/TEMSO

		Teriflunomide	
	Placebo (N=363)	7 mg (N=365)	14 mg (N=358)
Estimate (95% CI)	0.539 (0.466, 0.623)	0.370 (0.318, 0.432)	0.369 (0.308, 0.441)
Relative risk (95% CI)		0.688 (0.563, 0.839)	0.685 (0.554, 0.847)
P-value		0.0002	0.0005

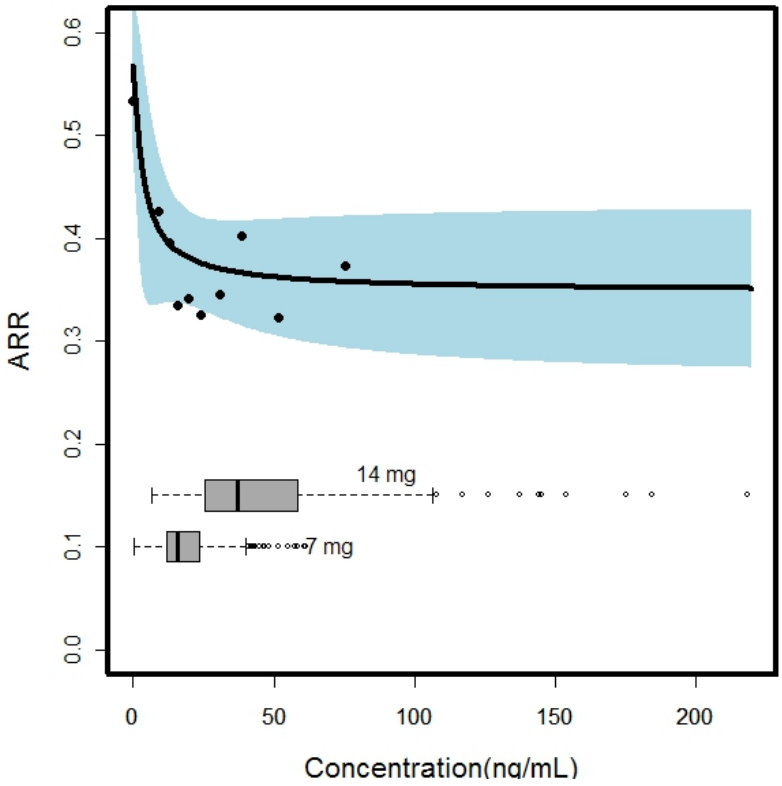
Some of the findings from the analyses for the secondary endpoints are summarized below:

1) The risk of disease progression was significantly reduced (29.8%) for 14 mg/day compared to placebo while the reduction observed (23.7%) for the 7 mg/day.
2) There were significantly fewer T1-Gd lesions per scan in 14 mg compare to 7 mg (p=0.0024).
3) The percentage of patients free from Gd-T1 lesions was significantly higher in 14 mg compared to 7 mg (p <0.001).
4) Difference in the number of unique active lesions per scan was statistically significant in 14 mg compared to 7 mg (p < 0.001).

In order to support or confirm the claim from the primary efficacy analyses Dr. Joo-Yeon Lee (Pharmacometrics) conducted the exposure-response analyses using steady-state mean concentration (MCONC) for each patient as a measure of exposure and ARR from one phase III study (EFC6049 (TEMSO))

The following Figure displays the model-predicted relationship between ARR and teriflunomide concentration with observed data at eight bins of ranked concentrations, which shows clear exposure-response relationship. The model predicts similar ARR at the median concentrations of each dose (0.38 and 0.37 at 16ng/ml (7mg/day) and 37ng/ml (14mg/day), respectively). However, it should be noticed that patients who are on the low end of exposure of 7mg may lose efficacy as it does not reach a plateau.

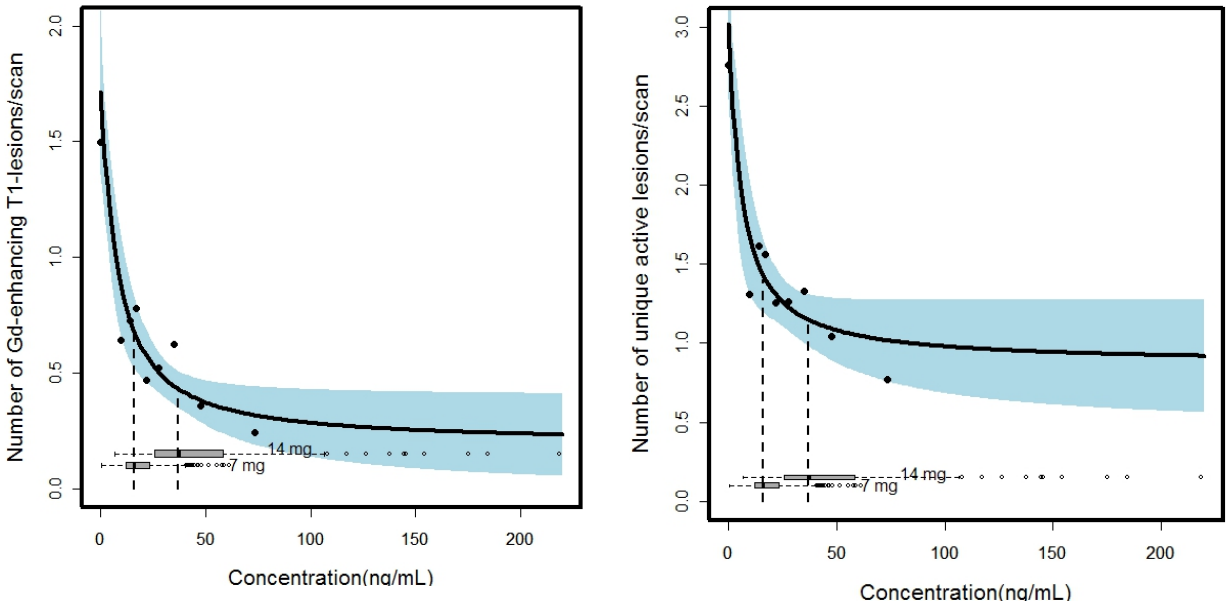
Figure: The model predicted relationship for ARR and teriflunomide concentration with 95% prediction interval (blue shaded area). The dots indicate the observed ARR at decile of teriflunomide concentration. Also two boxplots are the distribution of teriflunomide concentration at each dose.



In addition, the reviewer further looked into the relationship between MRI endpoints and concentration as the sponsor's claim for approval of 14 mg rather than 7 mg was mainly driven by the efficacy analyses with MRI endpoints where 14 mg showed superiority to 7 mg. Two MRI endpoints were examined: the total number of Gadolinium-enhanced T1 lesions per number of scans, and total number of unique active lesions per number of scans, which are consistent with the efficacy analyses.

The following Figure shows the results from the reviewer's analyses where the number of lesions for both endpoints clearly decrease concentration-dependent manner.

Figure: The model predicted relationship for the number of Gd-enhancing T1 lesions per scan and teriflunomide concentration relationship (left) and the relationship for the number of unique active lesions per scan (right) with 95% prediction interval (blue shaded area). The dots indicate the observed mean of the number of lesions at octile of teriflunomide concentration. Also two boxplots are the distribution of teriflunomide concentration at each dose. The broken vertical lines indicate the predicted lesions at the median of each dose



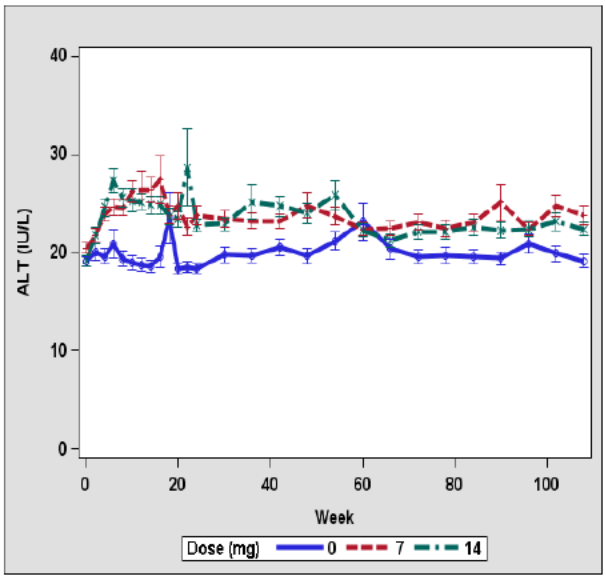
2.3.4 What are the characteristics of exposure-safety relationships?

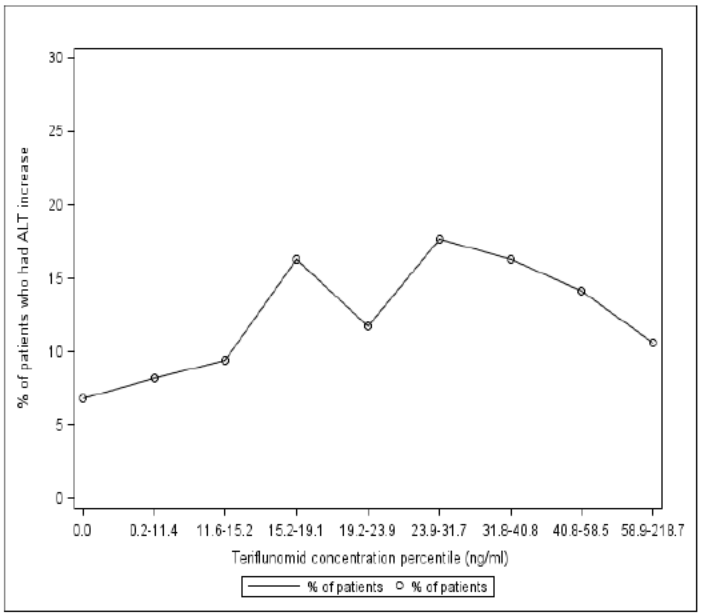
According to Dr. Joo-Yeon Lee's review, a clear exposure-response relationship is not apparent for some safety endpoints such as ALT increase.

To see the safety of teriflunomide related to concentration level, the incidence of ALT increase was analyzed as it was main concern for the safety of teriflunomide. Data from one phase II (HMR1726D/2001) and one phase III study (EFC6049 (TEMSO)) were pooled for exposure-safety analyses.

The left panel (A) of the following Figure shows the time profile of ALT level at each treatment group. Clearly teriflunomide shows higher risk in ALT increase compared to placebo but there is little difference between two dose groups. Instead of mean ALT level, the reviewer further looked into the incidence of ALT elevation taken from adverse event dataset where it is recorded by ULN (Upper Limit of Normal). The result is shown in the right panel (B) with no clear concentration-dependent increase in the incidence, although teriflunomide has higher probability than placebo.

Figure: The time profile (mean± se) of ALT level (IU/L) at each dose (left) and the percent of patients who had ALT increase at least once during the study (right).





(A) (B)

Those who had the incidence of ALT increase were divided by adverse event severity-mild, moderate and severe. Majority patients had mild condition in ALT elevation and a total of 4 patients had severe ALT increase; 2 patients in placebo, 1 patient in the lowest exposure range (0.2-11.4 ng/ml) and 1 patient in the concentration range 31.8-40.8 ng/ml (see following Table).

Table: The percent of patients who had ALT increase by severity: Study EFC6049 (TEMSO)

Severity	Concentration range (ng/mL)								
	Placebo (N=24)	0.2-11.4 (N=7)	11.6-15.2 (N=8)	15.2-19.1 (N=14)	19.2-23.9 (N=10)	23.9-31.7 (N=15)	31.8-40.8 (N=14)	40.8-58.5 (N=12)	58.9-218.7 (N=9)
Mild	50.0 (%)	42.9 (%)	62.5 (%)	71.4 (%)	70.0 (%)	60.0 (%)	78.6 (%)	83.3 (%)	77.8 (%)
Moderate	41.7 (%)	42.9 (%)	37.5 (%)	28.6 (%)	30.0 (%)	40.0 (%)	14.3 (%)	16.7 (%)	22.2 (%)
Severe	8.3 (%)	14.3 (%)	—	—	—	—	7.1 (%)	—	—

Best Available Copy

Given the efficacy and safety profile, the sponsor's proposed dose of 14 mg for approval seems to be reasonable.

2.3.5 Are the proposed dosage regimens for MS adequately supported by the clinical trials and consistent with the dose-response relationship?

The proposed dose of 14 mg is consistent with the exposure response analysis. See section 2.3.4.

2.3.6 Does teriflunomide prolong QT or QTc interval?

After repeated administration of teriflunomide (70 mg for 4 days followed by 14 mg for 8 days) in a placebo controlled thorough QT study with moxifloxacin as a positive control, teriflunomide did not show any potential for prolonging the QTcF interval compared with placebo. The largest upper bound of the 2- sided 90% CI for the mean difference between teriflunomide and placebo was below 10 ms, the threshold for concern as described in ICH E14 guidelines. Teriflunomide had no effect on heart rate. No QTcF values were ≥480 ms and no changes from baseline were >60 ms. Steady state mean concentrations of teriflunomide of 30.5 µg/mL (min-max: 12.3-53 µg/mL) had been reached and were within the range of exposure seen in patients. (For additional details, refer to IRT review)

Table: TQTc Analysis

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Teriflunomide	3	3.7	(0.7, 6.8)
Moxifloxacin 400 mg*	3	13.6	(10.6, 16.7)

2.2.7 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Teriflunomide was the main moiety circulating in plasma. The main plasma metabolite was TFMA, the levels of which were mostly LLOQ in healthy subjects. In the Phase 3 studies, low levels of 4-TFMA were observed. Assay was adequately validated for both moieties. Refer to section 2.6 for additional assay validation parameters.

2.2.8 What are the basic pharmacokinetic parameters of teriflunomide after single and multiple doses?

Single Dose Pharmacokinetics:

The single dose pharmacokinetic parameters in healthy volunteers across various studies are given in the following Table:

Table: Single dose mean (SD) pharmacokinetic parameters from Phase 1 studies

Dose (mg)	Study	N	Cmax (µg/mL)	tmax (hours)	AUC0-72 (µg.h/mL)	AUC0-168 (µg.h/mL)	t1/2z (h)
7	ALI6504	16	0.906 (0.198)	2.26 (1.00-16.0)	41.1 (5.70)	ND	ND
7	BEQ10169	41-45	1.06 (0.22)	2.00 (0.500-12.0)	49.8 (8.34)	100 (17.0)	243 (65.2)
14	ALI6504	14	1.79 (0.301)	1.50 (0.500-3.00)	81.3 (13.1)	ND	ND
14	BDR6639	25	1.66 (0.376)	2.00 (0.500-5.00)	74.5 (12.3)	ND	171 (59.9)
14	BEQ10169	40-43	2.25 (0.47)	1.50 (0.500-24.0)	102 (15.8)	203 (31.5)	259 (76.2)
14	POP6507	8	1.66 (0.253)	2.00 (1.00-4.00)	76.8 (8.43)	156 (18.1)	261 (106)
20	1001	16	2.68 (0.55)	1.00 (0.450-14.1)	121 (14.8)	255 (37.8)	240 (77.5)
20	1002	16	2.53 (0.224)	1.00 (0.500-4.00)	123 (15.1)	258 (33.7)	ND
20	1002	16	2.60 (0.373)	1.00 (0.500-48.0)	142 (18.7)	286 (44.3)	ND
70	INT6039	20	10.3 (1.59)	2.00 (0.500-36.0)	ND	ND	303 (120)
100	1001	16	13.4 (2.23)	2.00 (1.85-4.30)	ND	ND	ND

The pharmacokinetic parameters are quite consistent across studies. The pharmacokinetics of teriflunomide appeared linear in the does range of 7-20 mg.

Multiple Dose Pharmacokinetics:

There was no steady-state administration of teriflunomide to assess accumulation from repeated dose studies in healthy volunteers. Steady state parameters at the therapeutic dose were obtained from the population analysis in MS patients as shown in the following Table.

Table: Multiple doses mean (SD) pharmacokinetic parameters from Phase 3 Studies

Parameter	7 mg dose (n=424)		14 mg dose (n=410)	
	Mean (CV%)	Median, 5th – 95th percentiles	Mean (CV%)	Median, 5th – 95th percentiles
C_{max} (µg/mL)	0.805 (20.9)	0.796, 0.549 – 1.10	1.65 (23.2)	1.64, 1.08 – 2.34
C_{maxSS} (µg/mL)	19.5 (54.4)	16.7, 7.76 – 42.2	45.3 (64.9)	37.8, 15.6 – 89.9
C_{minSS} (µg/mL)	18.7 (56.1)	16.0, 6.95 – 41.5	43.7 (67.0)	36.2, 14.1 – 87.8
t_{maxSS} (h)	1.67 (79.6)	1.17, 0.844 – 4.83	1.88 (93.6)	1.17, 0.828 – 6.25
AUC_{0-24} (µg.h/mL)	15.4 (21.4)	15.3, 10.2 – 20.6	32.2 (22.8)	31.7, 21.6 – 46.1
AUC_{0-24SS} (µg h/mL)	458 (55.0)	392, 174 – 1000	1070 (65.9)	885, 353 – 2130
Rac AUC	30.3 (54.5)	25.8, 12.0 – 62.9	33.6 (62.8)	28.1, 11.8 – 73.7
$t_{1/2Beta}$ (h)	561 (104)	427, 194 – 1260	557 (64.4)	466, 192 – 1250

The median t1/2 with the 14 mg dose was 19.4 days (8-19 days). It takes 3-3.5 months to reach steady state.

Multiple dose pharmacokinetics (mean, %CV) in healthy volunteers was obtained following a supratherapeutic dose (70 mg fasted for 14 days)

Table: Multiple doses mean (%CV) pharmacokinetic parameters from Phase 1 Study

Parameters	70 mg for 14 Days			
	Cmax (µg/mL)	Tmax (h)	AUC0-24 (µg.h/mL)	Ctrough (µg/mL)
Day 1 (N = 10)	11.0 (30)	1.53 (1.00 , 8.30)	182 (24)	7.30 (24)
Day 7 (N = 9)	66.9 (25)	2.50 (0.50 , 8.00)	1360 (22)	55.6 (26)
Day 14 (N = 3)	113 (39)	4.00 (1.00 , 23.92)	2370 (39)	105 (35)

In addition, the steady state therapeutic pharmacokinetic parameters (mean, % CV) were obtained by dosing 70 mg QD for 4 days, followed by 14 mg QD for 8 days orally (Study TES10852).

Table: Multiple doses mean (%CV) pharmacokinetic parameters from Phase 1 Study

Parameters	70 mg QD for 4 days, followed by 14 mg QD for 8 days			
	Cmax (µg/mL)	tmax (h)	AUC0-24 (µg.h/mL)	Ctrough (µg/mL)

Day 12 (N = 59)	30.5 (27)	4.00 (0.00 , 23.8)	627 (27)	24.8 (32)

These values are somewhat below than the median values obtained from the population analysis, but are within the 5th and 95th percentiles.

2.2.9 What are the general ADME characteristics of teriflunomide?

The key ADME characteristics of teriflunoamide are summarized below:

Absorption:

- Following oral administration, plasma teriflunomide concentrations peaked at a median time of 1 to 4 hours.
- In a cross study comparison (IV and oral) after normalizing for dose, the bioavailability of teriflunomide seemed complete. Consistent with this in the radiolabeled study, <2% of the dose was unabsorbed (assuming that the cumulative radioactive dose excreted in the feces over 48 hours reflects the unabsorbed teriflunomide).
- Solubility of teriflunomide is low at pH values below 4.0 and increases at higher pH. There is no solubility limited absorption at the 14 mg teriflunomide doses which is soluble in 250 mL of buffers at pH 4.5 to 8.0
- It is a high permeability (213 x 10^{-7} cm.s^{-1}) using the Caco-2 TC7 cell culture model.

Distribution:

- In vitro, teriflunomide exhibited a high plasma protein binding in humans (99.5% to 99.7%). Protein binding was linear in human plasma in the concentration range 0.75 to 570 µg/mL [more than 10 times the mean steady-state teriflunomide plasma concentration (45 µg/mL) observed after repeated doses of 14 mg] (99.5% bound and 0.49% unbound), while at the concentration of 839 µg/mL the binding fraction decreased (98.7% bound and 1.26% unbound).
- Teriflunomide (at 50 µg/mL nominal concentration) appeared to be highly bound to serum albumin (>96%), and the binding was dependent upon the concentrations of albumin (unbound fraction 3.28% at 10 g/L and 0.41% at 60 g/L).
- Consistent with the in vitro results, the ex vivo binding was also high (99.7%) with mean unbound fractions being 0.25% to 0.27%.
- Radioactivity in blood (blood to plasma ratio ~0.5) and red blood cells (red blood cells to plasma ratio ~0.2) was lower than that in plasma.
- Following a single IV dose administration, teriflunomide had a limited Vss (11 liters compared to a volume of human plasma fluid of ~3 liters)

Metabolism:

In vitro:

- In human hepatocytes teriflunomide was metabolically stable.

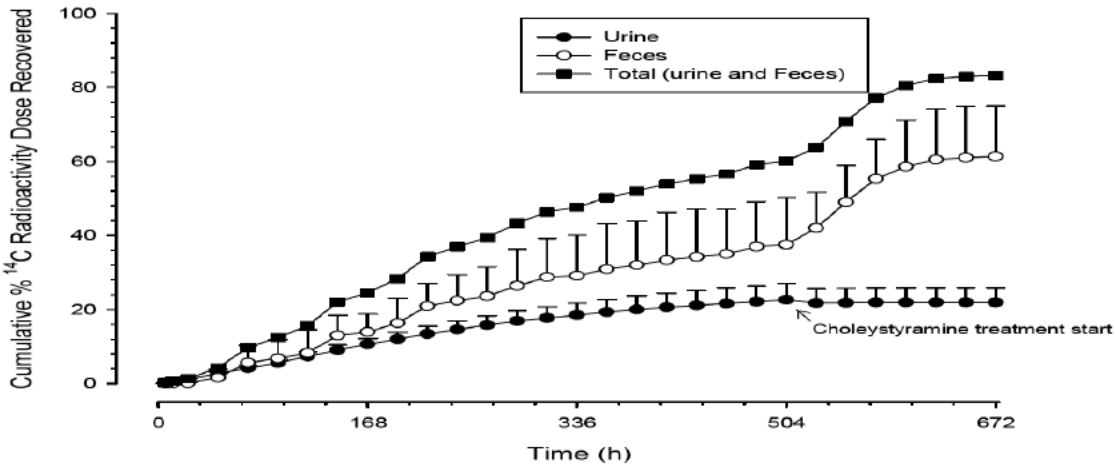
- In human liver microsomes teriflunomide was metabolized and two metabolites were observed: 4-TFMA oxanilic acid and 4-TFMA glycolanilide, accounting for 1.2% and 4.4% of total radioactivity, respectively.
- In human hepatocytes and microsomes, 4-TFMA (a minor metabolite of teriflunomide seen in vivo) was metabolized to 2-hydroxy-TFMA, N-acetyl-TFMA, and 4-TFMA oxalinic acid.
- Human cytochrome P450 (CYP) enzymes (CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 and 3A5) or flavine monoxidase (FMO) enzymes (FMOs 3 and 5) were not involved in the metabolism of teriflunomide.

In Vivo:

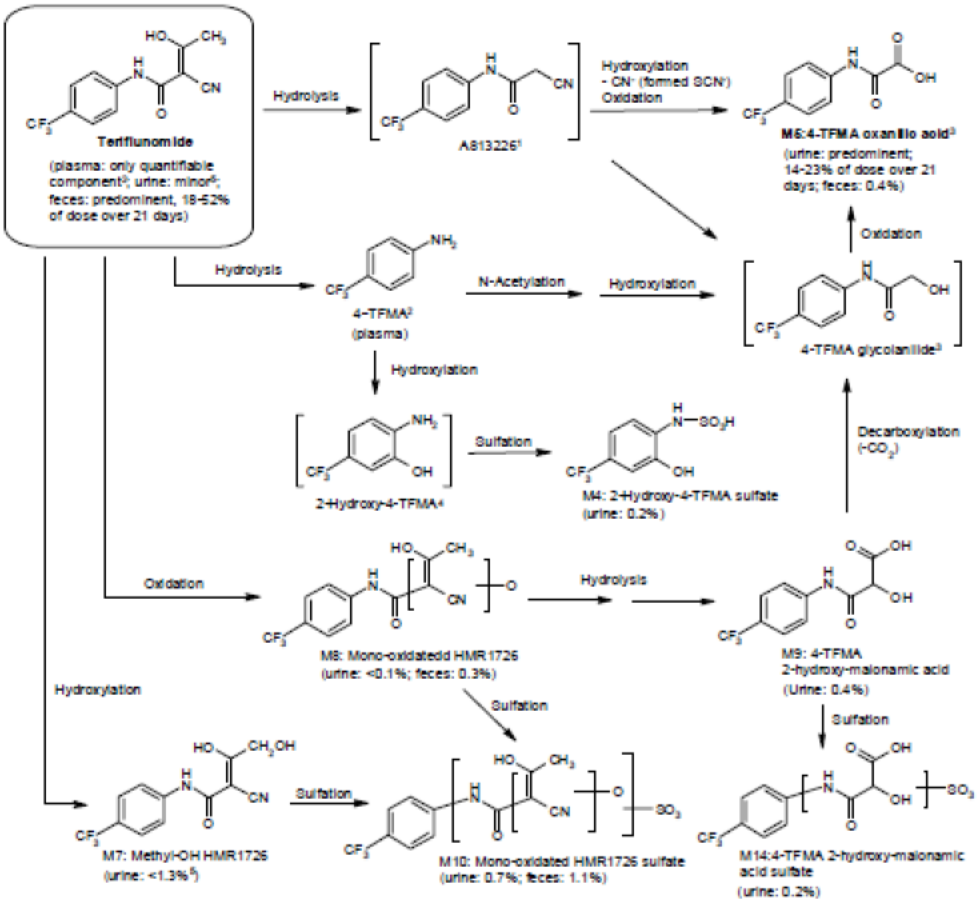
- In human, following a 70 mg/50 μCi single oral ^{14}C-teriflunomide, teriflunomide was ~20% metabolized. The primary biotransformation pathway for teriflunomide is hydrolysis, with oxidation being a minor pathway. Secondary pathways involved oxidation, N-acetylation and sulfate conjugation.
- ***In plasma***:
  - Unchanged teriflunomide was the only major component detected in systemic circulation
  - 4-TFMA was not detected in the single dose metabolism study, but was detected in very small amount after repeated dosing in clinical trials 4-TFMA plasma concentrations were measurable at relatively low concentrations after repeated teriflunomide doses of 7 mg (≤1.7 ng/mL) and 14 mg (≤5.31 ng/mL) for 468 weeks. On a molar basis (4-TFMA molecular weight 167 versus teriflunomide molecular weight 270), 4-TFMA concentrations at steady-state were approximately 12,000 and 17,000 times lower than the teriflunomide concentrations after 7 and 14 mg repeated doses at Week 36.
- ***In feces:***
  - 35.7% ±12.7 (17.8-52.5%%) of the dose was unchanged teriflunomide
  - <2% of the dose was 3 metabolites
  - Total recovery of radioactivity in the feces was 37.5±12.7%
- ***In urine:***
  - ≤1.3% of the administered dose was teriflunomide+ methyl hydroxyl teriflunomide, out of which 0.147% was unchanged teriflunomide.
  - 18.1% ± 3.3 (13.7-22.5%) of the dose was the metabolite 4-TFMA oxanillic acid.
  - In addition there were 8 other radioactive metabolites identified, total urinary metabolites accounted for 22.6±4.5% (16.7-28.6%) of the dose.

Total recovery of radioactivity between the urine and feces was 60.1±10.4%

Figure: Percent recovery of radioactivity



The sponsor has proposed the following metabolic pathway for teriflunomide:



Best Available Copy

Elimination:

- After administration of a single oral administration of 7 to 70 mg teriflunomide dose, with a teriflunomide $t_{1/2z}$ of 10 to 12 days.

- There was no assessment of teriflunomide $t_{1/2z}$ in healthy volunteers after repeated doses. Based on post-hoc individual prediction of pharmacokinetic parameters using the PopPK model of teriflunomide in healthy volunteers and MS patients, median terminal half-life was 17.8 and 19.4 days for the 7 mg and the 14 mg doses, respectively.
- After a single IV infusion administration of 10 mg teriflunomide, mean teriflunomide total body clearance was 30.5 mL/h.

Rapid Elimination Procedure:

The elimination of teriflunomide from the circulation can be accelerated by administration of cholestyramine or activated charcoal presumably by trapping the teriflunomide excreted unchanged in the gastrointestinal tract mainly by bile and also possibly by direct secretion and therefore interrupting the reabsorption process.

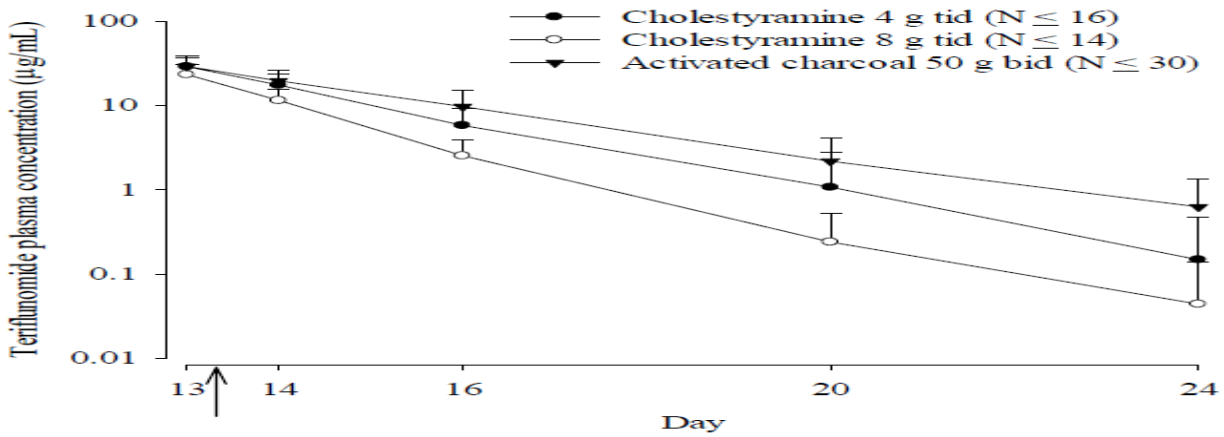
Cholestyramine is a cholesterol lowering agent. It is an ion exchange resin with a high affinity for biliary acids. Maximal dose administered to lower cholesterol is 24 g (8g tid) a day. AEs that could be experienced during treatment with cholestyramine include bowel disturbances, nausea, vomiting, and transient elevation of transaminases. Cholestyramine (4g tid) was better tolerated in the studies compared to 8g tid.

Activated charcoal given at the dose of 50 g, 2 or 4 times a day for 11 days is also efficient to bind and eliminate teriflunomide. It is generally well tolerated but may cause constipation.

Administration of cholestyramine (8 g tid for 7 days) increased the overall mean recovery of radioactivity from 60.1% to 83.2% of the administered dose over 28 days. There was increased excretion of radioactivity in feces particularly (37.5% to 61.3%) following cholestyramine treatment in the radiolabeled study. The apparent terminal half-life is reduced from ~20 days to 2-3 days.

Based on data from various studies, 8 g cholestyramine tid was the most efficient and 50 g activated charcoal bid was the least.

Figure: Mean (SD) teriflunomide plasma concentration-time profiles before and during rapid elimination procedure



Note: Arrow represents the start of the rapid elimination procedure (which lasted 11 days)

Table: teriflunomide recovery (3 regimens):

Treatment Description	Percent	%CV
Teriflunomide + Cholestyramine 8 g tid	99.8	0.432
Teriflunomide + Cholestyramine 4 g tid	99.6	0.805
Teriflunomide + Activated charcoal 50 g bid	97.8	2.53

In the clinical pharmacology studies, the higher increase in AST/ALT was seen in the phase of cholestyramine administration. Cholestyramine is also known to increase AST/ALT levels.

2.2.10 Do the pharmacokinetic parameters change with time following chronic dosing?

There was no steady-state administration of teriflunomide to assess accumulation from repeated dose studies in healthy volunteers. However, a PopPK analysis of teriflunomide in healthy volunteers and MS patients showed that plasma concentrations of teriflunomide accumulate over time following multiple oral doses of teriflunomide (see section 2.2.9). Based on post-hoc individual predicted pharmacokinetic parameters from this PopPK model, it takes ~90 to 100 days or 3 to 3.5 months to attain 95% of steady state concentrations based on a median $t_{1/2z}$ of ~8 to 19 days), and the estimated AUC accumulation ratio was 30.3 for 7 mg (median, 5^{th} - 95^{th} percentile: 25.8, 12.0 - 62.9) and 33.6 for 14 mg (median, 5^{th} - 95^{th} percentile: 28.1, 11.8 - 73.7).

2.2.11 What is the variability in the PK data?

In healthy subjects, after a single 7 and 14 mg dose, teriflunomide exhibited a low variability in Cmax, AUClast and AUC. The total and within-subject variability of teriflunomide Cmax were 20.5% and 12.4%, of AUClast were 27.0% and 7.5% and of AUC were 27.2% and 10.1%, respectively (analysis combining data from studies BDR6639 and BEQ10169).

The steady state data came from a population analysis of the completed Phase 3 studies. With a supratherapeutic dose (70 mg for 14 days), the variability was higher for both Cmax and AUC (39%). Steady state had not been reached in this study. Teriflunomide dosing of 70 mg of 4 days followed by 14 mg for 8 days produces steady state levels. Variability seen with this dosing (Study TES10852) showed inter-individual variability of 27% for both Cmax and AUClast (see section 2.2.9)

Based on the PopPK analysis of teriflunomide in healthy volunteers and MS patients, inter-patient variability in teriflunomide clearance, central volume, peripheral volume, and absorption constant in MS patients was large (CVs of 55.2%, 22.4%, 105%, and 149%, respectively). The variability in steady state Cmax and AUClast was 66.2%. The residual (intra-individual) variability was quite moderate with a 21.3% CV.

2.2.12 How do the pharmacokinetics of the drug in healthy volunteers compare to that in MS patients?

The pharmacokinetics of teriflunomide in patients was assessed through plasma samples collected in clinical efficacy/safety studies in MS patients treated with oral teriflunomide (7 or 14 mg) alone QD (Study 2001 with its extension LTS6048 and Study EFC6049 with its extension LTS6050). These concentrations were analyzed using descriptive statistics for each of the studies. The steady state trough concentrations from these two studies were similar as shown in the Table below.

Table: Teriflunomide steady-state Ctrough (ug/mL) at Week 36

Study		7 mg		14 mg
	N	mean (min-max)	N	mean (min-max)
2001/LTS6048	58	17.6 (0.6 – 58.4)	44	37.6 (3.1 – 196)
EFC6049/LTS6050	309	19.3 (0.1 – 64.4)	293	45.0 (0.1 - 235)

No steady state study was conducted in healthy volunteers. But a loading dose (70 mg for 3-4 days, then 14 mg for 8-11 days) was used in the drug interaction study. In the drug alone arm, the steady state trough concentrations ranged from 27.9-36.1 µg/ml. These are close to that observed in patients in the Phase 3 studies. Based on this minimal comparison, the steady state trough concentrations do not appear to be significantly different between MS patients and healthy subjects.

2.2.13 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Systemic exposure (C_{max} and AUC values) appears to increase in a dose proportional manner after single oral administration of 7 to 14 mg doses in healthy subjects.

Table: Assessment of Dose Proportionality:

		Ratio	
Parameter	**Dose ratio**	**Estimate**	**90% CI**
Cmax	(r) = 2	1.87	(1.77 to 1.98)
	Beta Estimate	0.90	(0.82 to 0.99)
AUClast	(r) = 2	2.42	(1.96 to 2.99)
	Beta Estimate	1.28	(0.97 to 1.58)
AUC	(r) = 2	1.62	(1.43 to 1.83)
	Beta Estimate	0.70	(0.52 to 0.87)

For C_{max} the regression model was 0.16 x dose $^{0.93}$ Pooled data from BEQ10169, POP6507 and POP11432
For AUC the regression model was 72.47 x dose $^{0.69}$
For AUC_{last} the regression model was 10.46 x dose $^{1.21}$

Dose proportionality in terms of trough concentrations of teriflunomide was also observed after 7 or 14 mg multiple oral dosing to MS patients at steady-state. In addition, dose was not a significant covariate of the teriflunomide pharmacokinetics.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

The intrinsic factors have been discussed below:

2.3.2 Effect of Renal Impairment:

Mean pharmacokinetic parameters were similar between severe renal impaired subjects (n=8) creatinine clearance <30mL/min) and matched subjects with normal renal function (creatinine clearance >80mL/min, n=8) after a single oral dose of teriflunomide at 14 mg. In addition, the fraction unbound in healthy subjects (0.25%) was similar to that in patients with severe renal impairment (0.25%).

Table: Effect of renal impairment

Severe Renal Impairment vs. Healthy (Cockroft-Gault)		
Parameter	**Estimate**	**90% CI**
Cmax	1.16	(0.97 to 1.39)
AUClast	1.02	(0.63 to 1.66)
AUC	1.03	(0.61 to 1.74)
t1/2z	0.99	(0.65 to 1.52)
CL/F	0.97	(0.57 to 1.64)
Unbound Cmax	1.15	(0.93 to 1.42)
Unbound AUClast	1.01	(0.64 to 1.60)
Unbound AUC	1.02	(0.62 to 1.66)

As seen in the above Table, the point estimates suggested no difference between the severe and the healthy group. There was once subject that had about twice the exposure than the rest of the subjects. This subject was on Actrapid, Protophan, ASS100, Simvastain, Bondiol, Allopurinol, Bisoprlol, Telmisartan. Other than simvastatin, which is an OATP1B1 substrate, no known mechanism for an interaction could be identified (teriflunomide is an OATP1B1 inhibitor). On the contrary, the subject with the lowest exposure in the severe group was on pravastatin, which is also an OATP1B1 substrate. No correlation to CrCL was identified for these subjects.

Patients with moderate or severe renal impairment were excluded from Phase 2 or 3 clinical studies.

Less than 2% of the administered dose is excreted unchanged in the urine. About 22% is excreted as metabolites and unchanged drug. Hence, the influence of renal impairment was likely to be minimal, although possibility existed of decreased protein binding or renal impairment adversely affecting hepatic metabolism and hence exposure of the drug. None of these contributed to a change in exposure in the severe renal impaired patients.

Dosage adjustment:

- Severe renal impaired subjects (CrCl <30 ml/min) do not need dosage adjustment. Therefore mild and moderate renal impaired subjects (CrCl >30 ml/min) also do not need dosage adjustment.

2.3.3 Effect of Hepatic Impairment:

Teriflunomide exposure (total and unbound) in the subjects with mild (Child-Pugh total score from 5 to 6) and moderate hepatic impairment (Child-Pugh total score from 7 to 9) was not appreciably different from those observed in healthy subjects after a single oral dose of 14 mg.

Parameter	Mild HI/healthy (N = 8)		Moderate HI/healthy (N = 8)		Moderate HI/mild HI (N = 8)	
	Estimate	90%CI	Estimate	90%CI	Estimate	90%CI
Cmax	0.99	(0.88-1.12)	0.95	(0.84-1.07)	0.96	(0.85-1.08)
AUClast	0.97	(0.65-1.44)	0.82	(0.55-1.22)	0.85	(0.57-1.25)
AUC	0.97	(0.64-1.46)	0.82	(0.55-1.23)	0.85	(0.56-1.27)
Cmax,u	1.01	(0.89-1.14)	0.90	(0.80-1.03)	0.90	(0.79-1.02)
AUCu	0.99	(0.69-1.42)	0.78	(0.55-1.12)	0.79	(0.55-1.14)
t1/2	1.00	(0.74-1.36)	0.90	(0.66-1.22)	0.90	(0.66-1.22)
t1/2eff	0.92	(0.62-1.35)	0.90	(0.61-1.32)	0.98	(0.66-1.44)

Based on PopPK study, ALT, AST and albumin did not affect teriflunomide pharmacokinetics of teriflunomide, except for bilirubin. No major alteration of exposure parameters could be observed for the 7 mg dose with higher bilirubin values. A 1.73-fold increase of mean $AUC_{0\text{-}24SS}$ was observed for the 14 mg dose between patients with a bilirubin > 17 µmol/L and the patients with bilirubin < 17 µmol/L (see following Table).

The distribution of bilirubin and albumin scores is shown in the following Figures. This shows that the majority of the patients had normal bilirubin levels (5.1-17 µmol/L), and normal albumin levels (35-50 g/L). The sponsor also mentions in the Integrated Summary of Safety that patients with hepatic impairment were excluded from the Phase 2/3 studies.

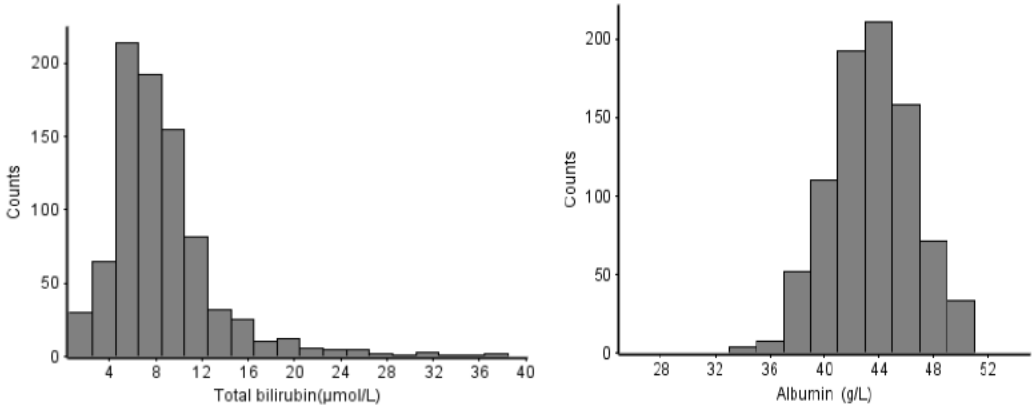
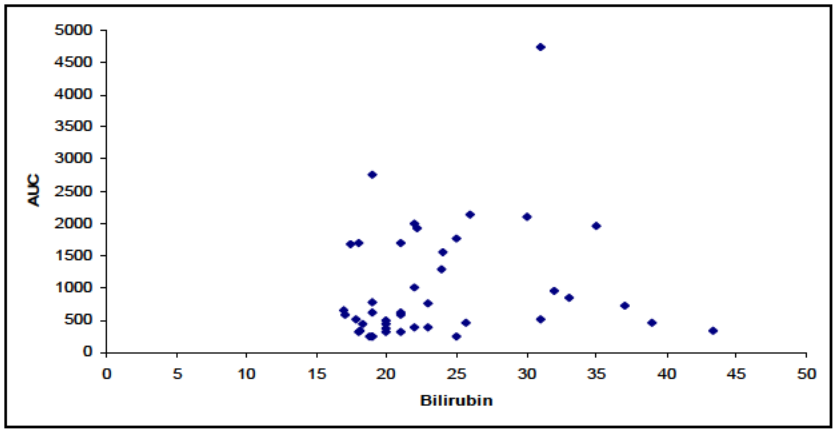


Table: Mean, coefficient of variation %, median, 5th and 95th percentiles of individual exposure parameters by bilirubin levels included in the final PopPK model for a 7 and 14 mg dose.

	$AUC_{0\text{-}24SS}$ (µg h/mL)	C_{maxSS} (µg/mL)	C_{minSS} (µg/mL)
7 mg			
Bilirubin < 17 µmol/L (n=399)	458 (56.0) – 391 (167, 1010)	19.5 (55.0) – 16.6 (7.27, 42.7)	18.7 (56.7) – 16.0 (6.68, 41.7)
Bilirubin > 17 µmol/L (n=25)	456 (39.1) – 443 (246, 760)	19.4 (38.2) – 18.8 (10.8, 32.0)	18.7 (39.8) – 18.2 (9.86, 31.4)
14 mg			
Bilirubin < 17 µmol/L (n=393)	1030 (65.5) – 881 (353, 2120)	43.9 (64.4) – 37.3 (15.3, 89.2)	42.4 (66.4) – 36.0 (14.1, 87.5)
Bilirubin > 17 µmol/L (n=17)	1790 (52.6) – 1700 (589, 4730)	75.7 (52.0) – 72.1 (25.0, 198)	74.0 (53.0) – 70.2 (24.0, 196)

The individual AUC for subjects with bilirubin >17 µmol/L is shown below:



This figure shows that there is one outlier with an AUC of 4730 µg.h/ml (bilirubin=31), which is driving the mean values to be 1.73 fold higher. Excluding this subject the AUC was 988 µg.h/ml which is not different from the mean value in subjects with bilirubin <17µmol/L (AUC 1030 µg.h/ml). According to the Safety Reviewer, this patient only had rhinitis on Day 424 and increased amylase and lipase on Day 1008 x 7 days. There were other subjects with bilirubin >31 that did not have such high exposures. Therefore, though the pharmacometrics review, suggests bilirubin to be a significant covariate in the POP PK analysis, the clinical relevance of this finding for subjects with higher bilirubin values is minimal.

Albumin data is not presented as no difference was observed and all patients had normal values of albumin.

Dosage adjustment:
No dosage adjustment is necessary patients with mild and moderate hepatic impairment. A study in severe hepatic impairment is not conducted and is not recommended in patients with severe hepatic impairment.

2.3.4 Effect of uric acid secretion:

The pharmacokinetic/pharmacodynamic analysis (conducted using teriflunomide plasma concentrations (mean trough concentrations after 8 weeks of treatment) from Study 2001 and Study EFC6049/TEMSO showed that an increase in teriflunomide plasma concentrations led to a decrease in uric acid. There was a decrease in uric acid levels of 26.5 % and 26.6% of mean baseline levels for the mean trough concentration at 7 mg dose (15.9 µg/mL) and at 14 mg dose (36.8 µg/mL). The mean baseline uric acid level was 23.9 % lower in female compared to male patients. Upon cessation of treatment and subsequent elimination of teriflunomide by cholestyramine, the values of uric acid in plasma returned to baseline/placebo values.

In the thorough QTc study (TES10852) which is conducted in healthy subjects, serum uric acid decreased by 71 to 82 µmol/L during treatment days (Day 5 and Day 13 post dosing) and was associated with an increase urinary clearance of uric acid. The values then progressively increased during washout to baseline values at Day 24 (end of washout). An in vitro study showed that teriflunomide was more potent than probenecid inhibiting tubular reabsorption of urate.

A decrease in serum uric acid was also observed with leflunomide (Perez-Ruiz F, Nolla JM. Influence of leflunomide on renal handling of urate and phosphate in patients with rheumatoid arthritis. J Clin Rheumatol. 2003 Aug;9(4):215-8)

This suggests that teriflunomide appears to be a uricosuric agent and blocks renal tubular reabsorption of urate.

In addition, lower serum values of uric acid have been associated with multiple sclerosis (Toncev G, Milicic B, Toncev S, Samardzic G (May 2002). "Serum uric acid levels in multiple sclerosis patients correlate with activity of disease and blood-brain barrier dysfunction". *European*

Journal of Neurology **9** (3): 221–6). In this literature study, MS patients have been found to have serum levels ~194 µmol/L, with patients in relapse averaging ~160 µmol/L and patients in remission averaging ~230 µmol/L. Serum uric acid in healthy controls is ~290 µmol/L.

Although it appears that the decrease in serum uric acid is drug related, the contribution of MS disease cannot be ruled out. An additive effect of drug and disease is also a possibility.

The effect of teriflunomide in uric acid secretion should be addressed in the labeling upon discussions with the Medical Officer.

2.3.5 Effect of age:

Elderly:

Clinical studies did not include patients over 65 years old.

MS typically occurs in young and middle-aged adults. The mean age of patients in the PopPK analysis was 38.2 years. There was a significant relationship between the patients' age and V2/F: V2/F was decreased by about 7 % for a 53-year old patient (95th percentile value) as compared to a 39-year old patient (median age in the study). This decrease of V2/F was related to ~20% $AUC_{0\text{-}24ss}$ increase observed only at the 14 mg dose. This % increase changes depending on the age cut off in subjects <64 years of age. At the 7 mg dose, no significant changes were observed. These age-related changes are unlikely to be clinically meaningful in these patients.

Table: Mean, coefficient of variation %, median, 5th and 95th percentiles of individual exposure parameters by age included in the final PopPK model for a 7 and 14 mg dose.

	$AUC_{0\text{-}24SS}$ (µg h/mL)	C_{maxSS} (µg/mL)	C_{minSS} (µg/mL)
7 mg			
Age < 53 years (n=398)	458 (55.3) – 392 (177, 1010)	19.5 (54.3) – 16.7 (7.76, 42.7)	18.8 (56.1) – 16.0 (7.03, 41.7)
Age > 53 years (n=12)	451 (52.8) – 434 (162, 946)	19.2 (51.4) – 18.5 (7.25, 39.7)	18.4 (53.8) – 17.7 (6.44, 39.2)
14 mg			
Age < 53 years (n=398)	1060 (65.7) – 884 (353, 2130)	45.0 (64.6) – 37.6 (15.6, 89.9)	43.4 (66.7) – 36.1 (14.1, 87.8)
Age > 53 years (n=12)	1290 (74.8) – 1010 (263, 3880)	54.6 (74.0) – 42.7 (11.6, 163)	53.1 (75.5) – 41.4 (10.5, 161)

Dosage adjustment:

Teriflunomide should be used with caution in patients older than 64 years, since there is no clinical experience in this population.

Pediatrics:

The safety and effectiveness of [redacted] (b) (4) in pediatric patients with MS below the age of 18 years have not yet been established.

2.3.6 Effect of Gender:

A population PK model indicated that CL/F was decreased by 23% in females as compared to males for a typical patient. In terms of steady state exposure, these changes increase of 31% (7 mg) and 17% (14 mg) in the $AUC_{0\text{-}24ss}$ for women versus men.

Table: Mean, coefficient of variation %, median, 5th and 95th percentiles of individual exposure parameters by gender

	$AUC_{0\text{-}24SS}$ (µg h/mL)	C_{maxSS} (µg/mL)	C_{minSS} (µg/mL)
7 mg			
Males (n=125)	376 (59.4) – 339 (132, 773)	16.1 (58.0) – 14.5 (5.86, 32.7)	15.4 (60.5) – 13.8 (5.24, 31.9)
Females (n=299)	492 (52.1) – 419 (203, 1060)	20.9 (51.2) – 17.9 (8.82, 45.1)	20.2 (52.9) – 17.2 (8.08, 43.7)
14 mg			
Males (n=115)	952 (58.2) – 809 (264, 1960)	40.4 (57.3) – 34.6 (11.7, 82.0)	39.1 (59.1) – 33.1 (10.5, 81.2)
Females (n=295)	1110 (67.7) – 930 (383, 2380)	47.1 (66.6) – 39.6 (16.8, 99.2)	45.5 (68.7) – 38.0 (15.4, 98.6)

Dosage adjustment:
No dosage adjustment is necessary.

2.3.7 Effect of Race:

A population PK model indicated that there was about 25% increase of V2/F in non-Caucasians (n=16) as compared to Caucasians and race was a statistically significant covariate. Majority of the patients were Caucasians (N=394). Other races were: Blacks (N=2), Asians (N=9), others (N=5), hence clinically meaningful differences based on these small numbers in a population PK cannot be derived.

Dosage adjustment:
Effect of race on the pharmacokinetics of teriflunomide cannot be adequately assessed due to a low number of non-white patients in the clinical program.

2.3.8 Effect of pregnancy or lactation:

Teriflunomide was found to be teratogenic in laboratory animals and therefore double contraception is required for all the teriflunomide studies. In addition, patients are instructed to follow a rapid elimination procedure with cholestyramine or activated charcoal to reach a certain plasma exposure, if they want to become pregnant or in case of suspected pregnancy. This exposure was 0.02 µg/ml as per the ARAVA label, but this limit has been (b) (4) based on new animal studies in this NDA. This will be reviewed by the Pharmacology/Toxicology reviewer.

2.3.9 Effect of genotype/phenotype of relevant metabolizing enzymes and transporters

The sponsor conducted comprehensive genotyping of ten drug metabolizing enzymes and five transporters of potential pharmacogenetic relevance to teriflunomide in 8 Phase 1 and 3 Phase 2/3 clinical trials. This was reviewed by Dr. Jeffery Kraft (Pharmacogenomics).

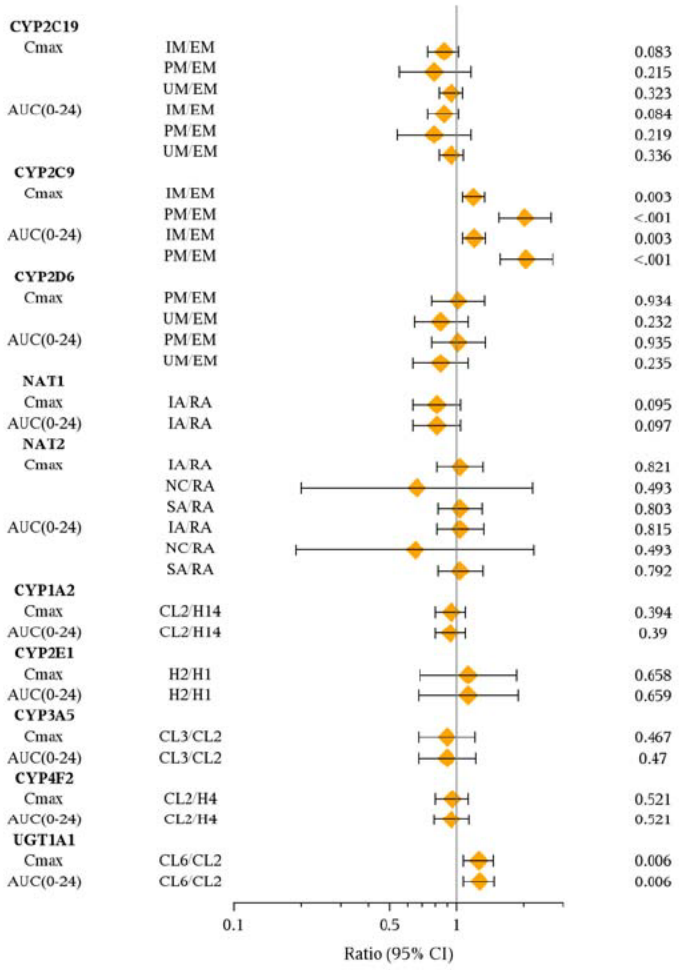
According to his review, teriflunomide concentrations were approximately 2 times higher in CYP2C9 poor metabolizers and approximately 25% higher in UGT1A1 poor metabolizers, compared to extensive metabolizers of each enzyme. These findings were not replicated across healthy subject and patient studies and could potentially be false-positives, particularly given the limited evidence for these pathways as major routes of metabolism in vitro. Otherwise, no significant effects of genotype/phenotype were identified.

No dose modification for any intrinsic or extrinsic factors has been proposed by the sponsor, although no effect of this magnitude was observed. The Pharmacometrics review identified an exposure/response relationship for efficacy but not for safety (particularly hepatotoxicity). Consequently, the exposure differences based on CYP2C9 or UGT1A1 genotype are not likely to be clinically relevant and dose adjustment is not indicated at this time.

BCRP has previously been associated with differences in teriflunomide exposure when administered as the prodrug, leflunomide (PMID: 20972558). The data submitted by the sponsor suggest that BCRP genotype does not have a major effect on systemic teriflunomide exposure. While tissue concentrations (e.g., liver) may differ according to BCRP genotype, additional clinical PK studies related to this transport pathway may be of limited utility.

Results of relationship between genotype/phenotype of enzymes or transporters and exposure from Phase 2/3 studies that showed an effect on CYP2C9 and UGT1A1 poor metabolism are summarized below. For results of Phase 1 SD and MD studies that did not show an effect of genotype, please refer to the Pharmacogenomics review.

Figure: Drug metabolizing enzyme genotype/phenotype effects on teriflunomide exposure in Phase 2/3 trials.



Best Available Copy

2.4 EXTRINSIC FACTORS

2.4.1 Is teriflunomide a substrate, inhibitor or inducer of CYP or other enzymes?

Terflunomide as a substrate, inhibitor or inducer of CYPs and other enzymes is shown in the following Table. All enzymes that were evaluated in in-vitro studies were given in the Table:

Table: Teriflunomide as a substrate, inhibitor or inducer of CYPs or other enzymes

CYPS	substrate	Inhibitor	Inducer*
1A2	X	X	X
2B6	X	X	Not evaluated
2C9	X	Yes	Yes
2C19	X	X	Co-induced

2C8	X	Yes	Co-induced
3A4	X	X	Yes
3A5	X	X	NA
2D6	X	X	NA
FMOs			
FMO 3	X		
FMO 5	X		

*with mRNA and enzyme activity

In vitro studies, teriflunomide was not a substrate of any CYPs or FMOs. It was an inhibitor of CYP2C8 and CYP2C9. Teriflunomide was an inducer of CYP3A4, suggesting that CYP2C9, 2C19 and 2C8 may be co-induced. It was not an inducer of CYP1A2. Induction of CYP2B6 was not evaluated in vitro, but an in vivo drug interaction study with a CYP2B6 substrate (bupropion) was conducted (see section 2.4.5), suggesting CYP2B6 is not induced as well, hence additional in vitro testing is not required. In vitro, terflunomide was not an inducer of CYP1A2, but in vivo study with caffeine suggested some induction (see section 2.4.5)

2.4.2 Is teriflunomide a substrate and/or inhibitor of any transporter system?

Table: Teriflunomide as a substrate, inhibitor or inducer of transporters

Transporters	substrate	Inhibitor	Inducer
Pgp	X	X	X
BCRP (intestinal and CNS efflux)	Yes	Yes	NA
OATP1B1 (hepatic uptake)	X	Yes	NA
OAT3 (renal uptake)	X	Yes	NA
OCT2 (renal uptake)	X	Yes (weak)	NA

In vitro, teriflunomide was a substrate of efflux transporter BCRP. It was an inhibitor of BCRP, OAT3, OATP1B1 and OCT2.

2.4.3 Is there an in vitro basis to suspect drug-drug interaction?

CYP450 Based Intercations:

The following Table shows the possible CYP based drug interactions based on predictions (I/Ki) from the results in vitro studies.

Table: Drug interaction potential: (If I/ki >0.1 interaction possible, If I/ki >1 interaction Likely)

CYP	Test Substrate	Test Inhibitor	Ki	I/Ki Total	I/Ki Unbound	DDI probability
1A2	Phenacetin	Furafylline	69 µM 18.6 µg/ml	2.4	0.006	Likely
2A6	Coumarin	Nicotine	>250 µM 68.5 µg/ml at 3 times the therapeutic levels	0.6	0.002	Unlikely
2B6	Bupropion	Ticlopidine	240 µM 64.8 µg/ml	0.6	0.002	Possible
2C9	Tolbutamide	Sulphenazole	8.6 µM 2.32 µg/ml	19.5	0.051	Likely
2C19	S-(+) mephenytoin	Tranylcypromine	158 µM 42.7 µg/ml	1.1	0.003	Likely
2C8	Paclitaxel	Quercetin mAb	0.1 µM 0.15 µM 0.04 µg/ml	1670 1116	4.342 2.901	Likely
3A4	Midazolam Testasterone	Ketoconazole	157 µM 42.2 µg/ml 105 µM 28.4 µg/ml	1.1 1.6	0.003 0.004	Likely
2D6	Bufaralol HCl	Quinidine	312 µM 84.2 µg/ml	0.5	0.001	Possible
2E1	Chlorzoxazone	4-Methylpyrazole	>250 µM 68.5 µg/ml	0.6	0.002	Unlikely

			at 3 times the therapeutic levels			

I=167 µM or 45.3 µg/ml with 14 mg QD, MW=270.2
Fraction Unbound: 0.25-0.27%

Based on the above Table, substrates of CYP1A2, 2B6, 2C9, 2C19, 2C8, 3A4 and 2D6 are all likely to show an interaction with teriflunomide. The sponsor conducted studies with substrates of all these CYP isozymes. Based on the rank order of I/Ki's, substrates of CYP2C8 and CYP2C9 are most likely to show an interaction with teriflunomide. Amongst these a drug interaction was shown with a substrate of CYP2C8, repaglinide, but not a significant pharmacokinetic interaction with a CYP2C9 substrate, warfarin (see section 2.4.5).

In vitro data (mRNA and enzyme activity) showed inductive effect on CYP2C9 and CYP3A activity at teriflunomide concentrations ≥15.4 µm (4.16 µg/mL) and ≥139 µm (37.5 µg/mL), respectively, but not on CYP1A1/1A2. Hence, teriflunomide could also reduce exposure of drugs that are substrates of CYP2C9 and CYP3A4. This was not observed in vivo. (See discussion in section 2.4.5).

The confirmation of these in vitro results was based on in vivo studies (See section 2.4.5 for additional details of in vivo findings and its correlation to in vitro findings).

Transporter Based Interactions:

- Teriflunomide is a substrate of BCRP in vitro
- Terifluniomide is an inhibitor of BCRP, OAT3, OATP1B1, OCT2 in vitro as shown in the Table below.

The sponsor has not conducted any in vivo studies to confirm these in vitro findings.

Teriflunomide as a substrate of transporters: No significant effect of BCRP (ABCG2) genotypes on teriflunomide was observed. According to Dr. Jeffery Kraft's review (Pharmacogenomics), given the lack of BCRP genotype effect throughout the studies (Phase 2/3), drug interaction studies related to BCRP will be of limited utility.

The net flux ratio for BCRP as a substrate using Funitremorgin as an inhibitor was 10.87. In a bi-directional transporter assay, the net flux ratio of ≥2 supports the need for conducting an in vivo study to confirm these findings. Therefore a drug interaction study with a BCRP inhibitor (cyclosporine, elacridar, eltrombopag or gefitinib) should be considered. But, teriflunomide is highly permeable drug. In a cross study comparison, the bioavailability appears to be complete. Therapeutic dose of 14 mg is soluble in 250 mL of buffers at pH 4.5-8.0. But at lower pH's, it is not quite soluble. The solubility in water is 31 mg/L. Given all this, the potential of an interaction with a BCRP inhibitor is probably questionable.

Teriflunomide as an inhibitor of transporter: For teriflunomide as an inhibitor of some transporters, the need for an in vivo study based on the Cmax/IC50 ≥ 0.1 is shown in this Table. The probable drugs that are substrates of the transporters that could be evaluated are given in the parenthesis. The drugs shown in red or blue are more likely to be co-administered in the MS population than the others. This is taken into consideration when an in vivo study is requested as a PMR.

Table: Drug Interaction Potential (Cmax/IC50 ≥ 0.1: interaction likely)

	Test Substrate	**Test Inhibitor**	**IC50** (μM)	**Cmax/IC50 (unbound or Total)**	**R-value***	**DDI Probability** (Cmax/IC50≥0.1)
P-gP	Digoxin	Verapimil	X			None
BCRP	Metho-trexate	Fumitre-morginC	0.146	1143**	-	Likely (with methotrexate, rosuvastatin, mitoxantrone, laptinib)
OAT3	Estrone-3-sulfate	Probencid	1.03	0.42	-	Likely (with zidovudine, acyclovir, ciprofloxacin, tenofir, methotrexate)
OATP1B1	Estradiol-17β glucuronide	Rifampin	7.4	22.56**	6.9	Likely (with rosuvastatin, pravastatin, pitavastatin, repaglinide, rifampin)
OCT2	Metformin	Cimetidine	>100	0.004	-	Unlikely

Cmax 167 μM Fu=0.25-0.27% faFg=1 Ka=0.1 Qh=1500
*If R values is ≥ 1.25 for OATP1B1, then a DDI study is needed
**Total Cmax/IC50

For BCRP and OATP1B1, a Phase IV requirement drug-drug interaction study with rosuvastatin should be requested, given the likelihood of its wide use. Rosuvastatin is a substrate of both OATP1B1 and BCRP. The only limitation of this study would be the ability to differentiate between the effect of teriflunomide on BCRP vs. OAT1B1. This will need to be addressed based on the magnitude of effect observed. A study with repaglinde and rifampin were conducted, which are also substrates of OATP1B1. For repaglinide, which is also a CYP2C8 substrate, a 2.3 fold increase in exposure was observed. In this case, the overall contribution of CYP2C8 or OAT1P1 inhibition cannot be made. Rifampin is also a non specific inducer of CYPs. About a 20% reduction in exposure was observed, with a 17% increase in Cmax. The increase in Cmax

in this case is not clear as Cmax is related to absorption and OATP1B1 is a hepatic uptake transporter.

For OAT3, a drug interaction study with methotrexate should have been considered. Methotrexate is indicated for the treatment of rheumatoid arthritis, although some research was conducted with methotrexate in MS patients (For example: Ashtari F, Savoj MR. Effects of low dose methotrexate on relapsing-remitting multiple sclerosis in comparison to Interferon β-1α: A randomized controlled trial. J Res Med Sci. 2011 Apr; 16(4):457-62.) At this time the use of methotrexate in MS is not likely to be significant but may be used off label in MS in the future. The ARAVA label, states that no PK interaction with methotrexate was observed, however, the risk of hepatotoxicity was increased. (Note for FOI: This study was a 6 month long study, where methotrexate levels were taken at baseline, Week 6, 12 and 24). The information about increased hepatotoxicity with co-administration should be addressed through labeling.

Mitoxantrone is used in MS, but has cardiac toxicity, hence the feasibility of conducting drug interaction study with this is low. In addition, based on discussions with the Clinical team, its use is diminishing.

Given this information, addition drug interaction studies with substrates of OAT3 may not be necessary.

2.4.4 What extrinsic factors (such as herbal products, diet, smoking and alcohol) influence exposure and or response and what is the impact of any differences in exposure on pharmacodynamics?

The effect of extrinsic factors like herbal products and smoking has not been conducted. Teriflunomide is not metabolized by any of the CYP enzymes.

2.4.5 Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

Influence of teriflunomide on the pharmacokinetics of concomitant drugs is summarized in the following Table:

Table: In Vivo Drug Interactions

Concomitant Medication (mechanism)	Co-medication Dose	Substrate Ratio (90% CI) AUC0-∞	Substrate Ratio (90% CI) Cmax	Dosage Adjustment Or Recommendations
Effect of other drugs on Teriflunomide*				

Rifampin (Inducer for CYPs, PgP)	600 mg QD	0.600 (0.55, 0.66) AUClast 0.79 (0.76-0.84)	1.17 (1.11, 1.22)	none
Effect of teriflunomide on other drugs+				
Repaglinide (CYP2C8, 3A4 (minor) OATP1B1 (minor))	0.25 mg SD (recommended 0.5-16 mg)	2.28 (2.04, 2.54)	1.64 (1.44, 1.87)	The magnitude of interaction could be higher at the recommended repaglinide dose. Recommend monitoring patients with concomitant use of drugs metabolized by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone may have higher exposure
R-Warfarin S- Warfarin (CYP2C9)	25 mg SD	1.0 (0.95, 1.05) 1.12 (1.08, 1.15)	1.10 (1.04. 1.17) 1.08 (1.0, 1.16)	INR monitoring recommended
		25% ↓ in peak INR		
Ethinylestradiol (CYP3A4. 2C9 UGT1A1, SULT1E1, OATP1B1 Levonorgestrel	0.03 mg QD 0.15 mg QD	1.54 (1.46,1.63) 1.41 (1.34, 1.49)	1.58 (1.48, 1.68) 1.33 (1.24, 1.42)	Consideration to be given to type and dose of oral contraceptive selected
Caffeine (CYP1A2) Paraxanthine	100 mg SD	0.45 (0.40, 0.50) 0.58 (0.55, 0.62)	0.82 (0.77, 0.87) 1.06 (1.03, 1.10)	Recommend caution with concomitant use of drugs metabolized by CYP1A2, such as duloxetin, alosetron, theophylline, tizanidine
Bupropion (CYP2B6)	150 mg SD (recommended 200-400mg)	0.93 (0.87, 0.99)	1.03 (0.94, 1.12)	none
Midazolam (CYP3A4)	2 mg SD	1.27 (1.14, 1.52)	1.13 (1.0, 1.28)	none
Omeprazole (CYP2C19)	20 mg SD	0.90 (0.82, 0.98)	0.93 (0.82, 1.05)	none
Metoprolol (CYP2D6)	100 mg SD	0.99 (0.93, 1.06)	1.06 (0.97, 1.17)	none

*Teriflunomide dose: 70 mg SD

+ Teriflunomide dosed to steady state in all studies (70 mg QD for 3-4 days then 14 mg QD for 8-11 days), as shown in the following Table

Table: Teriflunomide doses in Drug Interaction studies

Substrate	Teriflunomide dose	Day	C_{trough} (µg/ml)
Repaglinide	70 mg QD for 4 days then 14 mg QD for 8	12	29.7

Midazolam	70 mg QD for 3 days then 14 mg QD for 11	14	27.9
Oral contraceptive	70 mg QD for 4 days then 14 mg QD for 10	21[a]	41.3
Warfarin	70 mg QD for 3 days then 14 mg QD for 8	5	18.7
Cocktail	70 mg QD for 4 days then 14 mg QD for 9	12	30.0
Bupropion	70 mg QD for 4 days then 14 mg QD for 10	12	36.1

[a] *teriflunomide coadministered with oral contraceptive*

Due to the long half-life for teriflunomide, it would have taken several weeks of QD administration of 14 mg to approach steady state plasma concentration. Therefore, a loading dose of 70 mg for 3 to 4 days was administered followed by a maintenance dose of 14 mg for 8 to 11 days to reach steady state therapeutic concentrations. Teriflunomide concentrations achieved in the various interaction studies (Table above) were within 5th and 95th percentile of the range observed in the efficacy/safety studies, although the median steady state trough concentration in the Phase 3 studies was slightly higher (45 µg/ml).

Overall significant interactions were observed with:

1. **Rifampin:** A 40% decrease in teriflunomide AUC∞ and 17% increase in Cmax was observed with coadministration of a single dose of teriflunomide and multiple doses of rifampin. The % of AUC extrapolated in this study was >30% in many subjects, hence appears that differences based on AUC_{0-360} is more reliable. AUC_{0-360} decreased by 20% with coadministration. There was a 40% increase in peak levels of this moiety and AUC being unaffected when ARAVA® was administered with Rifampin. Reduction in teriflunomide exposure with rifampin (a CYP2B6, 2C8, 2C9, 2C19, 3A inducer, as well as an inducer of P-gp-) coadministration, suggests that CYPs and P-gp involvement was minor. The in vitro studies did not suggest that teriflunomide is a substrate of CYPS or P-gp. In addition to this, rifampin is a substrate of OAT1P1 and teriflunomide is inhibitor of this transporter. Changes in Cmax are likely to be due to absorption effects and not the inhibition of hepatic uptake. Hence, the mechanism behind these changes is not clear (see assessment through population analysis below).
2. **Repaglinide:** The AUC of repaglinide was increased by 2.3 fold with coadministration. A lower dose (0.25 mg) of repaglinide was used in this study. The recommended dose range is 0.5-16 mg, hence, the magnitude of interaction could be higher with higher dose of repaglinide. Teriflunomide is an inhibitor of both CYP2C8 and OATP1B1, and repaglinide is a substrate of both. The contribution of each of these to the overall increase in exposure cannot be established. Since the dose of repaglinide is titrated based on glucose monitoring, no dose reduction is recommended in the label. Dose reduction should be base don glucose monitoring.
3. **Warfarin:** No change in PK was observed, suggesting CYP2C9 involvement is negligible, but a 25% decrease in peak INR was observed.
4. **Oral Contraceptives:** ~60% increase in ethinyl estradiol exposure was observed. This effect does not appear to be related to CYP3A4 as a drug interaction study with midazolam, a sensitive substrate of CYP3A4 did not show any appreciable increase in midazolam levels. This increase may be due to inhibition of OATP1B1 by teriflunomide.
5. **Caffeine:** Caffeine and paraxanthine exposure was decreased by ~50%. Teriflunomide was not an inducer of CYP1A2 in vitro, but appeared to be in vivo based on this study.

Drug Interaction Assessment through Population Analysis:

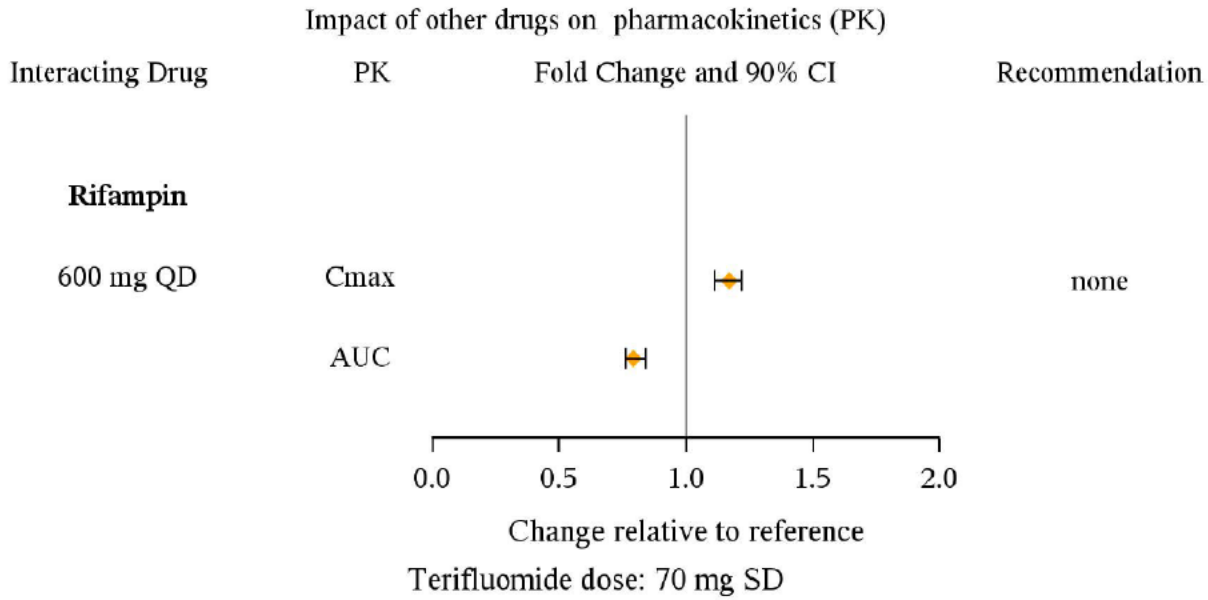
Effect of other drugs on teriflunomide: Apparent clearance of teriflunomide was increased by about 10% in case of coadministration of non specific inducers (amobarbital, carbamazepine, dexamethasone, efavirenz, isoniazid, modafinil, nevirapine, norethindrone, omeprazole, oxcarbamazepine, phenobarbital, phenytoin, pioglitazone, prednisone, prednisolone, primidone, rifabutin, rifampin, rifapentin, ritonavir, secobarbital, St John's wort, and troglitazone), leading to a decrease of the mean $AUC_{0\text{-}24ss}$ of around 2% and 7% for 7 mg and 14 mg doses, respectively, in the Pop PK analysis. Given, the number of drugs pooled together as inducers and the slight increase in exposure does not lend much value in this population analysis. Moreover, accurate dosing and timing information is not robust in a population analysis.

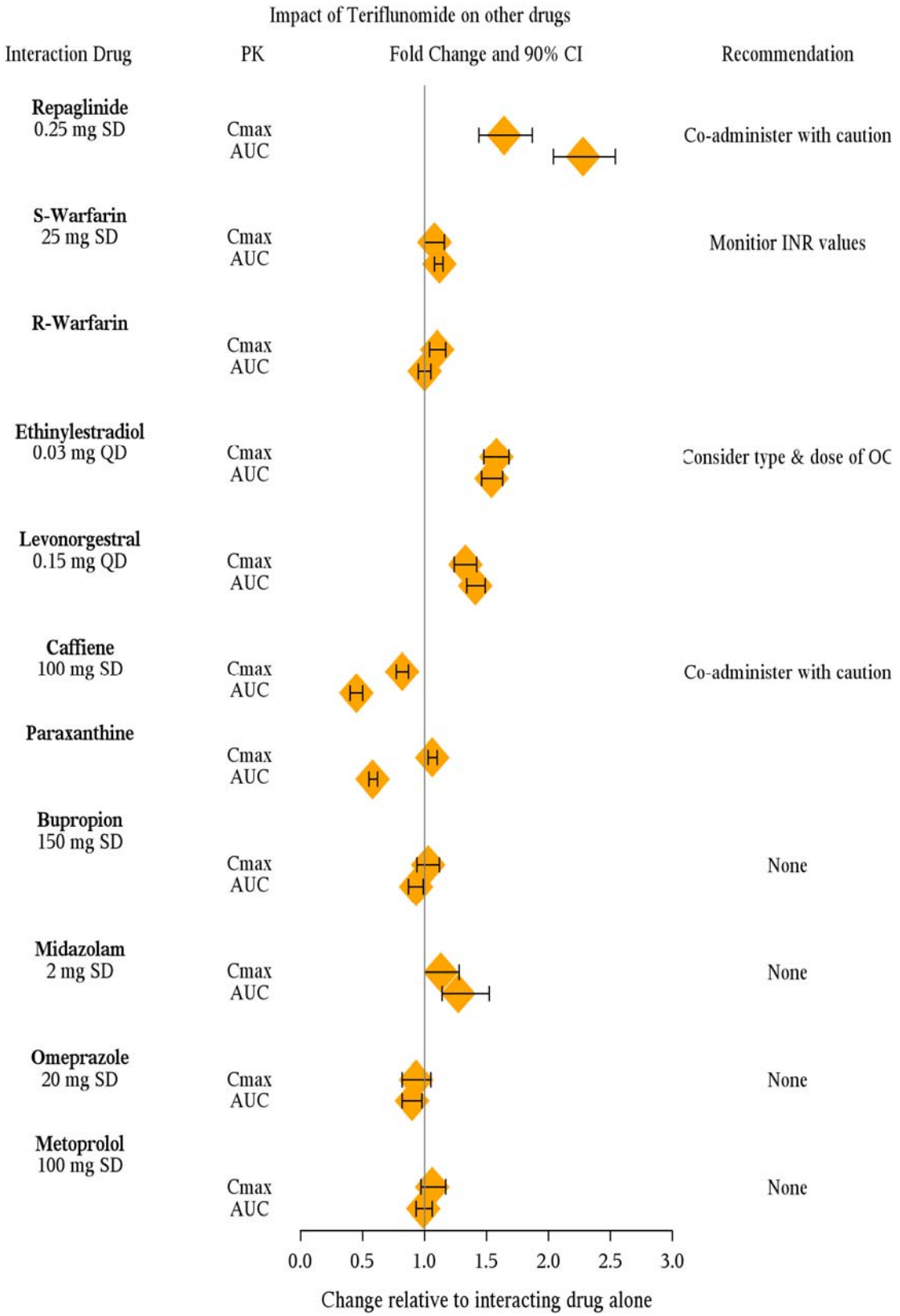
A 21-35% decrease in concentrations was observed in patients in Study EFC6049, but only when the potent CYP and transporter inducers were considered: carbamazepine, phenobarbital, phenytoin, and St John's Wort.

Table: Plasma concentrations of teriflunomide in presence of inducers

Dose	**Plasma concentrations (mean ±SD) at Week 36**	
	Without Inducer	**With Inducer**
7 mg	19.3 (11.1) µg/mL	12.7 (4.29) µg/mL
14 mg	45.0 (30.7) µg/mL	35.8 (19.4) µg/mL

Forest Plots for the drug interactions and dosing recommendations are given below:





*Teriflunomide dosed to steady state in all studies (70 mg QD for 3-4 days then 14 mg QD for 8-11 days)

Some discrepancies were observed between in vitro and in vivo results, these are summarized in the Table below:

Table: Discrepancy between in vitro and in vivo results:

Pathway	In vitro	In Vivo
CYP2C9	Inhibitor, inducer	None[a]
CYP3A4	Inducer, inhibitor	Inhibitor (weak)
CYP1A2	not an inducer	Inducer (weak)
CYP2C19	Inducer, inhibitor	None[a]

[a]effect as an inhibitor and inducer may be nullified

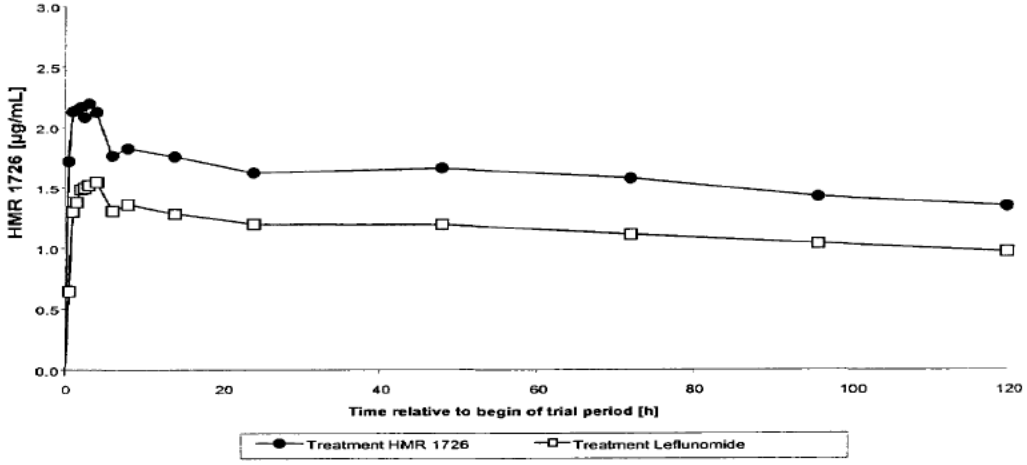
Based on the in vitro I/Ki, many CYPs fell into the criteria for possible or likely in vivo interactions. Although, based on rank order CYP2C8 inhibition was most significant. In vivo results show the same.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the relative bioavailability of Teriflunomide when given as (b) (4) or ARAVA tablets?

Teriflunomide is the active metabolite of leflunomide. The pharmacokinetics of leflunomide are primarily examined as the active metabolite (terflunomide or HMR1726).

The mean concentration time profiles of teriflunomide when administered as (b) (4) and ARAVA tablets are shown in the following Figure:



Best Available Copy

The relative bioavailability of leflunomide was approximately 70% that of HMRI726. Thus, a tablet containing 14 mg HMRI726 is expected to produce an exposure to HMRI726 that is comparable to a tablet containing 20 mg leflunomide.

The point estimates of teriflunomide (ARAVA/ (b) (4)) are given in the following Table:

Table: Relative Bioavailability of [(b) (4)] AND ARAVA:

Parameter	Ratio	90% CI
Cmax	63.25	57.64, 69.41
AUC(0-24h)	71.85	68.57, 75.29
AUC 0-72h)	72.57	68.67, 76.70
AUC0-120h)	70.97	67.16,74.99

2.5.2 Is the proposed to-be-marketed formulation of teriflunomide bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

The appearance of the clinical tablet used in the Phase 3 studies was changed slightly for the to-be-marketed tablet. For the 7-mg dosage strength, the formulation was changed from [(b) (4)] to a pale greenish-blue, hexagonal, film-coated tablet. For the 14-mg dosage strength, the formulation was changed from [(b) (4)] to a blue, pentagonal, film-coated tablet. The change in shape and color was compared in dissolution studies, which is reviewed by ONDQA. No in vivo bioequivalence study was performed and is not necessary to demonstrate similarity between the clinical trial and to-be marketed formulation.

2.5.3 What is the relative bioavailability of the various formulations of teriflunomide used in the clinical pharmacology studies and the clinical trials?

[(b) (4)] drug substance:

[(b) (4)]. The relative bioavailability of teriflunomide did not differ with particle size changes, thereby indicating that teriflunomide absorption is not dissolution-rate limiting, [(b) (4)] In addition, dosage strength proportionality was established by demonstrating that the 2x7 mg [(b) (4)] tablets are bioequivalent to the 1x14 mg [(b) (4)] tablet as shown in the Table below:

Table: Ratio estimates and 90% confidence interval for C_{max}, AUClast and AUC

Parameter	1 x 14 mg [(b) (4)] (test) vs. 1 x 14 mg [(b) (4)] (reference)	2 x 7 mg [(b) (4)] (test) vs. 1 x 14 mg [(b) (4)] (test)
Cmax	0.997 (0.943, 1.06)	0.965 (0.912, 1.02)
AUClast	1.03 (1.00, 1.06)	0.996 (0.969, 1.02)

AUC	1.01 (0.931, 1.10)	1.05 (0.965, 1.14)

(b) (4)

2.5.4 What is the effect of food on the bioavailability of the drug from the dosage form? Are there any dosing recommendations that need to be made regarding the administration of teriflunomide with relation to meals or meal types?

Food does not have a clinically meaningful effect on the Cmax or AUC of 7 and 14 mg teriflunomide tablets (b) (4). The to-be marketed tablets differed (b) (4) which will not change the food effect on the commercial Tablets. The 90% confidence interval for the Cmax was outside the bounds, but this decrease was believed to not be clinically meaningful.

Table: Fed/fasted ratio estimates and 90% confidence interval for C_{max} and AUC_{0-72}

Parameter	7 mg	14 mg
Cmax	0.82 (0.75, 0.91)	0.82 (0.75, 0.90)
AUC0-72	0.94 (0.90, 0.98)	0.97 (0.93, 1.01)

Table: Pharmacokinetic parameters under fed and fasted condition Mean ±SD (Geo mean)[%CV]

	7 mg – fasted	7 mg – fed	14 mg – fasted	14 mg – fed
Cmax (µg/mL)	0.906 ± 0.198 (0.887) [21.8]	0.740 ± 0.101 (0.734) [13.6]	1.79 ± 0.301 (1.77) [16.8]	1.47 ± 0.190 (1.46) [12.9]
tmax (h)	2.26 (1.00 - 16.00)	5.00 (0.50 - 12.18)	1.50 (0.50 - 3.00)	6.25 (2.00 - 24.00)
AUC0-72 (µg.h/mL)	41.1 ± 5.70 (40.7) [13.9]	38.8 ± 6.09 (38.4) [15.7]	81.3 ± 13.1 (80.3) [16.1]	78.3 ± 10.6 (77.7) [13.5]

For both tablets, food seemed to have a small effect on t_{max} (median: 5 hours for fed, 2.3 hours for fasted for 7 mg, and 6.3 hours for fed, 1.5 hours for fasted for 14 mg).

In the efficacy/safety studies, the patients were instructed that the drug could be taken either with or without food. Meal types are unlikely to affect the exposure of teriflunomide.

Dosing Recommendation:
Teriflunomide can be taken with or without food.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

The assay validation parameters of the major circulating moiety, teriflunomide, in the plasma is given below:

Matrix	Method	Validation Parameters
Plasma	HPLC-UV	LLOQ: 0.1 µg/ml for teriflunomide Curve range (µg/mL): 0.10-100 Between run accuracy: 0.02 Between run precision: 0.003 Within-run accuracy: 0.03 Within-run precision: 0.006

		Recovery: 93.2% Stability: room temp for 24 hrs, -20C fro 4 months, 3 freeze-thaw cycle CV% RE% ≤ 6.8 -5.0 to 1.7
	LC/MS/MS	LLOQ: 0.01 µg/ml for teriflunomide Curve range (µg/mL): 0.010-100 Between run accuracy -7.8 to 6.7 of nominal value Between run precision CV% 1.8 to 6.8% Within-run accuracy: -4.9 to 3.1 of nominal value Within-run precision: CV% 2.9 to 5.8% Recovery: 93.2% Stability: room temp for 24 hrs, -20C for 5 months, 7 freeze-thaw cycle
	LC/MS/MS	LLOQ: 0.1 µg/ml for teriflunomide Curve range (µg/mL): 0.100-25 Between run accuracy -7.0 to 3 of nominal value Between run precision CV% 1.9 to 8.8% Within-run accuracy: 3.0 to 7 of nominal value Within-run precision: CV% 1.9 to 12.6% Recovery: 93.2% Stability: room temp for 24 hrs, -20C for 480 days, 7 freeze-thaw cycle

These assays are acceptable from a CP perspective.

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.0 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions.

Is there any covariate which affects teriflunomide PK?

Yes, the sponsor's analysis showed that clearance (CL/F) was related to bilirubin and albumin plasma levels as well as on inducers co-administration and sex, and volume of distribution (V2/F) was related to patient's albumin plasma levels, age, race (Caucasians vs. non-Caucasians) and body weight.

The sponsor conducted the population PK analysis using dataset composed of 834 patients enrolled into a phase II (HMR1726D/2001) and a Phase III (EFC6049) study, and of 10 healthy subjects enrolled in a Phase I study (TDR10892).

The results showed that for a typical patient, CL/F was decreased of 23% in females as compared to males whereas CL/F was increased by about 10% in the patients who were co-administered with inducers. The influence of bilirubin on CL/F was also limited (4% decrease at bilirubin= 17 µmol/L compared to 7 µmol/L). CL/F was decreased of 3% when the albumin increased from its median value (43 g/L) to its 95th percentile value (48 g/L).
There was about 25% increase of V2/F in non-Cauccasians (n=16) as compared to Caucasians. V2/F was increased by 35% in a typical patient of 99.5kg (95th percentile of patient's weight) as compared to a patient with 68.3kg (median weight). The influence of albumin on V2/F was moderate with a decrease of 0.8 L (around 11 %) of V2/F for a typical patient with an albumin level of 53 g/L (95th percentile of albumin level in the population of the study) in comparison with a patient with an albuminemia of 43 g/L (median value of albumin). There was also a significant relationship between the patients' age and V2/F: V2/F was decreased by about 7 % for a 53-year old patient (95th percentile value) as compared to a 39-year old patient (median age in the study).

The effect of the covariates on the steady state exposure parameters was limited and below the inter-individual variability, except for bilirubin. For this covariate, while no major alteration of exposure parameters could be observed for the 7 mg dose, a 1.73-fold increase of mean AUC_{0-24SS} was observed for the 14 mg dose between patients with a bilirubin > 17 µmol/L and the patients with bilirubin < 17 µmol/L.

However, dose, renal function (measured by CLcr), ALT and AST on the PK of teriflunomide was not found to be statistically significant.

Also the sponsor's population PK analysis estimated the median terminal half-life ($t_{1/2\beta}$) as 427 hrs (17.8 days) and 466 hrs (19.4 days) at 7 mg and 14 mg, respectively, which gives approximately 89-97 days to reach steady-state.

Is there any significant exposure-response relationship? And does the relationship support the proposed dose?

Yes, it shows a clear exposure-response relationship for efficacy but the relationship is not apparent in some of safety endpoints such as ALT increase. The sponsor's proposed dose seems to be reasonable based on both the reviewer and sponsor's analyses.
The study of EFC6049, which is a randomized, double-blind, placebo-controlled, parallel-group design study with 108-weeks duration, is only pivotal study completed in this submission. In the study two doses were tested- 7mg/day and 14mg/day, and the sponsor is seeking the approval for 14 mg/day.

The primary endpoint was annualized relapse rate (ARR), and there were other secondary endpoints such as time to disability progression sustained for 12-week, total number of Gadolinium-enhanced T1 lesions per scan, total number of unique active lesions per scan, number of patients free of active lesions and burden of disease at week 108.

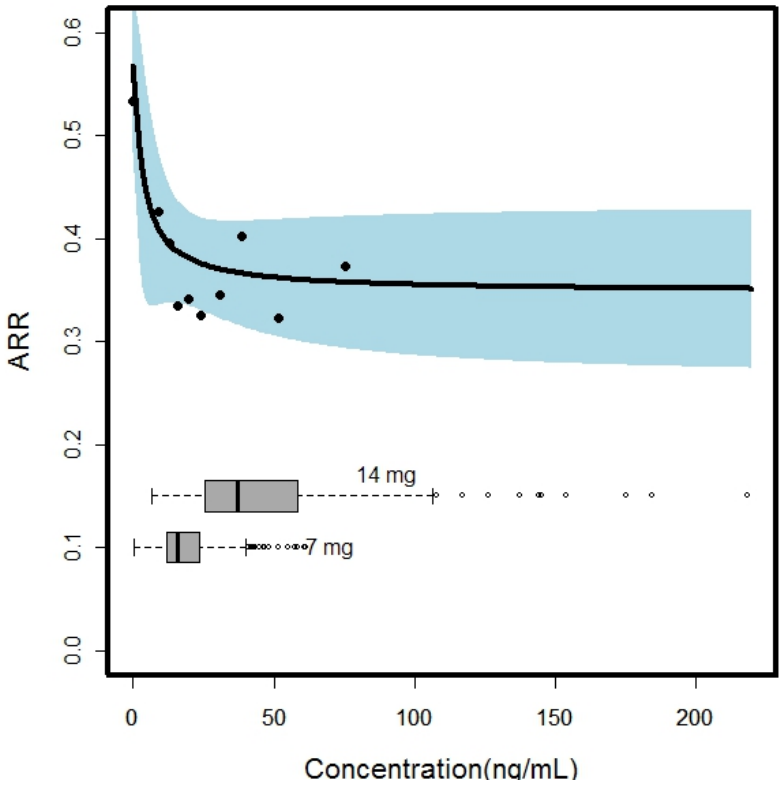
The primary analysis showed that teriflunomide significantly reduced annualized relapse rate (ARR) after a 2-year treatment: 0.539, 0.370, and 0.369 for placebo, 7 mg/day and 14 mg/day, respectively, corresponding to statistically significant risk reductions of 31.2% (p=0.0002) in the 7 mg group and 31.5% (p=0.0005) in the 14 mg group relative to placebo. Some of the findings from the analyses for the secondary endpoints are summarized below:

5) The risk of disease progression was significantly reduced (29.8%) by 14 mg/day compared to placebo while the reduction observed (23.7%) for the 7 mg/day.
6) There were significantly fewer T1-Gd lesions per scan in 14 mg compare to 7 mg (p=0.0024).
7) The percentage of patients free from Gd-T1 lesions was significantly higher in 14 mg compared to 7 mg ($p < 0.001$).
8) Difference in the number of unique active lesions per scan was statistically significant in 14 mg compared to 7 mg ($p < 0.001$).

In order to support or confirm the claim from the primary efficacy analyses the reviewer conducted the exposure-response analyses using data from one phase III study (EFC6049 (TEMSO)), and steady-state mean concentration (MCONC) for each patient was used as an exposure.

Figure displays the model-predicted relationship between ARR and teriflunomide concentration with observed data at eight bins of ranked concentrations, which shows clear exposure-response relationship. The model predicts similar ARR at the median concentrations of each dose (0.38 and 0.37 at 16ng/ml (7mg/day) and 37ng/ml (14mg/day), respectively). However, it should be noticed that patients who are on the low end of exposure of 7mg may lose efficacy as it does not reach a plateau.

Figure 1. The model predicted relationship for ARR and teriflunomide concentration with 95% prediction interval (blue shaded area). The dots indicate the observed ARR at decile of teriflunomide concentration. Also two boxplots are the distribution of teriflunomide concentration at each dose.

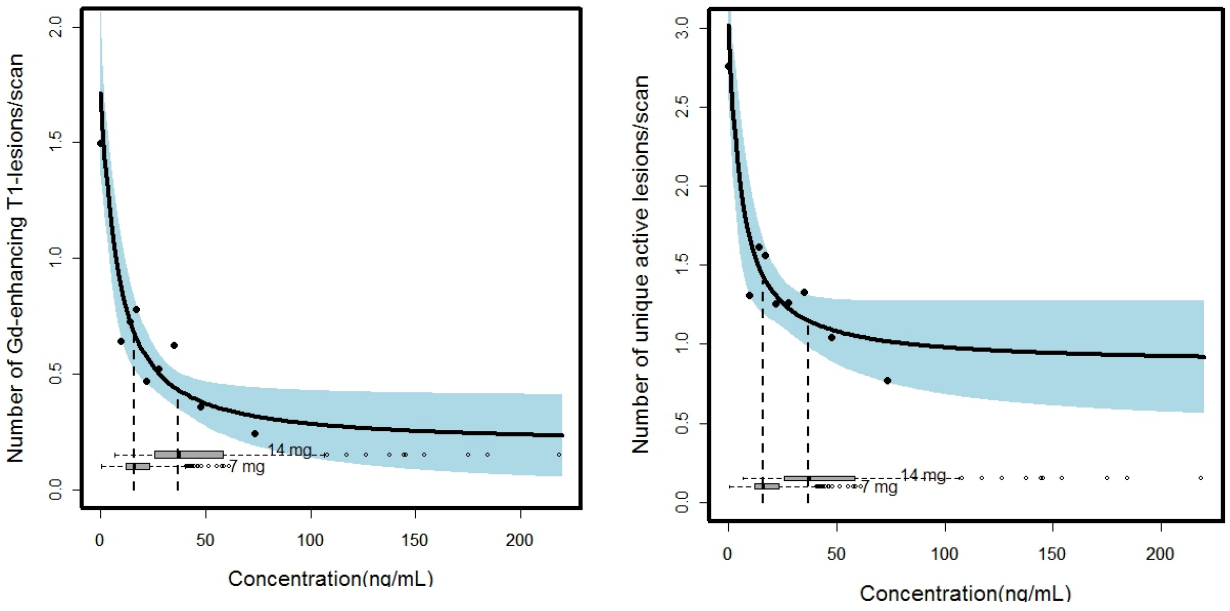


In addition, the reviewer further looked into the relationship between MRI endpoints and concentration as the sponsor's claim for approval of 14 mg rather than 7 mg was mainly driven by the efficacy analyses with MRI endpoints where 14 mg showed superiority to 7 mg. Two MRI endpoints were examined: the total number of Gadolinium-enhanced T1 lesions per number of scans, and total number of unique active lesions per number of scans, which are consistent with the efficacy analyses.

Figure shows the results from the reviewer's analyses where the number of lesions for both endpoints clearly decrease concentration-dependent manner.

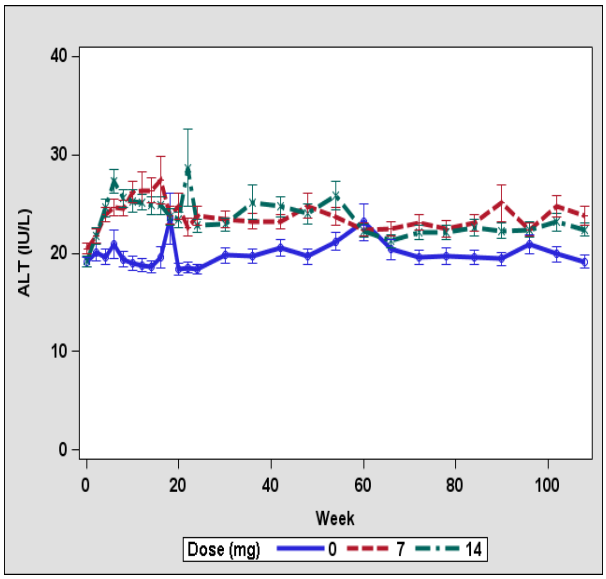
Figure 2. The model predicted relationship for the number of Gd-enhancing T1 lesions per scan and teriflunomide concentration relationship (left) and the relationship for the number of unique active lesions per scan (right) with 95% prediction interval (blue shaded area). The dots indicate the observed mean of the number of lesions at octile of teriflunomide concentration. Also two

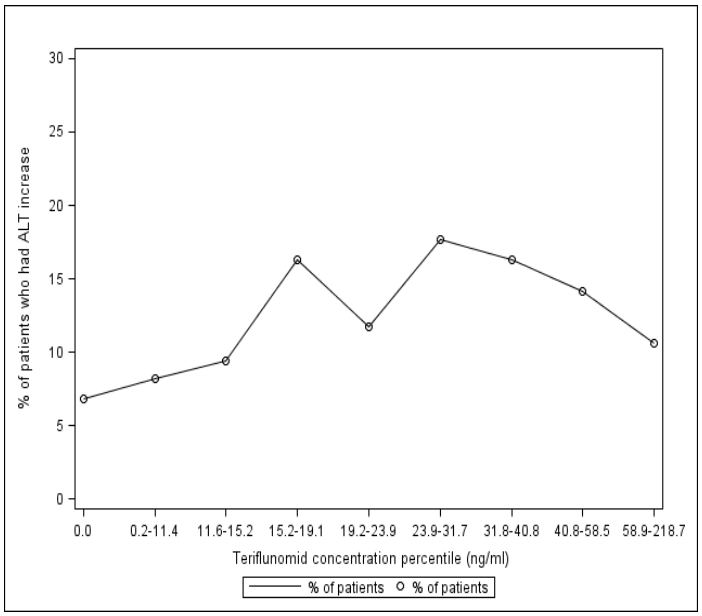
boxplots are the distribution of teriflunomide concentration at each dose. The broken vertical lines indicate the predicted lesions at the median of each dose.



To see the safety of teriflunomide related to concentration level, the incidence of ALT increase was analyzed as it was main concern for the safety of teriflunomide.
The left panel of Figure shows the time profile of ALT level at each treatment group. Clearly teriflunomide shows higher risk in ALT increase compared to placebo but there is little difference between two dose groups.
Instead of mean ALT level, the reviewer further looked into the incidence of ALT elevation taken from adverse event dataset where it is recorded by ULN (Upper Limit of Normal). The result is shown in the right panel of Figure with no clear concentration-dependent increase in the incidence, although teriflunomide has higher probability than placebo. Those who had the incidence of ALT increase were divided by adverse event severity-mild, moderate and severe. Majority patients had mild condition in ALT elevation and a total of 4 patients had severe ALT increase; 2 patients in placebo, 1 patient in the lowest exposure range (0.2-11.4 ng/ml) and 1 patient in the concentration range 31.8-40.8 ng/ml (see Table).
Given the efficacy and safety profile, the sponsor's proposed dose of 14 mg for approval seems to be reasonable.

Figure 3. The time profile (mean± se) of ALT level (IU/L) at each dose (left) and the percent of patients who had ALT increase at least once during the study (right).





Best Available Copy

Recommendations

The Division of Pharmacometrics has reviewed the submission (NDA 202992) and finds it acceptable, provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the labeling text.

Pertinent Regulatory Background

The sponsor is seeking the approval for teriflunomide for the treatment of patients with relapsing forms of multiple sclerosis (MS [redacted] (b) (4) Teriflunomide is the active predominant metabolite of leflunomide (Arava®), which has been approved for oral treatment of rheumatoid arthritis in 1998. Teriflunomide is an orally delivered immunomodulator targeting the immunoinflammatory basis of MS with both anti-proliferative and anti-inflammatory activity.
The doses of teriflunomide 7 mg/day and teriflunomide 14 mg/day were selected based on doses active in animal EAE models, and on pharmacokinetic data obtained with the parent compound leflunomide. Teriflunomide exposure after a single 20 mg dose of
leflunomide was ~ 70% of that after a single 20 mg dose of teriflunomide. It was anticipated that concentrations of teriflunomide active and safe in patients with RA would be active and safe in patients with MS. These 2 teriflunomide doses (7 mg/day and 14 mg/day) were shown to be active with a satisfactory safety and tolerability in the study of 2001. They were both selected for Phase 3 as insufficient evidence was obtained from this Phase 2 step, to select one dose only.
The sponsor proposes 14mg/day for approval based on benefit/risk profile of teriflunomide.

Results of Sponsor's Analysis

Population PK analyses

A population PK analysis had been conducted in a dataset composed of 834 patients (out of 841 patients randomized and treated by teriflunomide) enrolled into a phase II (HMR1726D/2001) and a Phase III (EFC6049) study, and of 10 healthy subjects enrolled in a Phase I study (TDR10892).

The combined teriflunomide and leflunomide datasets were used to develop the base structural analysis and to identify covariates significantly affecting teriflunomide pharmacokinetics in the combined dataset. Subsets of the data were then analyzed independently to verify consistency with main analysis results or to more closely examine specific effects among several subpopulations. Specifically, all data from subjects treated with teriflunomide were analyzed to verify consistency with PK parameter estimates obtained from the combined dataset.

The sponsor's final model was a two-compartment model parameterized in terms of an absorption constant (Ka, h^{-1}) characterizing the first-order absorption process from the depot to the central compartment, which was described by an apparent distribution volume V2/F (L). The peripheral compartment was related to the central one by an inter-compartmental clearance Q/F (L/h) and described by an apparent distribution volume V3/F (L). The elimination process from the central compartment was defined by an elimination clearance CL/F (L/h). The inter-individual variability was modeled through an exponential error model for all parameters (except

for Q/F for which no inter-individual term could be provided), while a proportional error model was used to model the residual variability.

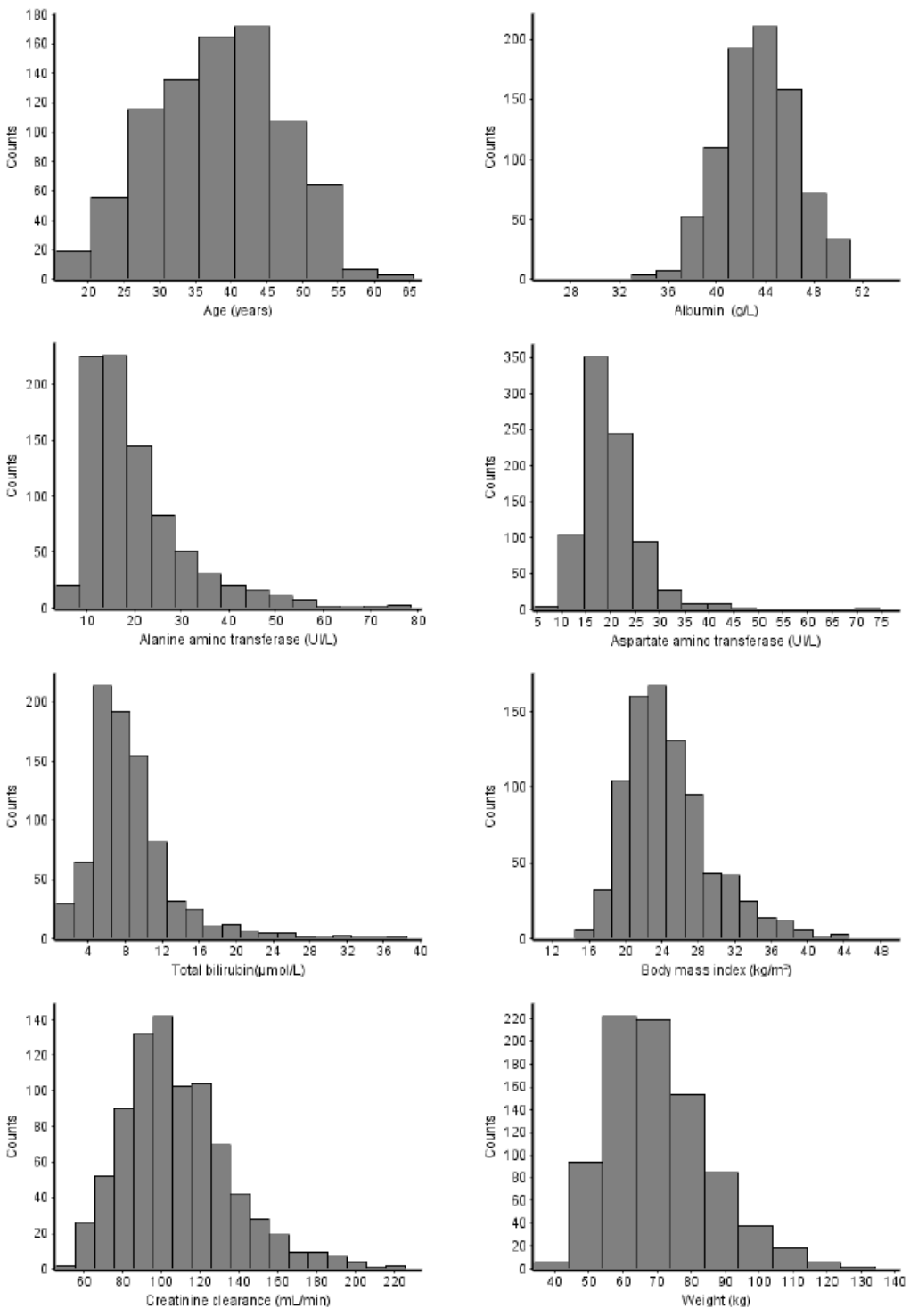
The covariates tested in the population PK analysis are gender (0 for males, 1 for females),age, dose,race (coded 1 for Caucasians, 2 for Blacks, 3 for Orientals, 4 for "Other races"), body weight(kg), BMI, Creatinine Clearance (CL_{CR} , ml.min), estimated glomerular filtration rate (GFR, mL/min), albumin (g/L), total bilirubin (µmol/L), alanine amino transferase (IU/L), aspartate amino transferase (IU/L). Also co-administration of any non-specific inducer (amobarbital, carbamazepine,dexamethasone, efavirenz, isoniazid, modafinil, nevirapine, norethindrone, omeprazole,oxcarbamazepine, phenobarbital, phenytoin, pioglitazone, prednisone, prednisolone, primidone, rifabutin, rifampin, rifampicin, rifapentin, ritonavir, secobarbital, St John'swort, troglitazone) was tested as INDU = 0 if none of the above concomitant medications was administered, INDU = 1 if at least one of the above concomitant medications was administered with at least 3 INDU administrations between –96 hours (4 days) and teriflunomide administration.
Table 1 summarizes the descriptive statistics for the covariates included in the population pk analysis, and Figure 4 displays the distribution of continuous covariates.

Table 1. Descriptive statistics of covariates included in the population PK analysis.

Covariate or characteristic	TotalData Set
Mean values (SD)	
Age (years)	38.1 (8.91)
Body Weight (Kg)	70.6 (15.3)
BMI (Kg/m²)	24.8 (4.75)
CL_{CR} (mL/min)	108 (28.4)
GFR (mL/min)	91.6 (18.0)
Albumin (g/L)	43.2 (2.98)
Bilirubin (µmol/L)	8.41 (4.92)
AST (UI/L)	19.4 (5.42)
ALT (UI/L)	19.7 (10.3)
Number of patients (%)	
EFC6049 STUDY (%)	716 (84.8 %)
2001 STUDY (%)	118 (14.0%)
TDR10892 (%)	10 (1.18%)
Sex (Males)	244 (28.9%)
Sex (Females)	600 (71.1%)
Caucasians (%)	812 (96.2%)
Blacks (%)	4 (0.47%)
Asians (%)	17 (2.01%)
Others (%)	11 (1.30%)
No co-administration of any non-specific inducer	629 (74.5%)
Co-administration of at least one inducer	215 (25.5%)

Best Available Copy

Figure 4. The distribution of continuous covariates in the population PK analysis.



Best Available Copy

The final PopPK model included four covariates on elimination clearance and four covariates on central distribution volume. CL/F was related to bilirubin and albumin plasma levels as well as on non specific inducers co-administration and sex according to the following equation:

$$CL/F = \left[\left[\theta_1 \times \left(\frac{BILI}{7}\right)^{\theta_7}\right] + \theta_8 \times INDU\right] \times \left(\frac{ALB}{43}\right)^{\theta_9} + \theta_{11} \times SEX$$

where 7 and 43 are the median bilirubin (BILI) and albumin (ALB) plasma concentration values in the dataset. Sex is coded zero for males and one for females.

V2/F was related to patient's albumin plasma levels, age, race (Caucasians vs. non-Caucasians) and body weight according to the following equation:

$$V2/F = \left[\theta_2 + \theta_6 \times (ALB-43) + \theta_{10} \times (WT-68.25) + \theta_{12} \times CAUC\right] \times \left(\frac{AGE}{39}\right)^{\theta_{13}}$$

where 43, 68.25 and 39 are the median albumin, weight and age values in the data set. Caucasians were coded zero while non-Caucasians were given the value of one. Table 2 summarizes the parameter estimates from the sponsor's final PK model.

Table 2. The parameter estimates from the sponsor's final PK model

Parameter	Estimate	% RSE	[95%CI] – (Shrinkage %)
Typical value of CL/F (θ_1, L/h) [a]	0.0197	3.43%	[0.0184 ; 0.0211] – (NA)
Effect of Bilirubin on CL/F (θ_7) [a]	-0.0457	18.4%	[-0.0625 ; -0.0289] – (NA)
Effect of Inducers co-administration on CL/F (θ_8) [a]	$1.95.10^{-3}$	16.5%	[$1.31.10^{-3}$; $2.60.10^{-3}$] – (NA)
Effect of Albumin on CL/F (θ_9) [a]	-0.266	24.0%	[-0.394 ; -0.138] – (NA)
Effect of Sex on CL/F (θ_{11}) [a]	$-4.45.10^{-3}$	17.2%	[$-5.98.10^{-3}$; $-2.92.10^{-3}$] – (NA)
Typical value of V2/F (θ_2, L) [b]	7.54	5.26%	[6.75 ; 8.34] – (NA)
Effect of Albumin on V2/F (θ_6) [b]	-0.0802	16.8%	[-0.107 ; -0.0532] – (NA)
Effect of Weight on V2/F (θ_{10}) [b]	0.0852	8.27%	[0.0711 ; 0.0993] – (NA)
Effect of Race on V2/F (θ_{12}) [b]	1.86	31.6%	[0.685 ; 3.03] – (NA)
Effect of Age on V2/F (θ_{13}) [b]	-0.221	27.6%	[-0.342 ; -0.0980] – (NA)
Q/F (θ_3, L/h)	0.857	46.4%	[0.0614 ; 1.65] – (NA)
V3/F (θ_4, L)	2.90	16.9%	[1.92 ; 3.88] – (NA)
Ka (θ_5, h^{-1})	2.81	11.6%	[2.16 ; 3.46] – (NA)
Inter-individual variability (CV%)			
CL/F	55.2%	5.11%	[52.3 ; 58.0] – (3.25%)
V2/F	22.4%	12.1%	[19.5 ; 25.0] – (47.9%)
V3/F	105%	17.4%	[85.0 ; 122] – (49.5%)
Ka	149%	12.8%	[129 ; 167] – (44.7%)
Block $\eta_{CL/F}$ - $\eta_{V2/F}$ [c]	0.230	31.8%	[0.0841 ; 0.377]
Residual variability			
σ^2	21.3%	0.967%	[21.1 ; 21.5]

F: bioavailability.

%RSE: Percentage of Relative Standard Error (100% * SE / Estimate).

95%CI: 95% confidence interval. θ and ω are the PopPK parameters (θ) and the variance of their associated inter-individual variability (ω). σ is the associated variance of the residual (intra-individual) error variable (ε).

a: in the expression of clearance including covariates effects, 7 and 73 are the median bilirubin (BILI) and albumin (ALB) plasma concentration values in the Total Data Set. Sex is coded zero for males and one for females.

b: in the expression of the distribution volume of the central compartment 43, 68.25 and 39 are the median albumin, weight and age values in the data set. Caucasians (CAUC) are coded zero while non-Caucasians take the value one.

c: the estimates is the correlation coefficient.

NA: not applicable.

Source: the sponsor's pop pk report, page5.

The sponsor's model indicates that for a typical patient, CL/F was decreased of 23% in females as compared to males whereas CL/F was increased by about 10% in the patients who were co-administered with an inducer. The influence of bilirubin on CL/F was limited (4% decrease at bilirubin= 17 µmol/L compared to 7 µmol/L). CL/F was decreased of 3% when the albumin increased from its median value (43 g/L) to its 95th percentile value (48 g/L).
There was about 25% increase of V2/F in non-Caucasians (n=16) as compared to Caucasians. V2/F was increased by 35% in a typical patient of 99.5kg (95th percentile of patient's weight) as compared to a patient with 68.3kg (median weight). The influence of albumin on V2/F was moderate with a decrease of 0.8 L (around 11 %) of V2/F for a typical patient with an albumin level of 53 g/L (95th percentile of albumin level) in comparison with a patient with an albuminemia of 43 g/L (median value of albumin). There was also a significant relationship between the patients' age and V2/F:V2/F was decreased by about 7 % for a 53-year old patient (95th percentile value of age in the study) as compared to a 39-year old patient (median value of age).
Dose, renal function (measured by CLcr), ALT and AST on the PK of teriflunomide was not found to be statistically significant.

Once the model qualified and validated, the additional steady-state PK parameters were calculated from the individual estimates from the sponsor's final model as follows;

- Distribution volume at steady state ($Vd_{SS} = V.\left(1 + \frac{k_{12}}{k_{21}}\right)$),
- Area Under the concentration versus time Curve (AUC):

  $$AUC = \frac{Dose}{CL}$$

  AUC is also the estimate of the area under the concentration versus time curve over 24 hours
  (dosing interval) at steady state ($AUC_{0\text{-}24SS}$).
- Estimates of maximum (C_{maxSS}) and minimum (C_{minSS}) concentrations obtained at steady state, calculated by maximizing and minimizing the following equations:
  - Two-compartment models:

    $$C_{SS} = A \times \frac{k_a}{k_a - \alpha} \times \left[\frac{e^{[-\alpha \times (t-Lag)]}}{1 - e^{(-\tau \times \alpha)}} - \frac{e^{[-k_a \times (t-Lag)]}}{1 - e^{(-\tau \times k_a)}}\right] + B \times \frac{k_a}{k_a - \beta} \times \left[\frac{e^{[-\beta \times (t-Lag)]}}{1 - e^{(-\tau \times \beta)}} - \frac{e^{[-k_a \times (t-Lag)]}}{1 - e^{(-\tau \times k_a)}}\right]$$

    where:
    C_{SS} = concentration at steady state,

Best Available Copy

$$C0 = \frac{\text{Dose x F}}{V},$$

$$A = C0 \text{ x } \frac{k_{21} - \alpha}{\beta - \alpha},$$

$$B = C0 \text{ x } \frac{k_{21} - \beta}{\alpha - \beta},$$

τ = time interval between two administrations (fixed to 24 hours),

$$\alpha = \frac{(k_{12} + k_{21} + k_{el}) + \sqrt{\left[(k_{12} + k_{21} + k_{el})^2 - (4.k_{21}.k_{el})\right]}}{2} \text{ and}$$

$$\beta = \frac{(k_{12} + k_{21} + k_{el}) - \sqrt{\left[(k_{12} + k_{21} + k_{el})^2 - (4.k_{21}.k_{el})\right]}}{2},$$

with $k_{el} = \frac{CL}{V}$.

- The maximization of the previous equation was performed using a validated R library. C_{minSS} was estimated 24 hours after dosing. Time to reach C_{maxSS} (t_{maxSS}) was given as a result of the maximization step. AUC, C_{maxSS} and C_{minSS} should be considered as theoretical estimations of drug exposure of a patient who would have received drug according to an accurate 24 hours dosing interval.

APPEARS THIS WAY ON ORIGINAL

- Absorption ($t_{1/2abs}$), distribution ($t_{1/2\alpha}$) and elimination ($t_{1/2\beta}$) half-lives:
  - $t_{1/2abs} = \frac{Ln2}{k_a}$ for first order input models,
  - for two-compartments models (linear elimination):

$$t_{1/2\alpha} = \frac{Ln2}{\alpha},$$

$$t_{1/2\beta} = \frac{Ln2}{\beta},$$

- The following additional parameters were also derived:
  - AUC accumulation ratio (Rac_{AUC}), computed as $Rac_{AUC} = \frac{AUC_{0\text{-}24SS}}{AUC_{0\text{-}24}}$,
  - Effective half-life, $t_{1/2eff}$, estimated to evaluate the relative importance of the distribution and elimination phase, computed as $t_{1/2eff} = \frac{Ln\ 2}{k_{eff}}$, with

$$k_{eff} = \frac{-Ln\left(1 - \frac{1}{Rac}\right)}{\tau}, \tau \text{ being the dosing interval (24 hours)}$$

Table 3 presents the steady-state PK parameters estimated from the sponsor's final model at each dose level. Notice that the median terminal half-life ($t_{1/2\beta}$) was estimated 427 hrs (17.8 days)

and 466 hrs (19.4 days) at 7 mg and 14 mg respectively, which gives approximately 89-97 days to reach steady-state.

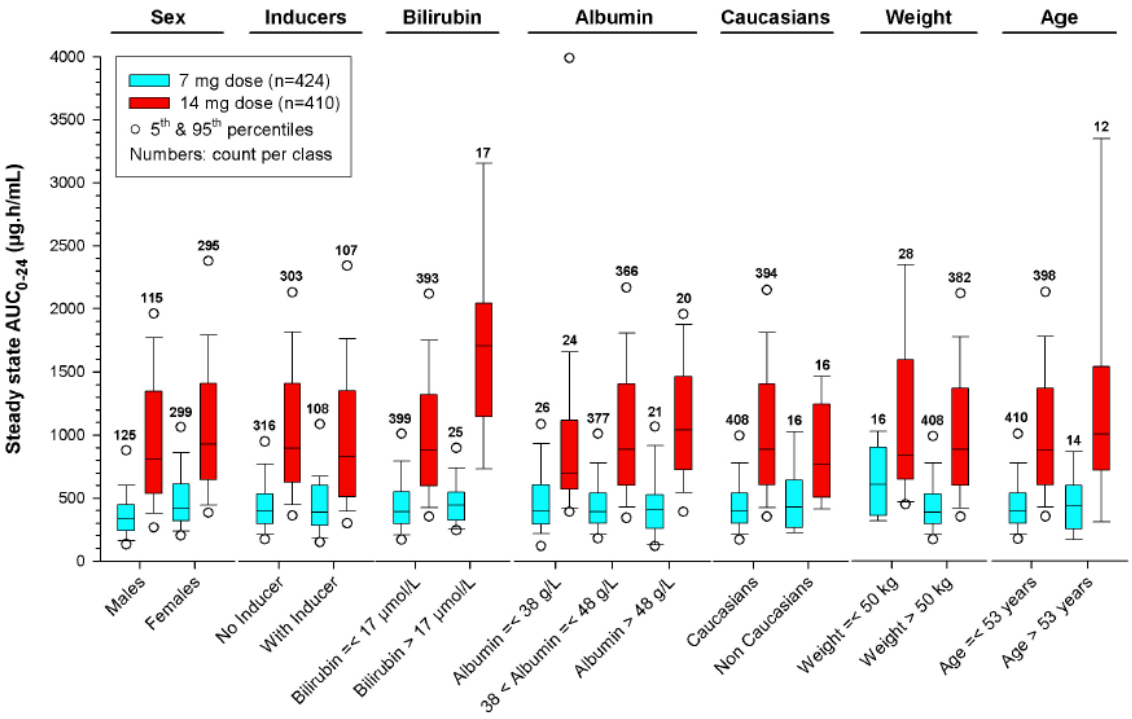
Table 3. Steady-state PK parameter estimates from the final PK model.

Parameter	7 mg dose (n=424)		14 mg dose (n=410)	
	Mean (CV%)	Median, 5th – 95th percentiles	Mean (CV%)	Median, 5th – 95th percentiles
AUC_{0-24} (µg.h/mL)	15.4 (21.4)	15.3, 10.2 – 20.6	32.2 (22.9)	31.7, 21.6 – 46.1
AUC_{0-24SS} (µg.h/mL)	458 (55.0)	392, 174 – 1000	1070 (66.2)	885, 353 – 2130
Rac AUC	30.3 (54.5)	25.8, 12.0 – 62.9	33.6 (62.8)	28.1, 11.8 – 73.7
C_{max} (µg/mL)	0.805 (20.8)	0.796, 0.549 – 1.10	1.65 (23.2)	1.64, 1.08 – 2.34
C_{maxSS} (µg/mL)	19.5 (54.1)	16.7, 7.76 – 42.2	45.3 (65.1)	37.8, 15.6 – 89.9
t_{maxSS} (h)	1.67 (79.6)	1.17, 0.844 – 4.83	1.88 (93.6)	1.17, 0.828 – 6.25
C_{minSS} (µg/mL)	18.7 (56.0)	16.0, 6.95 – 41.5	43.7 (67.1)	36.2, 14.1 – 87.8
$t_{1/2Ka}$ (h)	0.483 (142)	0.247, 0.171 – 1.73	0.671 (199)	0.247, 0.167 – 2.86
$t_{1/2Alpha}$ (h)	1.92 (41.3)	1.71, 1.15 – 3.55	1.78 (37.5)	1.64, 1.04 – 2.91
$t_{1/2Beta}$ (h)	561 (104)	427, 194 – 1260	557 (64.5)	466, 192 – 1250
$t_{1/2eff}$ (h)	496 (55.3)	420, 192 – 1040	551 (63.6)	458, 188 – 1220
Vd_{SS} (L)	12.5 (87.2)	10.8, 7.94 – 18.9	10.9 (30.6)	10.4, 7.20 – 15.8

Source: the sponsor's pop pk report, page 70.

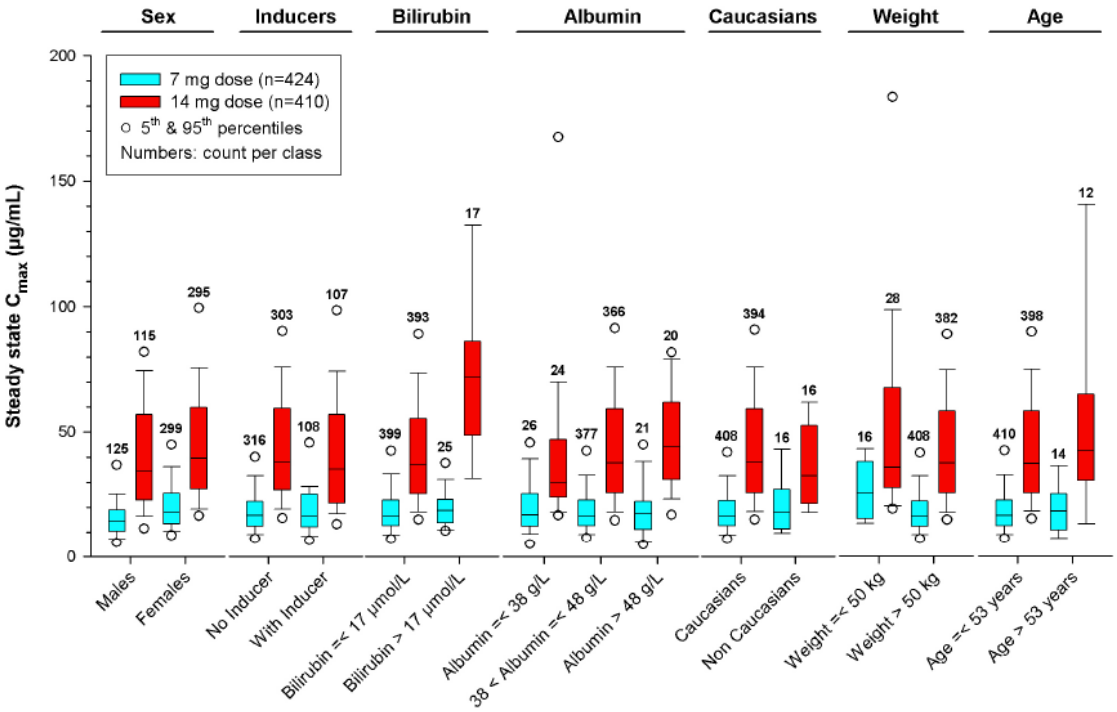
The sponsor also examined the effect of the covariates on the steady state exposure parameters. Most covariates were found to be minimal effect but 1.73-fold increase of mean AUC_{0-24SS} was observed for the 14 mg dose between patients with a bilirubin value greater than 17 µmol/L (n=17) and the patients with bilirubin value lower than 17 µmol/L although no major alteration of exposure parameters was observed for the 7 mg dose (Figure 5). Similar trend were observed for Cmax,ss and Cmin,ss (Figure 6, Figure 7).

Figure 5. AUC $0_{-24,SS}$ as a function of covariates



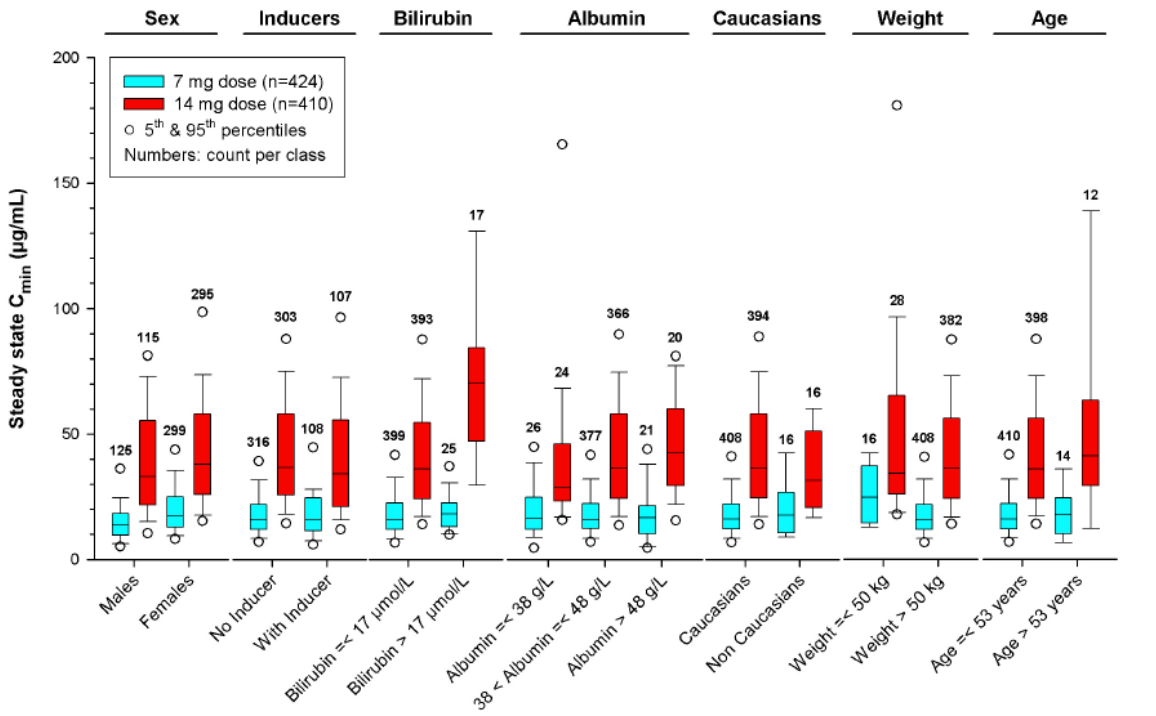
Source: the sponsor's pop pk report, page 74.

Figure 6. $C_{max,ss}$ as a function of covariates



Source: the sponsor's pop pk report, page 73.

Figure 7. $C_{min,ss}$ as a function of covariates



Source : the sponsor's pop pk report, page 75.

Exposure-Response Analyses

Data from one phase II (HMR1726D/2001) and one phase III study (EFC6049 (TEMSO)) were pooled for exposure-safety analyses whereas only one phase III study was included for exposure-efficacy analyses.

Steady-state mean concentration for each patient was used as an exposure in the analyses. Patient's characteristics such as sex, age, race, weight, CLCR, ALT, non-steroidal anti-inflammatory drugs (NSAID), Acetaminophen(ACET), Systemic steroids (STER) use, dose, baseline EDSS, baseline number of active lesion and co-medication use related to hepatotoxic, hematoxic and blood pressure were tested as a covariate.

Six endpoints were examined to relate to teriflunomide blood level: annual relapse rate (ARR: primary endpoint), time to disability progression sustained for 12-week (TDP), Total number of Gadolinium-enhanced T1 lesions / number of scans over the treatment period (NBT1NORM), total number of unique active lesions / number of scans over the treatment period (NBACTNORM), number of patients free of active lesions (T1GDFREE), burden of disease at week 108 (BOD).

For the safety analyses, twelve different safety variables were evaluated such as alanine aminotransferase (ALT), neutrophils, lymphocytes, white blood cells, lipase and amylase, Supine systolic (BPSYST) and diastolic (BPDIAST) blood pressure, alopecia, creatinine clearance

(CLCR), phosphate, uric acid. The variables were log-transformed except for phosphate and alopecia. For alopecia a binomial scale was used to represent the number of patients with alopecia: 0 indicating the patients free from alopecia and 1 indicating the patients with alopecia.

Efficacy Results

The sponsor's analyses showed that the endpoints of ARR and BOD were not significantly related to teriflunomide concentration. The detailed descriptions of the sponsor's analyses for efficacy endpoints are summarized below.

Annual Relapse Rate

Individual ARR was used for the response variable after taking log-transformation as Ln(ARR+1). The Quasi-poisson distribution was assumed for the response variable. However, the sponsor failed to link this endpoint to teriflunomide concentration.

Time to Disability Progression sustained for 12 weeks

The disability progression was defined as at least a 1-point increase on the EDSS from the baseline if the baseline is EDSS ≤5.5 or at least a 0.5-point increase from the baseline on the EDSS if the baseline is EDSS >5.5 and was persistent for at least 12 weeks.
The time to disability progression sustained for 12 weeks (TDP) was analyzed using a survival analysis model (Kaplan-Meier method) by mean teriflunomide concentrations category (0, 0 to 25th percentile, 25th percentile to median, median to 75th percentile and > 75th percentile). The range of each mean teriflunomide concentrations category and the mean and SD of mean teriflunomide concentrations in each category are summarized in Table 4.

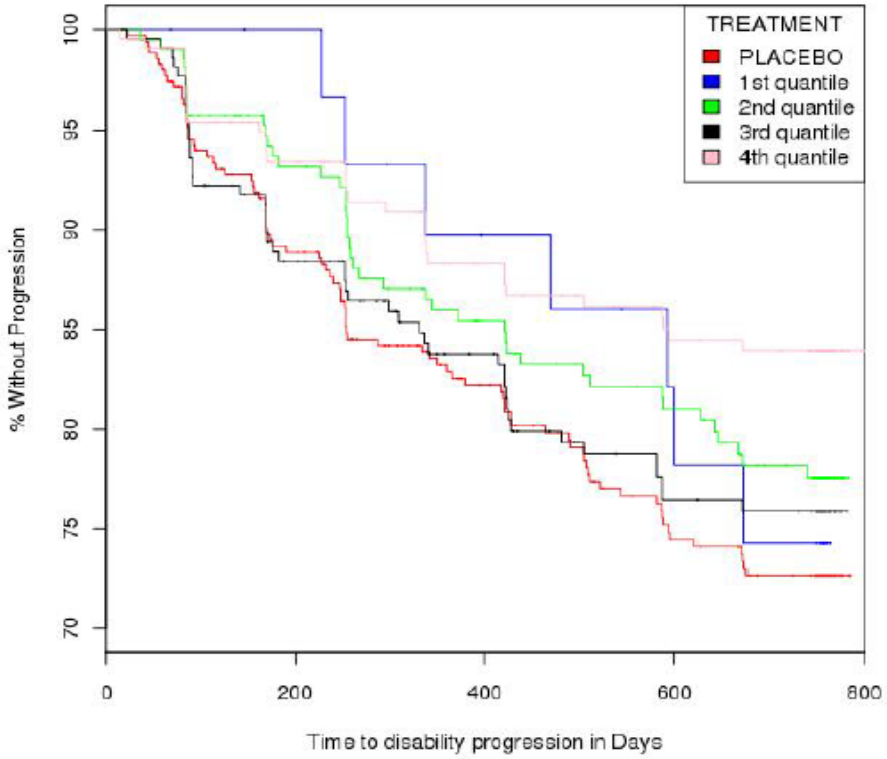
Table 4. Mean teriflunomide concentration category

Mean teriflunomide concentrations (MCONC) category	Range of each MCONC category , µg/mL	Mean (SD) in each MCONC category, µg/mL
MCONC = 0	0	0 (0)
0< MCONC ≤ P25	0 – 8.41	1.12 (2.59)
P25< MCONC ≤ Median	8.41 – 18.4	13.7 (2.66)
Median< MCONC ≤ P75	18.4 – 34.2	25.5 (4.66)
MCONC > P75	> 34.2	59.2 (27.7)

Source : the sponsor's PK/PD report, page 90.

The cox regression model showed a significant decrease of risk of disability progression as mean concentration increases (p-value=0.033), and the result is shown in Figure 8.

Figure 8. Kaplan Meier plot for time to disability progression sustained for 12 weeks at week 108 presented per mean teriflunomide concentrations category



Source : the sponsor's PK/PD report, page 91.

Total number of Gadolinium-enhanced T1 lesions per number of / Total number of unique active lesions per number of scans

For both endpoints the variables were log-transformed as log(NUM+1), and quasi-poisson distribution was assumed. The final models with parameter estimates are presented in Appendix. Although the sponsor successfully linked these variables to teriflunomid concentrations, the sponsor's model performed poorly in terms of prediction: precision estimates are 207% and 146%, average fold error values are 2.44 and 2.28 for Gadolinium-enhanced T1 lesions and unique active lesions, respectively.

Number of patients free of active lesions

A binomial scale was used to represent the number of patients free of active lesions: 0 indicating the patients who were not free active lesions and 1 indicating the patients free of active lesions. A logistic regression model was used to model the probability of patients to be free of active lesions in relation with the teriflunomide concentrations.
The predicted probability to be free of active lesions for 39 years old were 59.8%, 67.8% and 76.8% at placebo, 7mg and 14mg, respectively for those who had no active lesion at baseline whereas those were 16.2%, 21.4% and 30.1% for those who had at least one active lesion at baseline.

The final model with parameter estimates are presented below:

$$\Pr(AE = 1) = \frac{Exp(E)}{(1 + Exp(E))}$$

$$E = Logit[\Pr(AE = 1)] = \theta 1 + \theta 2 \times MCONC + \theta 3 \times NB0GT0 + \theta 4 \times AGE$$

Parameter	estimate	%RSE
Intercept, θ1	-1.22	27.9 %
Slope for MCONC, θ2	0.0217	15.5 %
Slope for NB0GT0, θ3	-2.04	7.70 %
Slope for AGE, θ4	0.0415	20.2 %

Source : the sponsor's PK/PD report, page 93.

Burden of Disease at week 108

The burden of disease (BOD) was the volume of abnormal brain tissue detected on MRI. The change from baseline in cubic root transformed BOD at week 108 (CRCBBOD) was used as the response variable after log-transformed as ln(CRCBBOD+1). However, the sponsor could not relate the variable to teriflunomide concentration.

Safety Results

The sponsor's analyses showed that Lipase, BPSYS and creatinine clearance were not found to be significantly related to mean teriflunomide concentrations. The brief summary of the sponsor's analyses for other variables are discussed below, and the final model with parameter estimates are presented in the Appendix.

ALT

The sponsor's final model indicates that the mean ALT for placebo group was 9.64% higher in patients with steroids co-administration compared to patients without steroids co-administration and 11.3% higher in male compared to female patients. Also the model predicts that ALT levels are 13.3% and 17.4% higher at the median concentrations of 7 mg and 14 mg (MCONC=15.9 µg/mL, 36.8 µg/mL, respectively) than placebo (MCONC=0).

Neutrophils

The mean neutrophil level for placebo group was 20.9% higher in patients with steroids co-administration compared to patients without steroids co-administration. The model predicts that neutrophils levels at 7mg and 14 mg decrease 14.4% and 21.0% of that in placebo group , which were estimated at the median concentrations of 7mg and 14mg (MCONC=15.9 μg/mL, 36.8 μg/mL, respectively).

Lymphocytes

Lymphocytes count model also shows that lymphocyte counts decrease in concentration dependent manner; 1.87, 1.66 and 1.60 at MCONC=0 (placebo), 15.9 μg/mL (7 mg) and 36.8 μg/mL (14 mg), respectively.

White blood cells

The mean white blood cell counts for placebo group was 15.0 % higher in patients with steroids co-administration compared to patients without steroids co-administration. Also the model predicts that WBC levels are 12.4% and 16.7% lower at the median concentrations of 7 mg and 14 mg (MCONC=15.9 μg/mL, 36.8 μg/mL, respectively) than placebo (MCONC=0).

Amylase/ Supine diastolic blood pressure

The relative effect of teriflunomide on amylase and supine diastolic blood pressure levels are negligible; compared to those of placebo group the amylase levels are 1.41% and 3.24% lower, and 0.94 and 1.63% higher at the median concentrations of 7 mg and 14 mg (MCONC=15.9 μg/mL, 36.8 μg/mL, respectively) based on the sponsor's model prediction.

Phosphate

The mean phosphate level for placebo group was 2.73 % higher in female compared to male patients, also phosphate levels are 8.56% and 11.5% lower at the median concentrations of 7mg and 14mg than that of placebo group.

Alopecia

The predicted probability of Alopecia were 3.0%, 3.8% and 5.3% at the placebo (MCONC=0), 7mg (MCONC=15.9 μg/mL) and 14mg (MCONC=36.8 μg/mL), respectively.

Uric Acid

Uric Acid levels appears to decrease with teriflunomide but there is little difference between two dose groups; 26.5% and 26.6% lower than placebo.

Reviewer's comments:

- *The sponsor's population PK analyses are acceptable. However, the conclusion on the effects of several covariates on PK should be understood with caution.*
    - *Majority patients in the dataset are normal or mild renal impaired subjects, only 10 subjects were moderately impaired and no subjects were severely impaired.*
    - *There is no elderly subject (age > 64 yrs).*
    - *Majority are Caucasian (96%) compared to non-Caucasian.*
- *For the sponsor's exposure-response analyses*
    - *The distributional assumptions for some of endpoints for the efficacy analyses may not be correct*
        - *Individual ARR is not count data anymore so quasi-poisson may not be right distributional assumption.*
        - *The reviewer recommends to use the number of relapse for a patient rather than individual ARR for the response variable using negative binomial model (individual study duration can be used as a offset variable).*

Reviewer's Analyses

Introduction

The sponsor's exposure-efficacy analyses for the primary endpoint (annualized relapse rate) showed no significant relationship between ARR and teriflunomide concentration. The analysis was conducted using individual ARR as a response variable with the assumption of quasi-poisson distribution for the variable. The reviewer re-assessed the relationship using the number of relapse as a response variable. A negative binomial model was applied in the analysis.
Also two MRI endpoints-the number of T1 Gd-enhancing lesions and unique active lesions were re-analyzed using negative binomial model as a sensitivity analysis.
In addition, the reviewer also looked into the safety measure such as the incidence of ALT increase as the liver toxicity is a main concern with teriflunomide safety.

Objectives

- To reassess the relationship between ARR and teriflunomide concentration.
- To examine whether the incidence of ALT increase is related to high teriflunomide concentration.

Methods

Data from one Phase III study (TEMSO) was used for both efficacy and safety analyses.
Unlike the sponsor's analysis, the number of relapse or lesion number in the MRI endpoints was used as a response variable using negative binomial distribution assumption. For the structure of the relationship Emax model was applied for both ARR and MRI endpoints to relate to concentration based on the exploratory look from the observed data. The detailed model applied for the analyses are presented below:
ARR-Concentration relationship

$$Y_i \sim NB(\mu_i, k)$$

$$\log(\mu_i) = \beta_0 \times (1 - f_i(concentration) + \log(t_i)$$

where
Y_i is the number of confirmed relapse for a patient i,
Ti is the annualized study duration for a patient I, i.e, study day/365.25, which is a offset variable to account for a patient's different study period in negative binomial model,
k is a dispersion parameter in the negative binomial model,
$f_i(concentration)$=0 if placebo

$$f_i(concentration) = \frac{E\max \times concentration}{EC_{50} + concentration}$$ if teriflunomide

MRI endpoints-concentration relationship

$$Y_i \sim NB(\mu_i, k)$$

$$\log(\mu_i) = E_0 + \frac{E\max \times concentration}{EC_{50} + concentration} + \log(s_i)$$

where
Y_i is the number of Gadolinium-enhanced T1 lesions or unique active lesions for a patient i,
si is the number of scan to be consistent with the sponsor's secondary endpoints.
k is a dispersion parameter in the negative binomial model.

Data Sets

Data sets used are summarized in Table 5.

Table 5. Analysis Data Sets

Study Number	Name	Link to EDR
EFC6049 (TEMSO)		

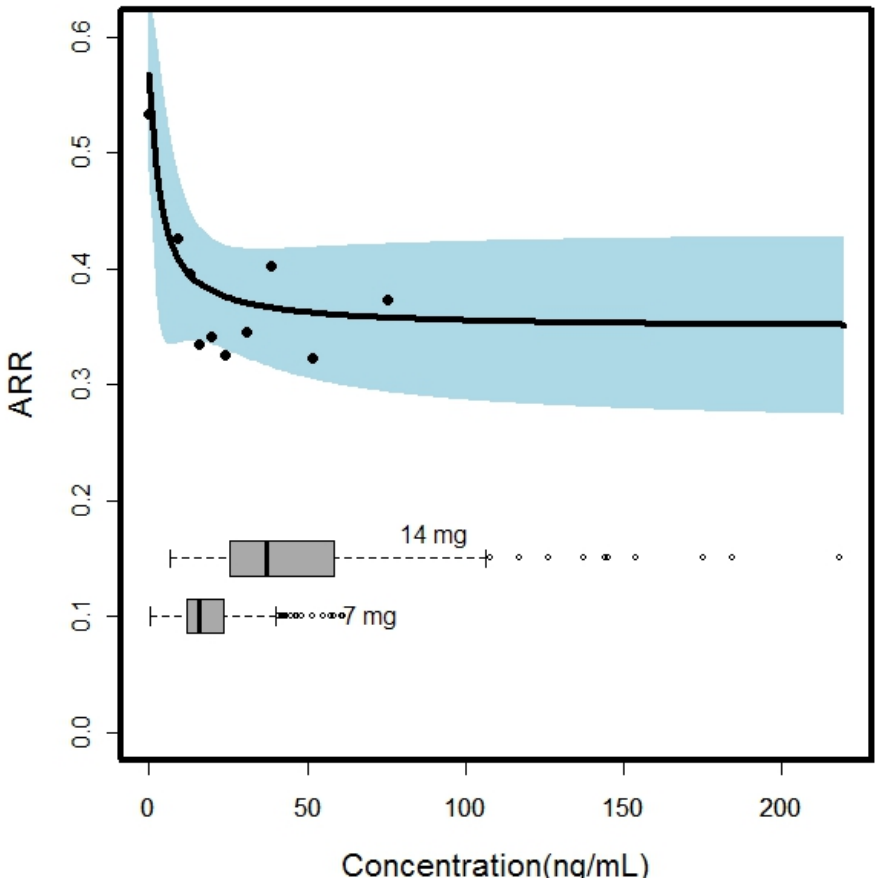
Software

SAS 9.2 and R 2.5 were used for the analysis.

Model Results

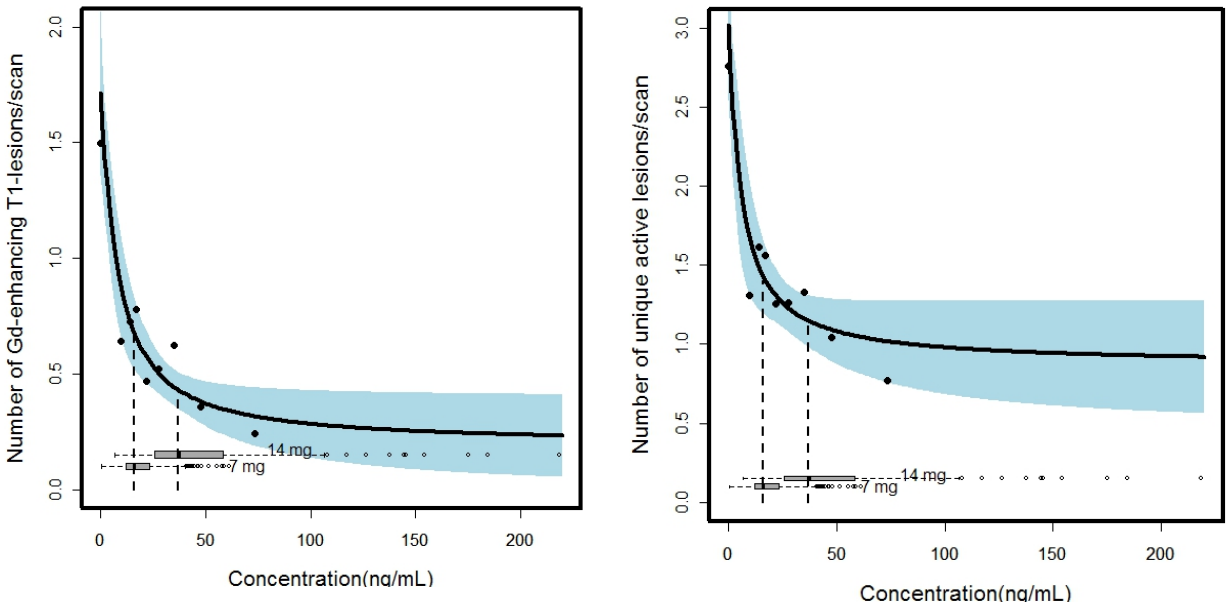
Figure 9 displays the model-predicted relationship between ARR and teriflunomide concentration with observed data at eight bins of ranked concentrations. Unlike the sponsor's conclusion that there is no significant relationship between ARR and concentration the reviewer could link ARR to concentration. The model predicts similar ARR at the median of each dose (0.38 and 0.37 at 7mg and 14mg). However, it is apparent that patients who are on the low end of exposure of 7mg may lose efficacy as it does not reach a plateau.

Figure 9. The model predicted relationship for ARR and teriflunomide concentration with 95% prediction interval (blue shaded area). The dots indicate the observed ARR at decile of teriflunomide concentration. Also two boxplots are the distribution of teriflunomide concentration at each dose.



In addition, the reviewer further looked into the relationship between MRI endpoints and concentration as the sponsor's claim for approval of 14 mg rather than 7 mg was mainly driven by the efficacy analysis with MRI endpoints where 14 mg showed superiority to 7 mg. Two MRI endpoints were examined: the total number of Gadolinium-enhanced T1 lesions per number of scans and total number of unique active lesions per number of scans to be consistent with the efficacy analysis. Figure 10 shows the results from the reviewer's analyses where the number of lesions for both endpoints clearly decrease concentration-dependent manner.

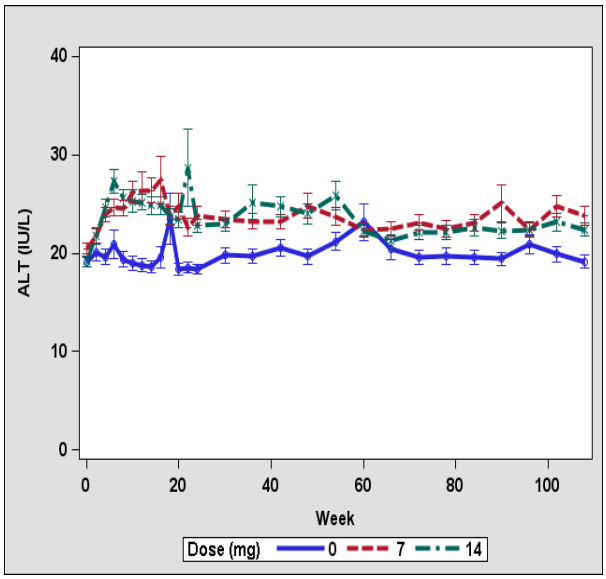
Figure 10. The model predicted relationship for the number of Gd-enhancing T1 lesions per scan and teriflunomide concentration relationship (left) and the relationship for the number of unique active lesions per scan (right) with 95% prediction interval (blue shaded area). The dots indicate the observed mean of the number of lesions at decile of teriflunomide concentration. Also two boxplots are the distribution of teriflunomide concentration at each dose. The broken vertical lines indicate the predicted lesions at the median of each dose.



As a next step, the incidence of ALT increase was analyzed. The left panel of **Figure 11** shows the time profile of ALT level for each dose group. Clearly teriflunomide shows higher risk in ALT increase compared to placebo but there is little difference between two dose groups. Instead of mean ALT level, the reviewer further looked into the incidence of ALT elevation taken from adverse event dataset where it is recorded by ULN (Upper Limit of Normal). The result is shown in the right panel of **Figure 11** with no clear concentration-dependent increase in the incidence, although teriflunomide has higher probability than placebo. Those who had the incidence of ALT increase were divided by adverse event severity-mild, moderate and severe (Table). Majority patients had mild condition in ALT elevation and a total of 4 patients had severe ALT increase; 2 patients in placebo, 1 patient in the lowest exposure range (0.2-11.4 ng/ml) and 1 patient in the concentration range 31.8-40.8 ng/ml.

Given the efficacy and safety profile the sponsor's proposed dose of 14 mg for approval seems to be reasonable.

Figure 11. The time profile (mean± se) of ALT level (IU/L) at each dose (left) and the percent of patients who had ALT increase at least once during the study (right): Study EFC6049(TEMSO).



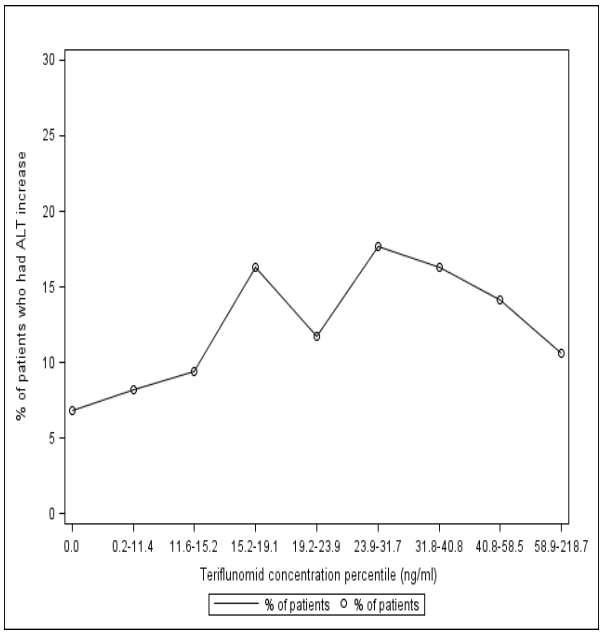


Table 6. The percent of patients who had ALT increase by severity: Study EFC6049(TEMSO).

		Concentration range (ng/mL)							
Severity	Placebo (N=24)	0.2-11.4 (N=7)	11.6-15.2 (N=8)	15.2-19.1 (N=14)	19.2-23.9 (N=10)	23.9-31.7 (N=15)	31.8-40.8 (N=14)	40.8-58.5 (N=12)	58.9-218.7 (N=9)
Mild	50.0 (%)	42.9 (%)	62.5 (%)	71.4 (%)	70.0 (%)	60.0 (%)	78.6 (%)	83.3 (%)	77.8 (%)
Moderate	41.7 (%)	42.9 (%)	37.5 (%)	28.6 (%)	30.0 (%)	40.0 (%)	14.3 (%)	16.7 (%)	22.2 (%)
Severe	8.3 (%)	14.3 (%)	—	—	—	—	7.1 (%)	—	—

Listing of Analyses Codes and Output Files

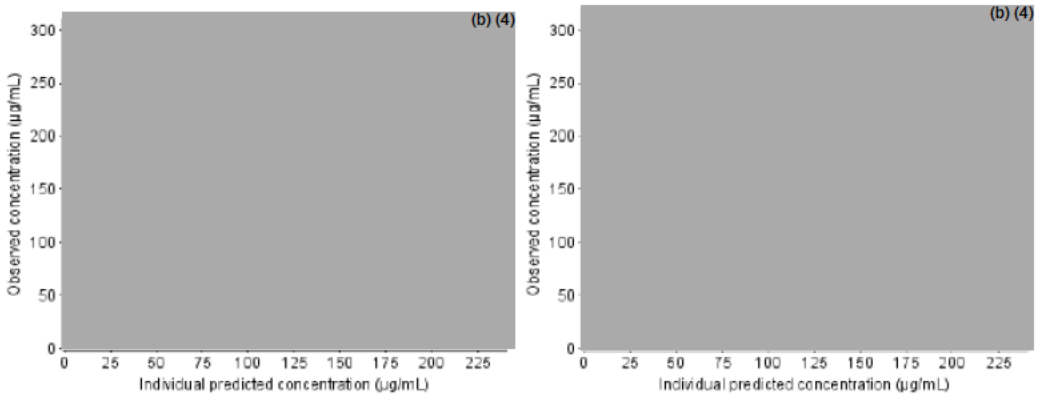
File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
efficay.sas	The reviewer's exposure-efficacy	

MRI.sas	analysis
P_alt.sas	The reviewer's exposure-safety analysis

Appears This Way On Original

APPENDIX

1. The model diagnostics for the sponsor's final population PK model.



2. The models with parameter estimates from the sponsor's exposure-safety analyses.

ALT

Ln(ALT)= ((θ1 x STER + θ2 x (1-STER)) x SEX+ (θ1 x STER + θ2 x (1-STER)) x θ3 x (1-SEX)) x (WT/Med WT)$^{\theta 4}$ + θ5 x (AGE/Med AGE)) x exp(ηE_0) + E_{MAX} x MCONC/ (EC_{50}+MCON).

Parameter	Estimate	RSE%
$\theta_{(1)}$ with Steroids	2.73	1.68
$\theta_{(2)}$ without Steroids	2.49	1.78
$\theta_{(3)}$ Sex effect	1.11	0.93
$\theta_{(4)}$ Weight effect	0.172	10.9
$\theta_{(5)}$ Age effect	0.277	15.6
E_{max}	0.204	12.0
EC_{50}	9.94	42.0
Inter-individual variability (%)	**Estimate**	**90% CI**
E_0	34.3%	[33.7 ; 34.9]
Residual variability		
Additive Error	0.554	[0.552 ; 0.556]

Neutrophils

$LnNeutro = \theta 1 \times STER + \theta 2 \times (1\text{-}STER) + \theta 3 \times (WT/Med\ WT) + \eta 0 + (E_{MAX} \times CONC)/(EC_{50}+MCONC)$

Parameters	Estimates	RSE%
$\theta_{(1)}$ with Steroids	1.38	2.87 %
$\theta_{(2)}$ without Steroids	1.19	3.26 %
$\theta_{(3)}$ Weight effect	0.210	17.3 %
E_{max}	-0.339	-7.61 %
EC_{50}	16.2	21.0 %
Inter-individual variability (%)	**Estimate**	**90% CI**
E0	54.1 %	[53.2% ; 55.1%]
Residual variability	**Estimate**	**90% CI**
Additive Error	0.495	[0.493 ; 0.497]

Lymphocytes

$LnLympho = \theta 1 + \theta 2 \times (WT / Med\ WT) + \eta 0 + (E_{MAX} \times MCONC)/(EC_{50}+MCONC)$

Parameters	Estimates	RSE%
$\theta 1$	0.504	6.20
$\theta 2$, weight effect	0.123	23.9
E_{MAX}	-0.202	7.47
EC_{50}	11.2	24.6
Inter-individual variability (%)	**Estimate**	**90% CI**
E_0	48.8 %	[48.0% ; 49.7%]
Residual variability	**Estimate**	**90% CI**
Additive Error	0.411	[0.409 ; 0.413]

White blood cells

$LnWBC = \theta 1 \times STER + \theta 2 \times (1\text{-}STER) + \theta 3\ (WT/Med\ WT) + \eta 0 + (E_{MAX} \times MCONC)/(EC_{50}+MCONC)$

Parameters	Estimates	RSE%
θ(1) with Steroids	1.84	1.66 %
$\theta_{(2)}$ without Steroids	1.70	1.77 %
θ (3) Weight effect	0.181	15.6 %
E_{MAX}	-0.260	6.94 %
EC_{50}	15.4	19.6 %
Inter-individual variability (%)	**Estimate**	**90% CI**
E_0	47.8%	[47.0% ; 48.7%]
Residual variability	**Estimate**	**90% CI**
Additive Error	0.416	[0.414 ; 0.417]

Amylase

LnAmylase = (θ1+ θ2 x (WT / Med WT) + θ3 x (AGE / Med AGE)) x CAUC + (θ1 + θ2 x (WT / Med WT) + θ3 x (AGE / Med AGE)) x θ4 x (1-CAUC) + η0 +SLP x MCONC.

Parameters	Estimates	RSE%
θ1	4.24	1.42 %
θ2 weight effect	-0.324	13.5 %
θ3 age effect	0.197	23.0 %
θ4 CAUC effect	1.06	1.37 %
SLP, MCONC effect	-0.000896	10.6 %
Inter-individual variability (%)	**Estimate**	**90% CI**
E_0	57.9%	[56.8% ; 58.9%]
Residual variability	**Estimate**	**90% CI**
Additive Error	0.351	[0.350 ; 0.353]

Supine diastolic blood pressure

LnBPDIAST = θ1 x (WT / Med WT) $^{\theta 2}$ + θ3 x (AGE / Med AGE) + η0 + (E_{MAX} x MCONC) / (EC50+MCONC)

APPEARS THIS WAY ON ORIGINAL

Parameters	Estimates	RSE%
$\theta_{(1)}$ E_0	4.22	0.270 %
$\theta_{(2)}$ Weight effect	0.0411	6.76 %
$\theta_{(3)}$ Age effect	0.0959	11.7 %
E_{max}	0.0358	64.5 %
EC_{50}	44.6	122 %
Inter-individual variability (%)	**Estimate**	**90% CI**
E_0	28.7 %	[28.1% ; 29.2%]
Residual variability	**Estimate**	**90% CI**
Additive Error	0.302	[0.301 ; 0.304]

Phosphate

$$\text{Phosphate} = \theta 1 \text{ x SEX} + \theta 2 \text{ x (1-SEX)} + \eta 0 + (E_{MAX} \text{ x MCONC}) / (EC_{50} + \text{MCONC})$$

Parameters	Estimates	RSE%
E_0 in Female	1.13	0.379 %
E_0 in Male	1.10	0.60 %
E_{max}	-0.169	6.42 %
EC_{50}	12.6	20.0 %
Inter-individual variability (%)	**Estimate**	**90% CI**
E_0	33.7%	[33.1% ;34.3%]
Residual variability (%)	**Estimate**	**90% CI**
Additive Error	0.352	[0.351;0.354]

Alopecia

Given the assumption that Pr is the probability of Alopecia, the model has the following structure:

$$\Pr(AE = 1) = \frac{Exp(E)}{(1 + Exp(E))}$$

$$E = Logit[\Pr(AE = 1)] = \theta 1 + \theta 2 \times MCONC$$

Parameter	estimate	RSE%
Intercept, θ1	-3.48	5.36 %
Slope for MCONC, θ2	0.0162	23.2 %

Uric Acid

$LnURICACID = (\theta 1 \times (WT/Med\ WT)^{\theta 2}) \times SEX + (\theta 1 \times (WT/Med\ WT)^{\theta 2}) \times \theta 3 \times (1-SEX) + \eta E_0 + ((E_{MAX} + \eta E_{MAX}) \times MCONC)/(EC_{50}+MCONC)$

Parameters	Estimates	RSE%
θ1, Weight effect	5.47	0.122 %
θ 2, Weight exponent	0.0836	5.97 %
θ 3, Sex effect	1.05	0.237 %
E_{MAX}	-0.311	1.81 %
EC_{50}	0.177	64.7 %
Inter-individual variability (%)	**Estimate**	**90% CI**
ηE_0	43.3 %	[42.5 %; 44.1 %]
ηE_{max}	33.6 %	[32.5 %; 34.9 %]
Residual variability (%)	**Estimate**	**90% CI**
Additive Error	0.350	[0.348; 0.351]

5.0 PHARMACOGENOMICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	202992
Submission Date	08/12/2011
Applicant Name	Sanofi-aventis
Generic Name	Teriflunomide
Proposed Indication	Relapsing multiple sclerosis
Primary Reviewer	Jeffrey Kraft, Ph.D.
Secondary Reviewer	Michael Pacanowski, PharmD, MPH

1 Background

Teriflunomide is proposed to be indicated for the treatment of patients with relapsing forms of multiple sclerosis (b) (4) . Teriflunomide is the predominant active metabolite of leflunomide, which is approved for the treatment of active rheumatoid arthritis. Teriflunomide reversibly inhibits mitochondrial dihydroorotate dehydrogenase (DHO-DH), blocking de novo pyrimidine synthesis and proliferation of peripheral T-and B-lymphocytes. This cytostatic effect decreases the number of activated lymphocytes available to enter the central nervous system.

The sponsor carried out comprehensive drug metabolism/transport genotyping analysis of several clinical studies to characterize teriflunomide PK variability. The purpose of this review is to determine if any genetic effects on PK are clinically relevant.

2 Submission Contents Related to Genomics

The sponsor submitted two clinical study reports related to pharmacogenomics (PMH0086 and PMH0091). Only summary results were provided by the sponsor; subject-level data were not reviewed. The sponsor has not proposed any labeling statements related to the results of these pharmacogenetic investigations.

Genotype data were analyzed for genetic variants in several CYPs (CYP2C19, CYP2C9, CYP2D6, CYP3A5, CYP4F2, CYP1A2), UGT1A1, UGT1A7, NAT1, NAT2, ABCG2, SLCO1B1, and SLCO1B3 in 8 single- and multiple-dose phase 1 studies (n=140 and n=128, respectively; **Table 1**) and in 3 phase 2/3 studies (n=1103; **Table 1**). The basic features of these studies are summarized below.

TABLE 1. Summary of clinical trials included in meta-analysis of genotype data.

Study	Phase	N	Dose	Multiple-dose	Endpoint	Study Day
ALI6504	1	16	7 mg x 1	No	Cmax, AUC0-72	1
ALI6504	1	14	14 mg x 1	No	Cmax, AUC0-72	1
BEQ10169	1	47	7 mg x 1	No	Cmax, AUC0-72	1
BEQ10169	1	47	14 mg x 1	No	Cmax, AUC0-72	1

TABLE 1. Summary of clinical trials included in meta-analysis of genotype data.

Study	Phase	N	Dose	Multiple-dose	Endpoint	Study Day
POP6507	1	8	14 mg x 1	No	Cmax, AUC0-72	1
POP11432	1	8	14 mg x 1	No	Cmax, AUC0-72	1
INT11697	1	20	70 mg QD x 4 + 14 mg QD x 8	Yes	Ctrough	12
INT11720	1	36	70 mg QD x 4 + 14 mg QD x 9	Yes	Ctrough	12
INT11932	1	17	70 mg QD x 4 + 14 mg QD x 10	Yes	Ctrough	12
TES10852	1	61	70 mg QD x 4 + 14 mg QD x 8	Yes	Cmax, AUC0-24, Ctrough	12
EFC6049 HMR1726D/2001 PDY6045/6	2/3	623 genotyped; 431 Ctrough, 372 Cmax/AUC0-24	7-14 mg	Yes	Ctrough, model-derived Cmax and AUC0-24	

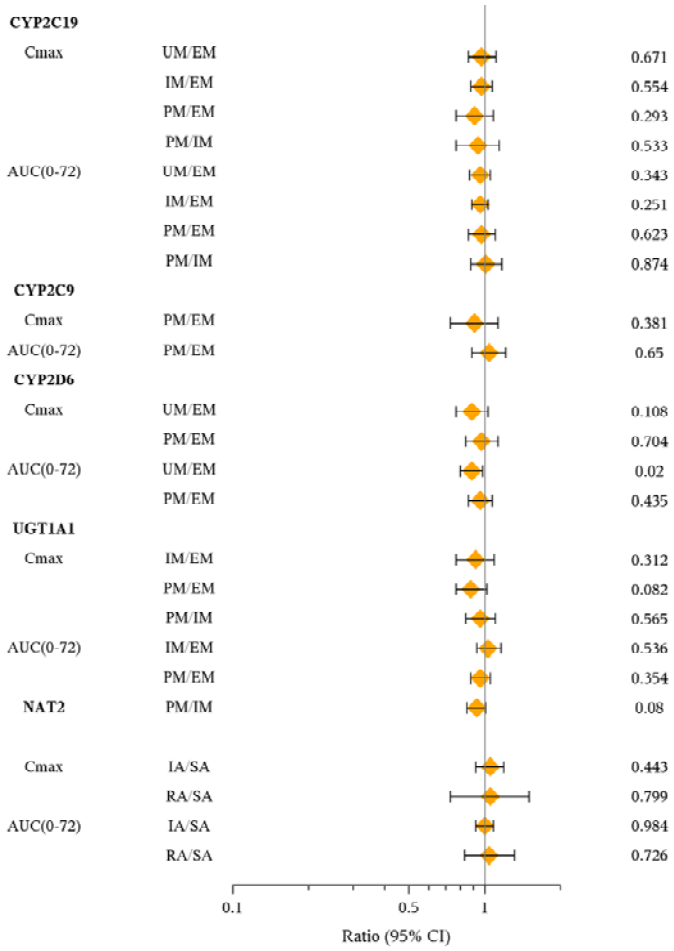
Phenotypes were predicted for each genotype for several of the CYP enzymes and NAT1/2 in a manner consistent with literature reports of function. Four different types of assays were used to measure genetic variation: Taqman Allelic Discrimination, Illumina GoldenGate, Taqman Real-Time PCR, and Fragment Analysis. The alleles tested and the phenotype inference were acceptable for the purposes of this exploratory analysis.

Log-transformed PK parameters Cmax (Day 1 and Day 12), AUC0-72 (only at Day 1), AUC0-24 (only at Day 12) and Ctrough at Day 12 of teriflunomide were analyzed using a linear fixed effects model for CYP2C19, CYP2C9, CYP2D6 and UGT1A1 phenotype with fixed terms for study, log(dose) (only for SD analysis), gender and phenotype. For all other transporters/enzymes, a linear fixed effects model with fixed terms for study, log(dose) (only for single-dose analysis), gender and genotype. Only p-values for the genotype main effect were reported.

3 Key Questions and Summary of Findings

3.1 Does the PK profile of teriflunomide differ by genotype/phenotype of relevant metabolizing enzymes and transporters?

Genotype data are summarized below for Phase 1 studies (SD & RD) as well as Phase2/3 studies (**Figures 1-4**). CYP2C9 and UGT1A1 poor metabolism were associated with higher teriflunomide Cmax and AUC in patient studies (nominally significant), but not in healthy subjects. None of the other genes tested showed a significant relationship between genotype/phenotype and exposure.



Best Available Copy

Figure 1. Drug metabolizing enzyme genotype/phenotype effects on teriflunomide exposure in SD Phase 1 trials

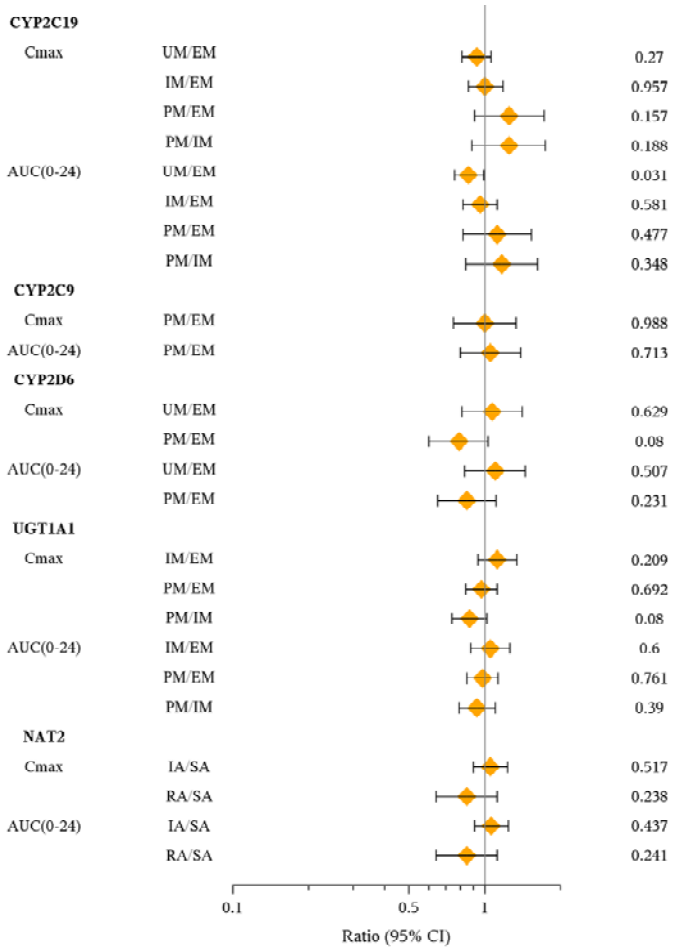
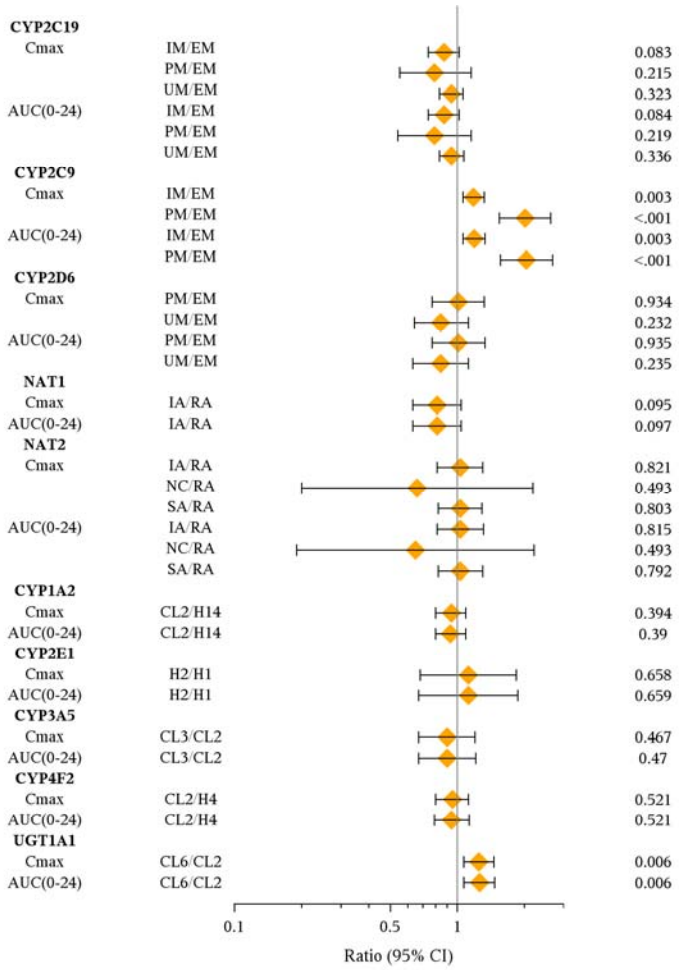


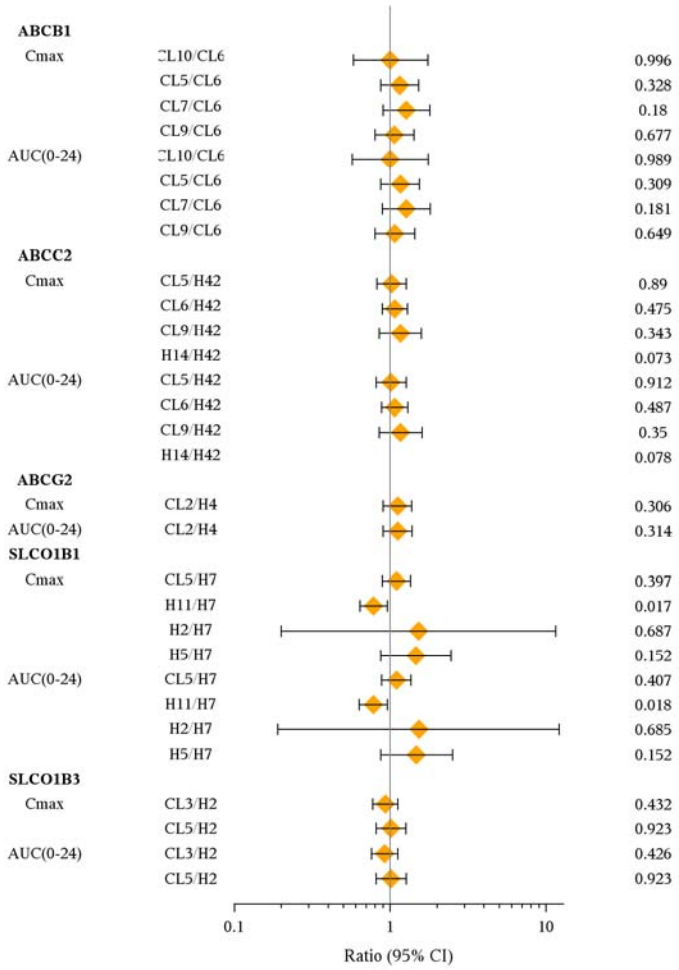
Figure 2. Drug metabolizing enzyme genotype/phenotype effects on teriflunomide exposure in RD Phase 1 trials

Best Available Copy



Best Available Copy

Figure 3. Drug metabolizing enzyme genotype/phenotype effects on teriflunomide exposure in Phase 2/3 trials.



Best Available Copy

Figure 4. Transporter genotype/phenotype effects on teriflunomide exposure in Phase 2/3 trials

4 Summary and Conclusions

The sponsor conducted comprehensive genotyping of ten drug metabolizing enzymes and five transporters of potential pharmacogenetic relevance to teriflunomide in 8 Phase 1 and 3 Phase 2/3 clinical trials.

Teriflunomide concentrations were approximately 2 times higher in CYP2C9 poor metabolizers and approximately 25% higher in UGT1A1 poor metabolizers, compared to extensive metabolizers of each enzyme. These findings were not replicated across healthy subject and patient studies and could potentially be false-positives, particularly given the limited evidence for these pathways as major routes of metabolism in vitro. Otherwise, no significant effects of genotype/phenotype were identified.

No dose modification for any intrinsic or extrinsic factors has been proposed by the sponsor, although no effect of this magnitude was observed. The Pharmacometrics review identified an exposure/response relationship for efficacy but not for safety (particularly hepatotoxicity).

Consequently, the exposure differences based on CYP2C9 or UGT1A1 genotype are not likely to be clinically relevant and dose adjustment is not indicated at this time.

BCRP has previously been associated with differences in teriflunomide exposure when administered as the prodrug, leflunomide (PMID: 20972558). The data submitted by the sponsor suggest that BCRP genotype does not have a major effect on systemic teriflunomide exposure. While tissue concentrations (e.g., liver) may differ according to BCRP genotype, additional clinical PK studies related to this transport pathway may be of limited utility.

5 Recommendations

The Genomics Group has reviewed the NDA submission for teriflunomide in the treatment of MS. Overall, the submitted results are satisfactory from the perspective of the Genomics Group. No additional action is indicated.

5.1 Post-marketing studies

None.

5.2 Label Recommendations

None.

6.0 INDIVIDUAL STUDY REVIEW

OF

CLINICAL PHARMACOLOGY STUDIES

Reviewer: Veneeta Tandon, Ph.D.

Team Leader: Angela Men, MD. Ph.D.

Reference ID: 3151674

TABLE OF CONTENTS

Reference ID: 3151674

Reference ID: 3151674

PK IN HEALTHY SUBJECTS:

Study 1001	**Investigation in healthy subjects of the bioavailability of a 20 mg oral dose of HMRl726 (Teriflunomide) compared to leflunomide, and of the pharmacokinetics, safety and tolerability of 20 mg and 100 mg oral doses of HMRl726**
Rationale:	To investigate the relative bioavailability of HMRl726 (the active metabolite of leflunomide) when given as 20 mg HMR1796 tablets compared to leflunomide 20 mg tablets. Studies of the pharmacokinetics of leflunomide have primarily examined the plasma concentrations of the active metabolite HMR1726.
Study Design	Following a loading dose of HMRl726 introduced for methodological reasons in trial period 1 (TP1), the first part of this study was a double-blind, randomized, two-period crossover study to investigate the relative bioavailability of a single oral dose of HMRl726 compared to a single oral dose of leflunomide (TP2, TP3). In a subsequent open period (TP4), the pharmacokinetics and metabolism of a higher oral dose of HMRl726 administered once on each of two consecutive days was investigated. At the end of the study (TP5), cholestyramine was administered for eleven days to accelerate the elimination of HMRl726 from plasma.
Study Population	N=16 Healthy Men (balanced ratio of slow and fast acetylators), 16 completed safety and PK evaluation, Age: 40-65 years
Treatment Groups	Treatment Period 1: Day 1: Loading dose of 20 mg HMR1726 (N=16) Treatment Period 2: Day 18: 20 mg HMRl726 or 20 mg leflunomide, according to the randomization schedule (N=8 each) Treatment Period 3: Day 38: 20 mg HMRI726 or 20 mg leflunomide, according to the randomization schedule Treatment Period 4: Day 44: 100 mg HMRl726 Day 45: 100 mg HMRl726 (no subject to have plasma concentration >100 µg/mL) Treatment Period 5: Days 51 to 61: 8 g cholestyramine three times daily, Day 63: Final examination (Plasma concentrations should decrease below 0.02 µg/ml) Treatment Period 6: Determination of Creatinine clearance Washout between periods: none
Dosage and	After an overnight fast for 10 hours, dosing was taken with 200 ml non-

<table>
<tr><td>Administration</td><td>carbonated mineral water.
A light breakfast not more than 1 hour before the cholestyramine dose</td></tr>
<tr><td>Sampling: Blood</td><td><u>For plasma HMR1726 and TFMA concentrations:</u>
Samples up to 465 hours post dose. Sampling was different for the 5 treatment periods. Samples after cholestyramine were taken up to 1488 hours post dose, if levels not <0.02 µg/ml then the subjects came at 4 week interval till this level was reached.</td></tr>
<tr><td>Urine</td><td><u>For Urine metabolites of HMR1726 and leflunomide:</u>
Up to 96 hours post dose</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td><u>Plasma HMR1726 and TFMA:</u>
<table>
<tr><td></td><td><u>HMR1726</u></td><td>TFMA</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>Capillary GC (b) (4)</td></tr>
<tr><td>Linear Range</td><td>0.1-100 µg/ml</td><td>0.5-50 ng/ml</td></tr>
<tr><td>LLOQ</td><td>0.01</td><td>0.5</td></tr>
<tr><td>QCs</td><td>0.2, 0.75, 2.5, 7.5, 25 and 80</td><td>0.8, 2.5, 8, 40</td></tr>
<tr><td>Interday precision</td><td>% CV <10.5</td><td>% CV <8.7</td></tr>
<tr><td>Intraday precision</td><td>% CV <6.2</td><td>% CV NA</td></tr>
<tr><td>Recovery</td><td>NA</td><td>NA</td></tr>
</table>
<u>Urinary Metabolites:</u>
<table>
<tr><td></td><td>4-TFMA oxanilic acid</td><td>Methy-hydroxy teriflunomide and leflunomide</td></tr>
<tr><td>Method</td><td>HPLC-UV</td><td>HPLC-UV</td></tr>
<tr><td>Linear Range (ng/ml)</td><td>25-10000</td><td>25-10000</td></tr>
<tr><td>LLOQ (ng/ml)</td><td>25</td><td>25</td></tr>
<tr><td>QCs (ng/ml)</td><td>75, 250, 750, 2500, 7500</td><td>50, 100, 1000, 5000</td></tr>
<tr><td>Interday precision</td><td>% CV <5.4</td><td>% CV <9.1</td></tr>
<tr><td>Intraday precision</td><td>% CV NA</td><td>% CV <6</td></tr>
<tr><td>Recovery</td><td>NA</td><td>92.2%</td></tr>
</table></td></tr>
<tr><td>PK Assessment</td><td>Cmax, Tmax, AUC0-t, t½. Parameters were corrected for the carryover of HMR1726 from the 1st study medication (loading dose of HMRl726) and the 2nd study medication (HMR1726 or leflunomide, according to the randomization schedule), as appropriate.</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
</table>

Reference ID: 3151674

PD Assessment	none
Pharmacokinetic Results:	**RELATIVE BIOAVAILABILITY OF TERIFLUNOMIDE AND LEFLUNOMIDE**

The pharmacokinetic parameters of HMR1726 (teriflunomide), when given as 20 mg Teriflunomide or Leflunomide is given in the following Table:

PK metrics of HMR1726 (means ± SD; TP2 and TP3; corrected for carryover)

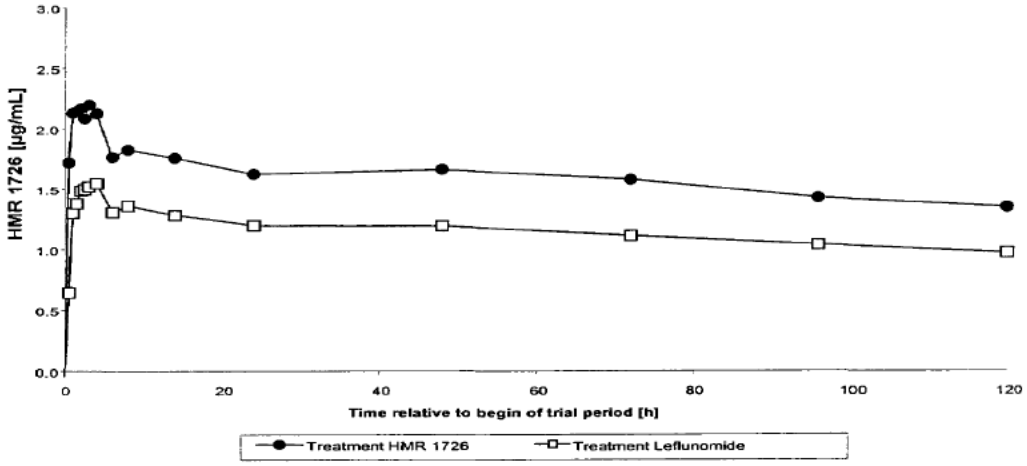
	HMR1726 (20 mg)			Leflunomide (20 mg)		
	all subjects (N = 16)	fast acetylators (N = 8)	slow acetylators (N = 8)	all subjects (N = 16)	fast acetylators (N = 8)	slow acetylators (N = 8)
C_{max} [µg/mL]	2.7 ± 0.5	2.5 ± 0.5	2.9 ± 0.5	1.7 ± 0.3	1.7 ± 0.4	1.6 ± 0.3
t_{max} [h]	2.3 ± 3.3	3.7 ± 4.3	0.8 ± 0.7	2.3 ± 1.2	1.8 ± 1.1	2.9 ± 1.0
AUC(0-24h) [µg*h/mL]	43.0 ± 5.6	42.0 ± 6.1	44.0 ± 5.1	30.9 ± 4.4	31.2 ± 5.3	30.6 ± 3.7
AUC(0-72h) [µg*h/mL]	121.0 ± 14.8	118.9 ± 16.0	123.1 ± 14.2	88.3 ± 15.1	89.4 ± 19.9	87.2 ± 9.6

Half-life [h] of HMR1726 (TP2 and TP3)

	HMR1726			leflunomide		
	all subjects N = 16	fast acetylators N = 8	slow acetylators N = 8	all subjects N = 16	fast acetylators N = 8	slow acetylators N = 8
Mean ± SD	240.0 ± 77.5	208.1 ± 49.6	272.0 ± 90.0	230.0 ± 82.7	203.0 ± 51.4	257.0 ± 101.8

Best Available Copy

The mean concentration time profiles after administration of the two treatments is shown in the following Figure:



- The disposition kinetics is the same for the two treatments.
- AUC and Cmax were lower after administration of leflunomide than after teriflunomide.
- No major differences were observed in slow and fast acetylators, except for Tmax and

T1/2 in the two groups. The Tmax was earlier after HMRl726 administration to slow acetylators, where as the Tmax was later after administration of leflunomide to the slow acetylators. The half-life considerably longer in slow acetylators, but still within the range observed in all studies.

Relative Bioavailability:

The relative bioavailability of leflunomide was approximately 70% that of HMRl726. Thus, a tablet containing 14 mg HMRI726 is expected to produce an exposure to HMRI726 that is comparable to a tablet containing 20 mg leflunomide.

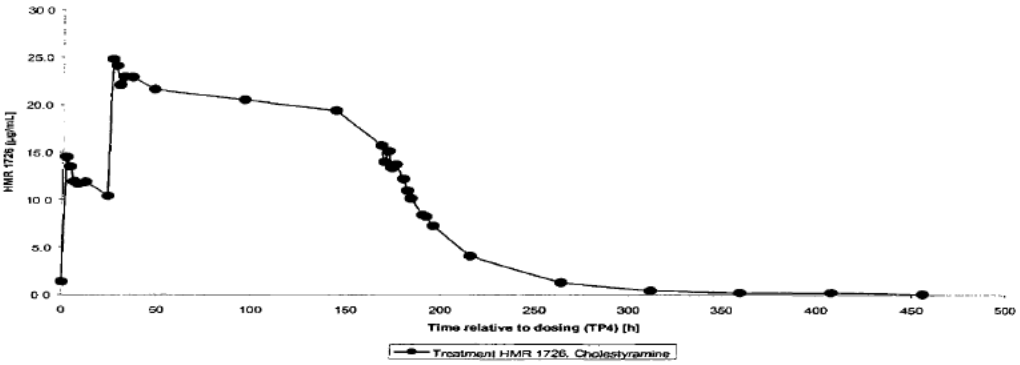
Point *estimates* for ratios of sample means (leflunomide by HMR1726)

Ratios and conventional confidence limits (*ln-transformed data*)	90% CI *lower limit (%)*	Ratio (%)	90% CI *upper limit (%)*
C_{max}	57.64	63.25	69.41
AUD(0-24 h)	68.57	71.85	75.29
AUD(0-72 h)	68.67	72.57	76.70
AUD(0-120 h)	67.16	70.97	74.99

Influence of Cholestyramine:

Cholestyramine decreased plasma levels of HMRI726 by 48% in 1 day, by 74% in 2 days and by 92% in 4 days. The mean time necessary to fall from an average plasma concentration of 15.8 µg/mL before cholestyramine dosing to below 0.1 µg/mL (quantification limit of the routine assay) was 8.6 days (N=13). In 7 cases follow-up after the final investigation was necessary to confirm that plasma concentrations of HMRl726 had decreased to below 0.02 µg/mL. Under cholestyramine the average half life was reduced from 10 days to 1 day.

Best Available Copy



TFMA in plasma: In most samples taken, TFMA in plasma was below the limit of quantification. In seven samples (3 subjects) taken between 48 and 168 h after administration of the first dose in TP4 concentrations above the limit of quantification were determined. The TFMA concentrations in these samples ranged between 0.516 and 0.909 ng/mL.

Metabolites in Urine:

Transient excretion of the glucuronides of leflunomide and HMRI726 (measured together as the molecule X91 0228) was detected in urine after a 20 mg dose, but a continuous excretion was seen after a 200 mg dose of HMR1726. An excretion of TFMA-oxanilic acid was also seen.

Safety	Headache was the main AE observed.
Conclusion	The relative bioavailability of leflunomide was approximately 70% that of HMRl726. Thus, a tablet containing 14 mg HMRI726 is expected to

	produce an exposure to HMRI726 that is comparable to a tablet containing 20 mg leflunomide.

Appears This Way On Original

<table>
<tr><th>Study 1024</th><th>Pilot, single dose study with intravenous terifliunomide</th></tr>
<tr><td>Rationale:</td><td>An intravenous teriflunomide (A77 1726, active metabolite of leflunomide) was developed to characterize the IV PK and the metabolism of A77 1726 and the formation of TFMA</td></tr>
<tr><td>Study Design</td><td>A single dose of intravenous teriflunomide</td></tr>
<tr><td>Study Population</td><td>N=6 Healthy Men
Age: 40-55 years</td></tr>
<tr><td>Treatment Groups</td><td>Day 1: A77 1726 (teriflunomide) infusion
Day 15: First day of 4 g cholestyramine dosing
Day 16: Second day of 4 g cholestyramine dosing
Day 17: Third day of 4g cholestyramine dosing</td></tr>
<tr><td>Dosage and Administration</td><td>10 mg A77 1726 over 2 hours after over night fast, double labeled with ^{13}C</td></tr>
<tr><td>Sampling: Blood</td><td><u>For plasma A77 1726 (HMR1726) and TFMA concentrations:</u>
Intense sampling for first 24 hours during and after infusion
Additional samples between Day 2 and 14 and then further samples till Day 22 (504 hours) after Cholestyramine administration on Day 15.</td></tr>
<tr><td>Urine</td><td><u>For Urine metabolites: TFMA-oxanilic acid, hydroxyl-methyl-leflunomide glucoronide and hydroxyl- methyl-A77 1726 glucuronide and other metabolites of A77 1726:</u>
Before infusion and 24 hours after infusion</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td><u>Plasma A77 1726 and TFMA:</u>
<table>
<tr><th></th><th><u>A77 1726</u></th><th>TFMA</th></tr>
<tr><td>Method</td><td>HPLC</td><td>Capillary GC</td></tr>
<tr><td>Linear Range</td><td>0.1-100 µg/ml</td><td>1-100 ng/ml</td></tr>
<tr><td>LLOQ</td><td>0.1 µg/ml</td><td>1 ng/ml</td></tr>
<tr><td>QCs</td><td>0.378, 2.42, 19.6, 96.8 µg/ml</td><td>2.5 10.3, 41.3 82.5 ng/ml</td></tr>
<tr><td>Interday precision</td><td>% CV < 8.3</td><td>% CV <6.4</td></tr>
<tr><td>Intraday precision</td><td>% CV <3.5</td><td>% CV <6.1</td></tr>
<tr><td>Recovery</td><td>93%</td><td>NA</td></tr>
</table>
<u>Urinary Metabolites:</u>
<table>
<tr><th></th><th>4-TFMA oxanilic acid</th><th>Methy-hydroxy teriflunomide and leflunomide glucuronide</th></tr>
<tr><td>Method</td><td>LC-MS-MS</td><td>HPLC-UV</td></tr>
<tr><td>Linear Range</td><td>0.05-10 µg/ml</td><td>0.05-10 µg/ml</td></tr>
</table></td></tr>
</table>

Reference ID: 3151674

	LLOQ	0.05 µg/ml	0.05 µg/ml
	QCs	0.2, 1.0, 4, 8 µg/ml	0.2, 1.03, 4.11, 8.2 µg/ml
	Interday precision	% CV <5.4	% CV <9.1
	Intraday precision	% CV NA	% CV <6
	Recovery	105%	92.2%
PK Assessment	Cmax, Tmax, AUC0-t, t½, CLtot, Vss		
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs		
PD Assessment	none		
Pharmacokinetic Results:	**PK OF IV TERIFLUNOMIDE AND ITS METABOLITES**		

The concentration profile characteristics of A77 1726 after constant infusion of 10 mg were:

Characteristic	Mean	Minimum	Maximum
C_{max} [mg/l]	1.240	1.05	1.51
t_{max} [h]	2.17	2.00	3.00
AUD(0-23 h) [mg·h/l]	20.50	18.1	22.1
AUD(0-48 h) [mg·h/l]	41.21	35.1	43.9
AUD(0-96 h) [mg·h/l]	76.05	60.5	82.5
AUD(0-336 h) [mg·h/l]	204.80	156.7	235.8
AUDC [mg·h/l]	335.13	228.1	414.0
% extrap.	37.8	31.3	46.3

The model dependent parameters were:

Characteristic	Mean	Minimum	Maximum
AUC [mg·h/l]	350.51	225.6	484.8
% extrap.	40.3	30.4	52.0
$t_{1/2.1}$ [h]	263.1	196	356
$t_{1/2.2}$ [h]	1.1114	0.554	1.773
CL_{tot} [ml/min]	0.5081	0.344	0.739
CL_{tot} [ml/h]	30.49	20.6	44.3
CL_{tot} [ml/h/kg BW]	0.3691	0.264	0.472
MT_{vss} [h]	378.6	281	513
V_{ss} [l]	10.931	10.36	12.47
V_{ss} [l/kg BW]	0.1342	0.121	0.143
V_c [l]	6.934	5.45	8.53
V_c [l/kg BW]	0.0847	0.073	0.093

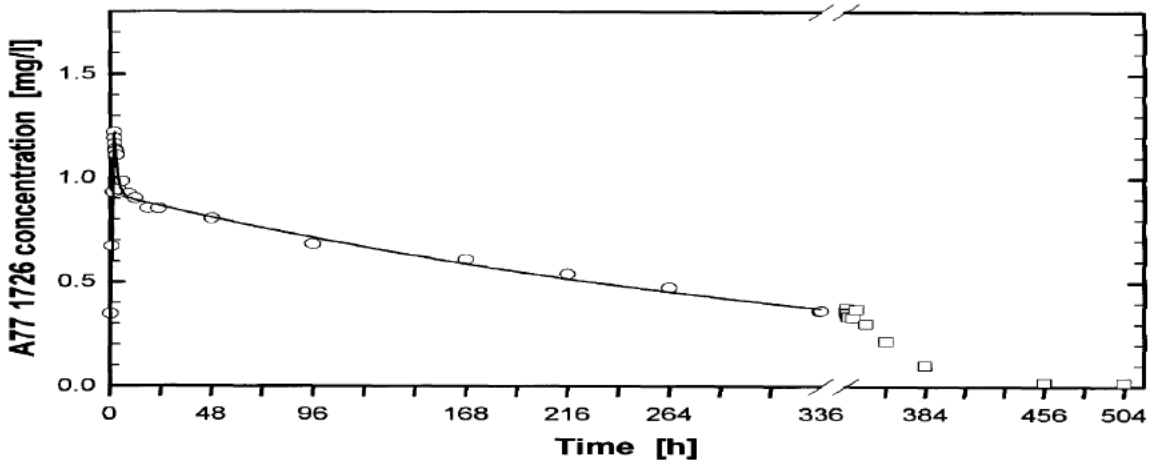
- Mean t1/2 of A77 1726 is 10 Days, same as that seen after oral administration of leflunomide
- Plasma concentration of TFMA were below LOQ (1 ng/ml)
- Urine concentrations of TFMA-oxanilic acid were below LOQ (50 ng/ml)
- Mean concentrations of [$^{13}C_2$]-TFMA-oxanilic acid (assayed by LCMSMS) increased

Reference ID: 3151674

from 0.0073 µg/ml in 0-2 hour urine to 0.0702 µg/ml in 8-24 hour urine. Total recovery of [$^{13}C_2$]- TFMA-oxanilic acid in the first 24 hours after starting A77 1726 infusion ranged between 0.54% and 0.99% of the A771726 dosed. Measurement of the [[$^{12}C_2$]-/[$^{13}C_2$]-]-TFMA oxanilic acid isotope ratio showed that at least 98% of the double ^{13}C -label was retained in the metabolite, indicating that TFMA is not a significant intermediate in the metabolic breakdown of A771726.

- Methyl-hydroxy-leflunomide glucuronide and *methyl-hydroxy*A77 1726 glucuronide were not detected in urine, suggesting that these metabolites are derived from leflunomide, and not from A77 1726.
- No other metabolites were detected in urine.

After cholestyramine administration, the concentrations were below the LOQ as shown below (data on the right indicate concentrations measured after start of cholestyramine):



Safety	Headache was the main AE observed
Conclusion	• TFMA-oxanilic acid is the sole metabolite of A77 1726 in the urine. • Absence of other metabolites suggest that they come from leflunomide and not from A77 1726 • TFMA is not an intermediate in the breakdown of A77 1726

<table>
<tr><th>Study BEX6038</th><th>Mass Balance and Metabolism of ^{14}C-HMR1726 (Teriflunomide) in Healthy Male Volunteers</th></tr>
<tr><td>Rationale:</td><td>To investigate the absorption, metabolism and excretion of ^{14}C - HMR1726 in healthy male subjects following oral administration of ^{14}C -HMR1726. This includes:
• Overall balance of excretion of the administered radioactivity (mass balance)
• Profile of metabolites in plasma, urine and feces (metabolite profiling) including the identification of the observed metabolites
• Determination of descriptive pharmacokinetic parameters for HMR1726 and its metabolite, trifluoro-methyl-aniline (TFMA) in plasma
• Determination of descriptive pharmacokinetic parameters for ^{14}C - radioactivity in blood and plasma.</td></tr>
<tr><td>Study Design</td><td>single-center, open-label, non-randomized, single-dose study</td></tr>
<tr><td>Study Population</td><td>N=6 Healthy Men (balanced ratio of slow and fast acetylators),
Age: 18-55 years</td></tr>
<tr><td>Treatment Groups</td><td>none</td></tr>
<tr><td>Dosage and Administration</td><td>Single dose of 70 mg (50 µCi) 14C-HMR1726 oral solution after overnight fast.
After administration of the study medication, subjects rinsed the mouth twice with 30 mL of water each, and then with 173 mL of water. The dosing vials were checked for the residual radioactivity and this amount was subtracted from the dose administered to the subject.
Batch: FRA-00208</td></tr>
<tr><td>Sampling: Blood</td><td><u>For plasma HMR1726 and TFMA concentrations:</u>
Samples up to 672 hours post dose</td></tr>
<tr><td>Urine</td><td><u>For Urine metabolites of HMR1726 and leflunomide:</u>
Up to 96 hours post dose</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td><u>Plasma HMR1726 and TFMA:</u>
<table>
<tr><td></td><td>HMR1726</td><td>TFMA</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>Capillary GC (b) (4)</td></tr>
<tr><td>Linear Range</td><td>0.1-100 µg/ml</td><td>0.5-50</td></tr>
<tr><td>LLOQ</td><td>0.01 µg/ml</td><td>0.5 (ng/ml)</td></tr>
<tr><td>QCs</td><td>0.2, 0.75, 2.5, 7.5, 25 and 80 µg/ml</td><td>1.5,7.5, 35</td></tr>
<tr><td>Interday precision</td><td>0.7 – 4.0</td><td>-1.1-4.3</td></tr>
<tr><td>Intraday precision</td><td>1.1 – 4.3</td><td>5.0 – 11.7</td></tr>
</table></td></tr>
</table>

Reference ID: 3151674

	Urinary Parent and Metabolites: HMR1726 Method: LC-MS-MS Linear Range (ng/ml): 10-250 LLOQ (ng/ml): 10 ng/ml QCs (ng/ml): 30, 100, 200 Interday precision: -10.3 - -3.5 Intraday precision: 4.0 – 9.4 Recovery: NA
PK Assessment	Total Radioactivity: Cmax, Tmax, AUClast, AUC, t1/2z, and λz Urinary pharmacokinetic parameters (Ae0-t, Fe0-t, CLR0-t) Metabolite profiling - characterized in plasma, urine, and feces
Safety Assessment	Vital signs, ECG , Clinical laboratory, BP, heart rate, AEs
PD Assessment	none
Pharmacokinetic Results	**MASS BALANCE**

Descriptive statistics - Mean±SD (CV%) – for the % recovery of the radioactivity are provided in the table below.

Table: Percentage of radioactive dose recovered in urine and feces at specified intervals after a single oral dose of 70 mg (50 µCi) HMR1726 to healthy male subjects:

Time (h)	% Recovered in urine	% Recovered in feces	% Recovered
0-504	22.6±4.49	37.5±12.7	60.1±10.4
(HMR1726 treatment)	(19.9)	(33.8)	(17.3)
504-672	0.560±0.296	20.1±7.29	20.7±7.54
(Cholestyramine treatment)	(52.8)	(36.2)	(36.4)
0-672	21.9±3.95	61.3±13.7	83.2±14.3
(Total)	(18.0)	(22.4)	(17.2)

N=6 up to 504 h post-dose, N=5 after 504 h post-dose, Subject 1005 exited study at 528 h post-dose.

The mean pharmacokinetic parameters of radioactivity and HMR1726 after 70 mg (50 µCi) oral administration of 14C-HMR1726 are summarized in the table below.

Reference ID: 3151674

Analyte	Matrix	C_{max} (µg/mL)[a]	t_{max} (h) [b]	AUC_t (µg*h/mL)[c]	AUC (µg*h/mL)[c]	$t_{1/2z}$ (h)
^{14}C-radioactivity	Blood	4.91±0.414 (8.42)	2.54 1.00-4.00	990±143 (14.4)	1390±330 (23.7)	282±69.1 (24.5)
	RBC	2.07±0.112 (5.42)	12.0 3.00-24.0	400±48.6 (12.1)	553±128 (23.1)	244±93.3 (38.2)
	Plasma	9.27±0.701 (7.56)	2.54 1.00-4.00	1910±337 (17.6)	2520±615 (24.4)	239±53.5 (22.4)
HMR1726	Plasma	9.99±1.01 (10.1)	2.52 2.00-4.00-	2030±343 (16.9)	2730±665 (24.3)	247±57.3 (23.2)

[a]) - µg equivalents/mL (blood and plasma) or µg equivalents/g (RBC) unit for radioactivity,

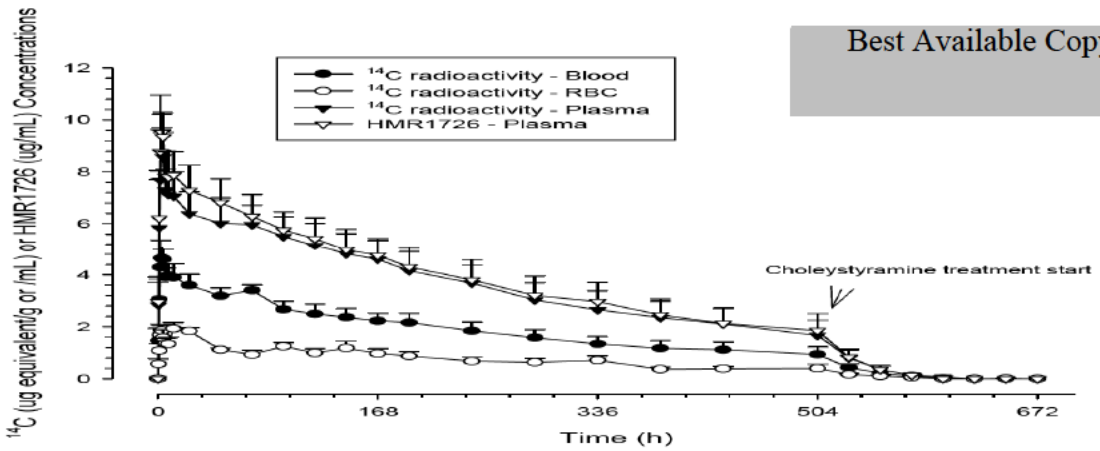
[b]) - median and range are provided for t_{max} values,

[c]) - µg equivalents*h/mL (blood and plasma) or µg equivalents*h/g (RBC) unit for radioactivity, N = 6 heathy subjects; Mean±SD (CV%) provided for all radiokinetic and pharmacokinetic paramenters except t_{max}.

- Mean AUClast of radioactivity in blood and RBC was 51.8% and 20.9% of that in plasma, respectively. These results suggested that the radioactivity in the blood component was mainly distributed in plasma. HMR1726 was the major component in plasma. Radioactivity and HMR1726 concentration-time profiles were superimposable. Plasma radioactivity and HMR1726 exposure (Cmax and AUCt) and all other PK characteristics (tmax, AUC, and t1/2z) were similar.
- Low concentrations (0 to 31.9 ng/mL) of HMR1726 were detected in very few urine samples (21 out of 180 samples).
- A small fraction of the administered dose (0.147%) was excreted unchanged in urine.
- Plasma TFMA concentrations were below the quantitation limit (LLOQ; 0.5 ng/mL) in all plasma samples collected up to 504 h post 14C-HMR1726 dose.

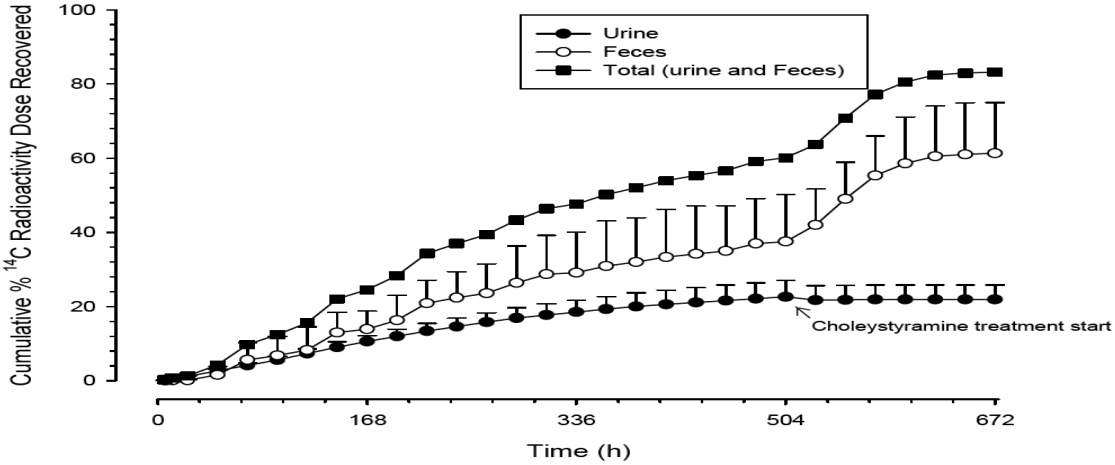
Figure - Mean (SD) concentration-time profiles of radioactivity (blood, RBC, and plasma) and HMR1726 (plasma) after oral administration of 70 mg (50 µCi) solution of 14C-HMR1726

Best Available Copy



N = 6 up to 528 h post-dose, N = 5 after 528 h post-dose; Subject 1005 exited the study.
Cholestyramine treatment started at 504 h post-dose.

Figure - Mean (SD) cumulative percentage of radioactive dose recovered in urine and feces at specified intervals after a single oral dose of 70 mg (50 µCi) 14C-HMR1726



Metabolite Profiling and Indentification:

Plasma:
The recovery of radioactivity after the extraction of the pooled plasma samples at 1, 4, 24, 72, 120, and 504 hours post dose ranged from 97.0% to 100.9%, with an average of 98.7 ± 1.4%. Unchanged HMR1726 was the only radioactivity peak detected in the pooled plasma at the all time points analyzed.

Urine:
The recovery of dosed radioactivity from urine collected between 0-504 h (0-21 days) ranged from 16.7% to 28.6% with an average of 22.6 ± 4.5%
At least nine radioactive peaks were detected in addition to HMR1726 as given below:

Table– Percent Distribution of [$_{14}$C]-HMR1726 and Its Metabolites in Urine from Human after Oral Dosing

Samples Analyzed		M1001	M1002	M1003	M1004	M1005	M1006	Mean	SD
Metabolite ID	HPLC Rt (min)	% Dose	% Dose	% Dose	% Dose	% Dose	% Dose	% Dose	% Dose
M1	15.3	0.1	0	0	0	0	0	0	0
M9	26.5-28.0	0.5	0.1	0.6	0.4	0.7	0.3	0.4	0.2
M4	28.8-29.8	1.6	1.1	1.4	0.7	1.8	1.2	1.3	0.4
M5	31.3-32.3	21.0	19.1	15.6	13.7	22.5	17.0	18.1	3.3
M10	33.3-34.0	1.2	0.4	0.3	0.7	0.9	0.8	0.7	0.3
M6	35.8-36.8	0.3	0	0.5	0.1	0.4	0.3	0.3	0.2
M14	37.8-38.5	0.4	0	0.6	0	0.1	0	0.2	0.2
M7+HMR1726	44.0-45.5	1.5	2.5	0.3	1.1	1.2	1.1	1.3	0.7
M8	58.5	0	0.2	0	0	0.1	0	0.0	0.1
Total Recovered in 21 Days		26.6	23.4	19.3	16.7	28.6	20.8	22.6	4.5
Total Identified		26.2	23.4	18.9	16.5	27.2	20.5	22.1	4.2

Feces:

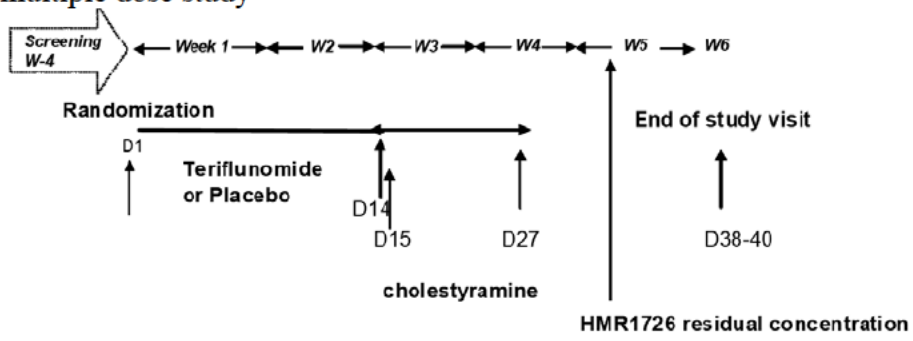
The recovery of radioactivity in the pooled fecal homogenate samples ranged from 93.9% to 102.7%, with an average of 98.8 ± 2.6%. At least three radioactive peaks were detected in addition to HMR1726

Table– Percent Distribution of [^{14}C]-HMR1726 and its Metabolites in Feces from Human after Oral Dosing

Samples Analyzed		M1001	M1002	M1003	M1004	M1005	M1006	Mean	SD
Metabolite ID	HPLC Rt (min)	% Dose	% Dose	% Dose	% Dose	% Dose	% Dose	% Dose	% Dose
M5	32.5	0.5	0.4	0.5	0.5	0.3	0.3	0.4	0.1
M10	33.0	1.1	1.3	1.6	1.3	0.6	0.6	1.1	0.4
HMR1726	45.3-45.5	34.5	41.6	52.5	41.0	17.8	26.7	35.7	12.2
M8	50.0-58.3	0.3	0.3	0.2	0.2	0.2	0.2	0.3	0.1
Total Recovered in 21 Days		36.5	43.7	54.8	43.1	19.1	27.8	37.5	12.7
Total Identified		36.5	43.7	54.8	43.1	19.0	27.8	37.5	12.7

Safety	One subject had elevated ALT > 3 x ULN (ie, > 123 U/L) after the washout. The value was 144 U/L on Day 29 (at 672 hours after dosing, when HMR1726 concentrations were <0.01 µg/mL).

Conclusion	• The route of excretion of ^{14}C labeled HMR1726 derived radioactivity 37.5% in feces, 22.6% in urine, with total recovery of 60.1%. Cholestyramine administration increased total recovery to 83.2% (range 58.4-92.1%) Plasma: • HMR1726 is the major circulating species in the plasma. • Plasma TFMA concentrations are below LOQ. Urine: • In urine, at least nine metabolites were detected. TFMA oxanilic acid was the major component in urine and accounted for 13.7-22.5% of dose (78.7-81.9% of radioactivity) over 21-day collection period. Each of other metabolites accounted for less than 3% of dose. • 0.147% of HMR1726 is excreted unchanged in the urine Feces: • In feces, at least three metabolites were detected in addition to unchanged HMR1726. Unchanged HMR1726 was the predominant component in feces and accounted for 17.8- 52.5% of dose (93.0-96.2% of radioactivity) over 21-day collection period. Each of other metabolites accounted for less than 2% of dose. • The proposed biotransformation pathways include: 1) Oxidation, 2) Hydrolysis, and 3) Sulfate conjugation.

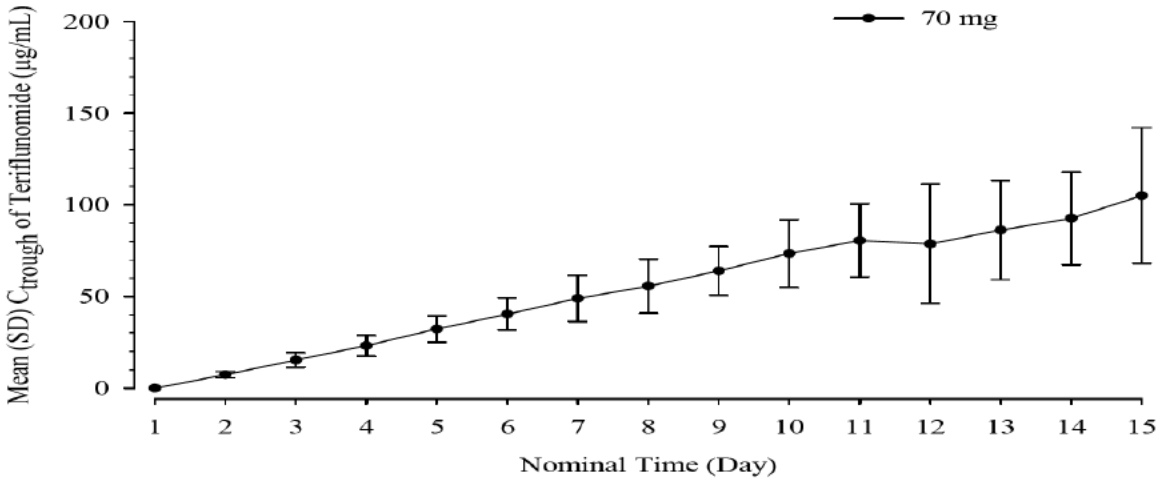
<table>
<tr><td>Study TDR10892</td><td>Randomized, double-blind, placebo-controlled study of the tolerability and pharmacokinetics of a 14-day repeated oral dose of 70 mg teriflunomide (HMR1726) in healthy male and post menopausal female subjects</td></tr>
<tr><td>Rationale:</td><td>To assess the repeat dose safety and tolerability</td></tr>
<tr><td>Study Design</td><td>single-center, double-blind, randomized, placebo-controlled, 14-day multiple dose study
 
</td></tr>
<tr><td>Study Population</td><td>N=13 Healthy Men randomized and treated (10 on Teriflunomide, 3 on placebo); Completed: 4 ((13 on Teriflunomide, 2 on placebo), PK and safety on 13
Age: 18-65 years</td></tr>
<tr><td>Treatment Groups</td><td>None</td></tr>
<tr><td>Dosage and Administration</td><td>Dose: 70 mg (5 tablets of 14 mg) for 14 days
Administration: oral under fasted conditions
Batch number(s): 6J69
8 g cholestyramine 3 times daily for 13 days from Day 15 to Day 27 in order to increase the elimination of teriflunomide. Additional cholestyramine treatment was to be given in case teriflunomide concentrations were still above 0.02 µg/mL at the end of cholestyramine treatment.
Duration of observation: 38 to 40 days</td></tr>
<tr><td>Sampling: Blood</td><td>For plasma A77 1726 (HMR1726) concentrations:
At predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours post dose on Days 1, 7 and 14; and at predose on Days 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13; and on Day 28 after the last cholestyramine treatment</td></tr>
<tr><td>Urine</td><td>Day 1 and 14: 6β-hydroxycortisol/cortisol</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>Plasma A77 1726:
<table>
<tr><td></td><td>A77 1726</td></tr>
<tr><td>Method</td><td>LC-MS-MS</td></tr>
<tr><td>Linear Range (µg/ml)</td><td>0.1-25 and
0.01-3</td></tr>
<tr><td>LLOQ (µg/ml)</td><td>0.1 µg/ml</td></tr>
</table></td></tr>
</table>

Reference ID: 3151674

	QCs (µg/ml)	0.3, 3.75, 20 and 0.02, 0.5, 2.5	
	Interday precision	% CV <7.67 and 5.89	
	Intraday precision	NA	
	Recovery	93%	
PK Assessment	Cmax, AUC0-24, and tmax on Days 1, 7 and 14, and Ctrough on Days 1 to 15 The ratio of urinary 6β-hydroxycortisol/cortisol was assessed on Day- 1 and Day 14		
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs		
PD Assessment	none		
Pharmacokinetic Results:	**MULTIPLE DOSE PK (SUPRATHERAPEUTIC DOSE)**		

Mean trough plasma concentrations are shown in the following Figure:

Figure - Mean (SD) teriflunomide trough plasma concentrations on Days 1-15 (N = 3 to 10)



Note: N = 10 (Days 1 to 4), 9 (Days 5 to 10), 6 (Day 11) or 3 (Days 12 to 15)

Steady state was not reached in 14 days of dosing.

Mean (SD) teriflunomide pharmacokinetic parameter values are shown in the following Table:

Table - Teriflunomide pharmacokinetic parameters (Mean, SD) (%CV)[Geo Mean]

Parameters \ Day	Day 1 (N = 10)	Day 7 (N = 9)	Day 14 (N = 3)
C_{max} (µg/mL)	11.0 ± 3.40 (31) [10.5]	66.9 ± 16.6 (25) [65.0]	113 ± 44.4 (39) [108]
t_{max} (h)	1.53 (1.00 , 8.30)	2.50 (0.50 , 8.00)	4.00 (1.00 , 23.92)
AUC_{0-24} (µg.h/mL)	182 ± 44.7 (25) [176]	1360 ± 305 (22) [1330]	2370 ± 933 (39) [2250]
C_{trough}* (µg/mL)	7.30 ± 1.72 (24) [7.12]	55.6 ± 14.7 (26) [53.8]	105 ± 37.1 (36) [100]

Exposure accumulation ratios and 90% CI for teriflunomide C_{max} and AUC_{0-24} are shown in the following Table:

Table - Exposure ratios and 90% confidence intervals for teriflunomide C_{max} and AUC_{0-24}

Parameter	Comparison	Ratio	
		Estimate	90% CI
C_{max}	Day 7/Day 1	5.89	(5.43 to 6.39)
	Day 14/Day 1	11.7	(10.3 to 13.2)
AUC_{0-24}	Day 7/Day 1	7.22	(6.83 to 7.63)
	Day 14/Day 1	13.4	(12.3 to 14.7)

N = 10 on Day 1; N = 9 on Day 7, N = 3 on Day 14

- Following repeated daily oral administration of 70 mg doses to healthy subjects for 14 days, teriflunomide was absorbed with a median t_{max} of 1.5 to 4 hours, Tmax range was very variable.
- There was an increase in exposure from Day 1 to Day 7 to Day 14
- Only 3 subjects were evaluable on Day 14, with Day 14/Day 1 C_{max} and AUC_{0-24} ratios being 11.7 and 13.4, respectively.
- Mean (SD) Day 14/Day -1 6β- hydroxycortisol/cortisol ratio, based on the 3 subjects who completed the study, was 0.74 (0.15), which is not suggestive of CYP3A induction.

Safety	Moderate ALT increase occurred 5-14 days after last treatment. These were reversible within 1-3 weeks.
Conclusion	Steady state was not reached in 14 days. Study was stopped due to transaminase increase. Only 3 subjects took the Day 14 dose.
Review Comment	Multiple dose TFMA data are not available from this study

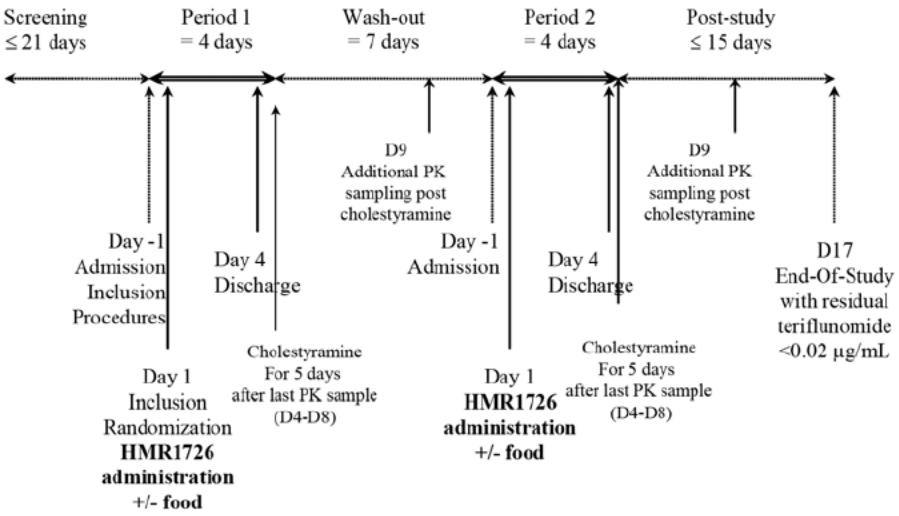
FOOD EFFECT STUDY

<table>
<tr><td>Study ALI6504</td><td>An open-label, randomized, single-dose, 2-parallel groups with 2 sequence, 2-treatment crossover study to investigate a potential food effect on the bioavailability of 7 and 14-mg teriflunomide tablets in healthy subjects</td></tr>
<tr><td>Rationale</td><td>To assess effect of food with the Phase 3 tablet</td></tr>
<tr><td>Study Design</td><td>Single-center, open-label, randomized, single-dose study with 2 parallel groups and a 2-treatment by 2-sequence crossover. The subjects received 7 mg or 14 mg teriflunomide in each of 2 treatment periods, under fed conditions in one period and fasted conditions in the other period. Each treatment period was followed by a washout period with administration of cholestyramine to accelerate elimination of teriflunomide.</td></tr>
<tr><td>Study Population</td><td>N= Randomized: 30 (16 in the 7-mg group and 14 in the 14-mg group)
Age: Healthy male (18 to 60 years old) and postmenopausal female (45 to 60 years old)</td></tr>
<tr><td>Treatment Groups</td><td>Group 1: Single dose of 7 mg (1 tablet of 7 mg)
Group 2: Single dose of 14 mg (1 tablet of 14 mg)
<table>
<tr><th>Sequence</th><th colspan="2">Period</th></tr>
<tr><th></th><th>1</th><th>2</th></tr>
<tr><td>1</td><td>Treatment A (fasted)</td><td>Treatment B (fed)</td></tr>
<tr><td>2</td><td>Treatment B (fed)</td><td>Treatment A (fasted)</td></tr>
</table>
Treatment A = 7 mg or 14 mg teriflunomide administration in fasted conditions
Treatment B = 7 mg or 14 mg teriflunomide administration in fed conditions

2 treatment periods (admission on Day-1, administration on Day 1, pharmacokinetic sample collection from Day 1 to Day 4, cholestyramine administration from Day 4 to Day 8) separated by a 3-day waiting period
End-of-study visit, 17 days after last teriflunomide administration in Period 2 (when teriflunomide concentration had decreased to lower than 0.02 µg/mL, A residual concentration of less than 5% of the expected C_{max} was anticipated at predose in Period 2)

Duration of treatment: 4 days in each period
Duration of observation: Total duration per subject was 50 days (7 weeks)</td></tr>
</table>

Best Available Copy

<table>
<tr><td></td><td> 
</td></tr>
<tr><td>Dosage and Administration</td><td><u>Administration:</u> oral route, in fed (high fat breakfast) or fasted conditions
In fed condition, the subjects received a standardized high fat breakfast (815 calories, approximately 52% fat, 33% carbohydrate, 15% protein
Batch number(s):
7- mg tablets: FRA-00983
14- mg tablets: FRA-00984</td></tr>
<tr><td>Sampling: Blood</td><td><u>For plasma A77 1726 (HMR1726) concentrations:</u>
Day 1 to Day 4 (predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 6.5, 7, 8, 9, 10, 12, 16, 24, 48, 72 hours post dose) and during the washout periods on Day 9.</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td><u>Plasma Teriflunomide:</u>
<table>
<tr><td></td><td>Teriflunomide</td></tr>
<tr><td>Method</td><td>HPLC</td></tr>
<tr><td>Linear Range (µg/ml)</td><td>0.1-25
0.01-3</td></tr>
<tr><td>LLOQ (µg/ml)</td><td>0.1 and 0.01</td></tr>
<tr><td>QCs (µg/ml)</td><td>0.3, 3.75, 20 and
0.02-,5, 2.5</td></tr>
<tr><td>Interday precision</td><td>% CV < 9.47</td></tr>
<tr><td>Intraday precision</td><td>% CV <6.24</td></tr>
</table></td></tr>
<tr><td>PK Assessment</td><td>Cmax, AUC0-24, and tmax</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic</td><td>FOOD EFFECT</td></tr>
</table>

Reference ID: 3151674

Results:	**(7 and 14 mg Phase 3 Tablet)**

The pharmacokinetic parameters and profile of the two doses under fed and fasted conditions are given below:

Table: Teriflunomide pharmacokinetic parameters:

	7 mg – fasted	7 mg – fed	14 mg – fasted	14 mg – fed [b]
N	16	12	14	14
C_{max} (µg/mL)	0.906 ± 0.198 (0.887) [21.8]	0.740 ± 0.101 (0.734) [13.6]	1.79 ± 0.301 (1.77) [16.8]	1.47 ± 0.190 (1.46) [12.9]
t_{max}[a] (h)	2.26 (1.00 - 16.00)	5.00 (0.50 - 12.18)	1.50 (0.50 - 3.00)	6.25 (2.00 - 24.00)
AUC_{0-72} (µg.h/mL)	41.1 ± 5.70 (40.7) [13.9]	38.8 ± 6.09 (38.4) [15.7]	81.3 ± 13.1 (80.3) [16.1]	78.3 ± 10.6 (77.7) [13.5]

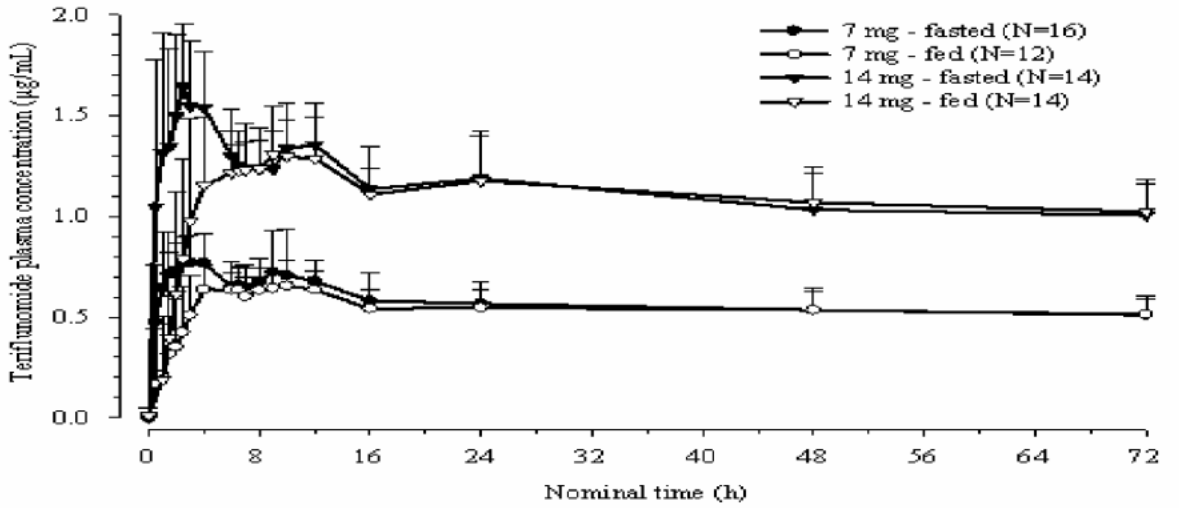
Tabulated values are Mean ± SD (Geometric Mean) [CV%], N= number of subjects

[a] Median (Min - Max)

[b] After exclusion of one subject whose predose concentration in Period 2 was >5% of C_{max}, mean (SD) C_{max} and AUC_{0-72} values were 1.45 (0.192) µg.h/mL and 77.8 (10.9) µg.h/mL, respectively, and median (min-max) t_{max} was 6.00 (2.00-24.00) h.

Best Available Copy

Mean (SD) teriflunomide plasma concentrations



Estimates of fed/fasted ratios with 90% CIs for teriflunomide – 7 mg

Parameter	Group / Comparison	Estimate	90% CI
C_{max} (µg/mL)	Fed vs. Fasted	0.82	(0.75 to 0.91)
AUC_{0-72} (µg.h/mL)	Fed vs. Fasted	0.94	(0.90 to 0.98)

Estimates of fed/fasted ratios with 90% CIs for teriflunomide – 14 mg

Parameter	Group / Comparison	Estimate	90% CI
C_{max} (µg/mL)	Fed vs. Fasted	0.82	(0.75 to 0.90)
AUC_{0-72} (µg.h/mL)	Fed vs. Fasted	0.97	(0.93 to 1.01)

[a] No difference in the conclusion of food effect after exclusion of one subject whose predose concentration in Period 2 was > 5% Cmax. • Administration of single oral doses of teriflunomide tablets at 7 mg and 14 mg with a high fat breakfast showed a small decrease in mean Cmax of 18% (90% CI: [0.75; 0.91] and [0.75; 0.90] for 7 mg and 14 mg, respectively) • No relevant change in mean AUC0-72 compared to the fasted conditions (90% CI wholly within [0.80; 1.25]). • A delay in median tmax by 2.75 hours (7 mg) to 4.75 hours (14 mg), was observed in fed conditions as compared with fasted conditions.	
Safety	The number of subjects reported with TEAE was higher (ranging from 5 to 8 subjects in each treatment group) during the washout with cholestyramine. Significant AEs included ALS and AST increases. These were asymptomatic, not associated with increase in bilirubin, and reversible within 2 weeks
Conclusion	• Although the Cmax decreased by 18% and the 90% CI was outside the acceptable limits, this is not clinically significant, given the long half life of the drug; the steady state plasma concentrations will show a flat profile. • For the same reasons, the delay in Tmax in not going to matter. • More overall the efficacy studies were done without regard to food.
Dosage Adjustment	None. Teriflunomide can be administered with or with out food,

RELATIVE BIOAVAILABILITY

<table>
<tr><td>Study BDR6639</td><td>Comparative bioavailability between tablets made with [redacted] product and tablets made with [redacted] product using a single dose of 14 mg teriflunomide in healthy volunteers</td></tr>
<tr><td>Rationale</td><td>• If the bioavailability of the [redacted] product is significantly higher than that of the [redacted] product, the need for a manufacturing specification will be confirmed, and a “biological” rationale for the required particle size will be generated.
• If equal bioavailability is shown, the [redacted] could be avoided.</td></tr>
<tr><td>Study Design</td><td>Single-center, open, randomized, single-dose, 3-period crossover, 3-sequence study with a 21-day washout between doses of teriflunomide. Cholestyramine was to be administered for 5 days in each period to accelerate elimination of teriflunomide.</td></tr>
<tr><td>Study Population</td><td>N= Randomized: 27, 25 completed
Age 18-45 years (mean 27.9 years)
Race: 23Caucasians, 1 Black, 2 Asian, 1 mixed
Two subjects prematurely discontinued the study due to AEs after receiving the study medication in the first period (appendicitis and tonsillitis)</td></tr>
<tr><td>Treatment Groups</td><td>Treatment A: 1x14 mg [redacted] teriflunomide (N=26) TEST
Treatment B: 1x14 mg [redacted] teriflunomide (N=25) REFERENCE
Treatment C: 2x7 mg [redacted] teriflunomide(N=26) TEST

Washout: 21 days between treatments</td></tr>
<tr><td>Dosage and Administration</td><td>All subjects received all 3 treatments
Subjects also received cholestyramine on Days 6-10, 8 g TID</td></tr>
<tr><td>Sampling: Blood</td><td><u>For plasma A77 1726 (HMR1726) concentrations:</u>
In each period, blood samples for PK assessments were to be collected at the predose time point on Day 1 and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, and 120 h after dosing on Day 1. Washout samples were to be collected on Day 11 of Periods 1, 2, and 3 and Day 21 of Period 3 (not used for PK analysis).</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td><u>Plasma Teriflunomide:</u>
<table>
<tr><td></td><td>Teriflunomide</td></tr>
<tr><td>Method</td><td>HPLC</td></tr>
<tr><td>Linear Range (µg/ml)</td><td>0.1-25
0.01-3</td></tr>
<tr><td>LLOQ (µg/ml)</td><td>0.1
and 0.01</td></tr>
</table></td></tr>
</table>

Reference ID: 3151674

	QCs (µg/ml)	0.3, 3.75, 20 0.02-,5, 2.5	
	Interday precision	% CV < 6	
	Intraday precision	-0.8 to 1.0%	
	Recovery	NA	
PK Assessment	Cmax, AUC0-24, and tmax , T1/2		
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs		
PD Assessment	none		
Pharmacokinetic Results:	**BIOEQUIVALENCE** (b) (4)		

Teriflunomide pharmacokinetic parameters are summarized in the following Table:

Table: Summary of teriflunomide plasma PK parameters after oral administration of 1x14 mg (b) (4) teriflunomide tablets (Treatment A), 1x14 mg (b) (4) teriflunomide tablets (Treatment B) or 2x7 mg (b) (4) teriflunomide tablets (Treatment C):

Treatment	$T_{1/2z}$ (h)	T_{max} (h)	C_{max} (µg/mL)	AUC_{0-120h} (µg.h/mL)	AUC (µg.h/mL)
A (n=26)	169 ± 62.5 (36.9) [160]	2.00 (0.75, 5.00)	1.67 ± 0.569 (34.1) [1.61]	116 ± 20.4 (17.5) [114]	305 ± 100 (32.8) [289]
B (n=25)	171 ± 59.9 (35.0) [162]	2.00 (0.500, 5.00)	1.66 ± 0.376 (22.6) [1.62]	113 ± 19.9 (17.6) [112]	310 ± 130 (41.9) [288]
C (n=26)	181 ± 51.9 (28.6) [174]	1.76 (0.750, 6.08)	1.59 ± 0.304 (19.1) [1.56]	113 ± 26.4 (23.4) [109]	327 ± 108 (33.0) [311]

Associated ratios and confidence intervals:

Parameter	Test 2x7 mg (b) (4) (Treatment C)	Test 1x14 mg (b) (4) (Treatment A)	Ratio	90% confidence interval
C_{max} (µg/mL)	1.56	1.62	0.965	0.912 – 1.02
AUC_{0-120h} (µg•h/mL)	115	115	0.996	0.969 – 1.02
AUC (µg•h/mL)	307	292	1.05	0.965 – 1.14

The 90% confidence intervals for teriflunomide PK parameters (Cmax, AUC0-120h, and AUC) were within the acceptable range (0.80-1.25) of bioequivalence for all the formulations.

Safety	The most frequent TEAEs were in the system organ classes "gastrointestinal disorders" and "infections and infestations".
Conclusion	• Teriflunomide tablets (1x14 mg) manufactured with (b) (4) product showed similar bioavailability to teriflunomide tablets

	(1x14 mg) manufactured with [redacted] product. • Two teriflunomide tablets of 7 mg manufactured with [redacted] product showed similar bioavailability to 1 teriflunomide tablet of 14 mg manufactured with [redacted] product.
EDR Link	
Study BEQ10169	**A randomized, open-label, 2 parallel 2-way crossover, single dose bioequivalence study comparing 7 mg and 14 mg Test tablets to 7 mg and 14 mg Reference tablets of HMR1726 (teriflunomide) in healthy subjects**
Rationale	Primary objective: To determine, after single oral administration, the bioequivalence between 7 mg and 14 mg Test tablets and 7 mg and 14 mg Reference tablets of HMR1726, respectively. Secondary objective: To assess, after single oral administration, the clinical and laboratory safety of 7 mg and 14 mg Test tablets and 7 mg and 14 mg Reference tablets of HMR1726.
Study Design	Single center, open-label, randomized, single-dose, 2-treatment by 2-sequence crossover study performed in two parallel groups
Study Population	N= Randomized: 94, completed 84 (43 in 7 mg and 41 in 14 mg) Age 18-45 years (mean 27.9 years) Race: 55 Caucasians, 21 Black, 13 Asian, 5 Other Two subjects prematurely discontinued the study due to AEs after receiving the study medication in the first period (appendicitis and tonsillitis)
Treatment Groups	Treatment A: 7 mg without [redacted] (N= 43) TEST Treatment B: 7 mg with [redacted] (N=43) REFERENCE Treatment C: 14 mg without [redacted] (N=41) TEST Treatment D: 14 mg with [redacted] (N=41) REFERENCE
Dosage and Administration	Each subject received a single oral dose (either 7 mg for Group 1 or 14 mg for Group 2) of HMR1726 test formulation and a single dose of HMR1726 reference formulation on Day 1 of each period under fasted conditions with 240 mL of noncarbonated water. Subjects also received cholestyramine on Days 27-29, 8 g TID Batch numbers (Test) 6J68 and 6J69 for the 7 mg and 14 mg Batch numbers (Ref) FRA-00435 and FRA-00436 for the 7 mg and 14 mg
Sampling: Blood	For plasma A77 1726 (HMR1726) concentrations: Day 1 after HMR1726 dosing at 15, 30, and 45 minutes, and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 288, 456, and 624 hours, and also at the follow-up visit after cholestyramine treatment.
Urine	none
Feces	none

Analysis	Plasma Teriflunomide: Teriflunomide: Method: HPLC; Linear Range (µg/ml): 10-3000 ng/ml, 0.01-3 µg/ml; LLOQ: 10 ng/ml and 0.01 µg/ml; QCs: 25, 500, 250 ng/ml, 0.02-,5, 2.5 µg/ml; Interday precision: % CV < 8.9; Intraday precision: -1.2 to 0%
PK Assessment	Cmax, AUC0-24, and tmax , T1/2
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none
Pharmacokinetic Results:	**BIOEQUIVALENCE [With and without (b) (4)]**

Teriflunomide pharmacokinetic parameters are summarized in the following Table:

Table: Comparison of mean (standard deviation) pharmacokinetic parameters of HMR1726 following a single oral administration of 7 mg and 14 mg teriflunomide tablet

PK Parameter	7 mg		14 mg	
	Test	Reference	Test	Reference
C_{max} (µg/mL)	1.08±0.270 (24.9) [1.05]	1.06±0.215 (20.2) [1.04]	2.12±0.408 (19.2) [2.08]	2.25±0.467 (20.7) [2.21]
t_{max} (h)	2.00 (0.500-48.0)	2.00 (0.500-12.0)	2.00 (0.300-24.0)	1.50 (0.500-24.0)
AUC_{0-624h} (µg.h/mL)	224±53.6 (23.9) [219]	228±52.1 (22.9) [222]	472±107 (22.7) [461]	468±103 (22.1) [457]
AUC (µg.h/mL)	275±87.1 (31.7) [263]	270±77.1 (28.5) [261]	556±145 (26.1) [539]	579±162 (28.0) [557]
$t_{1/2z}$ (h)	256±71.4 (27.9) [246]	243±65.2 (26.8) [234]	242±58.3 (24.1) [235]	259±76.2 (29.4) [248]

Table- Point estimates (geometric mean), ratios, and 90% confidence intervals for 7 mg doseGroup

Reference ID: 3151674

PK Parameter	7 mg – Test		7 mg - Reference		Ratio	90% confidence interval
	N	Mean (Geometric Mean)	N	Mean (Geometric Mean)		
C_{max} (µg/mL)	45	1.08 (1.05)	45	1.06 (1.04)	1.01	(0.96, 1.07)
$AUC_{0\text{-}624h}$ (µg.h/mL)	44	224.33 (218.46)	45	227.78 (222.32)	0.99	(0.96, 1.01)
AUC (µg.h/mL)	41	274.97 (263.35)	41	270.20 (260.82)	1.00	(0.97, 1.04)
$t_{1/2z}$ (h)	41	256.19 (246.48)	41	242.87 (234.31)		

Table- Point estimates (geometric mean), ratios, and 90% confidence intervals for 14 mg dose group

PK Parameter	14 mg – Test		14 mg - Reference		Ratio	90% confidence interval
	N	Mean (Geometric Mean)	N	Mean (Geometric Mean)		
C_{max} (µg/mL)	43	2.12 (2.08)	43	2.25 (2.21)	0.96	(0.92, 1.00)
$AUC_{0\text{-}624h}$ (µg.h/mL)	42	472.12 (461.03)	41	468.02 (457.14)	1.00	(0.96, 1.04)
AUC (µg.h/mL)	36	556.23 (538.86)	40	579.49 (557.27)	0.98	(0.94, 1.03)
$t_{1/2z}$ (h)	36	242.35 (234.58)	40	259.38 (248.23)		

Safety	Three subjects discontinued treatment due to TEAEs. One of these subjects had a serious adverse event (severe headache) which quickly resolved with paracetamol, and the other 2 subjects had increased transaminase levels (<3 x ULN for AST and ALT) with associated GGT increase but no bilirubin increase.
Conclusion	• 7 mg tablets manufactured without (b) (4) (Test formulation) were bioequivalent to 7 mg tablets manufactured with (b) (4) (Reference formulation) • 14 mg tablets manufactured without (b) (4) (Test formulation) were bioequivalent to 14 mg tablets manufactured with (b) (4) (Reference formulation)

IN VITRO STUDIES

Report 10274	**Protein Binding of ^{14}C A77 1726 to serum proteins**
Study Design	Equilibrium dialysis 37°C between phosphate buffer (pH 7.4) and plasma
Results	**PROTEIN BINDING**

A77 1726 is highly bound to serum proteins. The percentage of unbound metabolite remained below 0.3% over the entire range of concentrations in serum employed in this study (0-204 µg/ml)

Initial concentration ^{14}C-A77 1726 in serum µg ml^{-1}	Concentration in serum at equilibrium µg ml^{-1}	Concentration of unbound ^{14}C-A77 1726 at equilibrium µg ml^{-1}	Concentration of bound ^{14}C-A77 1726 at equilibrium µg ml^{-1}	% bound	% unbound
0.14	BELOW LIMITS OF ACCURATE DETECTION				
20.5	18.80	0.05	18.75	99.73	0.27
40.8	36.95	0.10	36.85	99.73	0.27
60.9	55.00	0.15	54.85	99.73	0.27
81.2	74.65	0.20	74.45	99.73	0.27
102	93.35	0.24	93.11	99.74	0.26
128	117.50	0.29	117.21	99.75	0.25
155	139.50	0.35	139.15	99.75	0.25
181	160.00	0.39	159.61	99.76	0.24
204	183.50	0.45	183.05	99.76	0.24

Each value is the mean of two determinations

Conclusions	^{14}C-teriflunomide was found to be highly bound to human plasma protein (99.7% to 99.8%) with no significant effect of concentration over the range of 0.14 to 204 µg/mL.
Report 14543	**To determine the extent of binding to patient plasma with low plasma albumin concentrations**
Study Design	The extent of binding was measured in plasma taken from a total of 28 patients with kidney disease who presented albumin concentrations in the range 20 - 34 mg/ml (compared to the accepted normal value of 40 mg/ml). Plasma was obtained by centrifugation of heparinized blood taken from a panel of patients. Protein binding was carried out using equilibrium dialysis at 37°C between phosphate buffer (pH 7.4) and plasma or a purified human albumin solution. The equilibration time was 4 hours. From a selected group of 9 patients, whose plasma albumin concentration had been previously determined, a

Best Available Copy

Reference ID: 3151674

	portion of their plasma was adjusted to an albumin concentration of 40 mg/ml (physiological conditions).
Results	**PROTEIN BINDING IN PATIENTS WITH HYPOALBUMINEMIA**

The % unbound in patients with hypoalbunemia was 1.82%±0.61% (range 1.17-2.96%) at an albumin content of 20-34 mg/ml. When additional albumin was added, the mean % unbound was 1.93±0.39%.

In purified albumin at albumin concentrations 10-60 g/L, the mean % unbound ranged from 0.41-3.30%, suggesting that binding depended on the concentration of albumin. Higher the albumin, more the binding. These results were similar to that obtained from the previous study.

Albumin Concn. ($g\ l^{-1}$)	Concn. at equilibrium ($\mu g\ equiv.\ g^{-1}$)		Amount bound ($\mu g\ equiv.\ g^{-1}$)	% bound	% unbound	Mean % bound (±SD)	Mean % unbound (±SD)
	Donor	Receptor					
10	54.7	1.82	52.9	96.67	3.33	96.70 ± 0.025	3.30 ± 0.025
	52.7	1.73	50.9	96.72	3.28		
	53.8	1.78	52.0	96.70	3.30		
	54.2	1.75	52.5	96.76	3.24		
	54.5	1.71	52.8	96.86	3.14		
	53.6	1.81	51.8	96.62	3.38		
15	53.3	0.912	52.4	98.29	1.71	98.29 ± 0.015	1.71 ± 0.015
	53.0	0.921	52.1	98.27	1.73		
	53.3	0.904	52.4	98.30	1.70		
30	51.0	0.402	50.6	99.21	0.79	99.20 ± 0.012	0.80 ± 0.012
	51.0	0.412	50.5	99.19	0.81		
	50.5	0.409	50.1	99.19	0.81		
55	46.8	0.228	46.6	99.51	0.49	99.57 ± 0.052	0.43 ± 0.051
	46.2	0.186	46.1	99.60	0.40		
	47.0	0.187	46.8	99.60	0.40		
60	49.4	0.221	49.2	99.55	0.45	99.59 ± 0.035	0.41 ± 0.035
	49.2	0.190	49.1	99.61	0.39		
	49.4	0.192	49.2	99.61	0.39		

Conclusions	• No significant correlation between patient plasma albumin concentration and extent of unbound fraction was evident. However, with purified albumin, the higher the albumin, more the binding. • There was no significant difference between albumin from hypoalbuminemia patients and that after adding albumin. The slight increase in % unbound can be accounted for by the variation in the sample

Reference ID: 3151674

Report 015182	**Protein Binding of ^{14}C A77 1726 to serum proteins at high concentrations**
Study Design	Equilibrium dialysis 37°C between phosphate buffer (pH 7.4) and plasma
Results	**PROTEIN BINDING AT HIGH CONCENTRATIONS**
A77 1726 is highly bound to plasma proteins. Over the concentration range 89-573 µg/ml, the mean binding was 99.5% (range 99.25-99.78%).The binding was constant over this concentration range. However at 839 µg/ml binding was diminished (98.7%) and the free-fraction was over double that seen at the lower concentrations, showing some saturation at higher concentration.	
Conclusions	Teriflunomide was highly bound to plasma. The mean binding was 99.5% (range 99.25-99.78%)

Appears This Way On Original

IN VITRO METABOLISM STUDIES

Report 2005-0050	**In vitro Metabolism of [^{14}C]-HMR1726 in Hepatocytes from Humans**
Study Design	The in vitro metabolism of ^{14}C-teriflunomide was assessed in human hepatocytes. ^{14}C-teriflunomide (10 µM, 2.7 µg/mL) was incubated for 4 hours.
Results	**METABOLISM OF HMR1726 IN HUMAN HEPATOCYTES**
No prominent metabolites were observed after incubation of [^{14}C]-HMR1726 with human hepatocytes for 4 hr. [^{14}C]-HMR1726 was metabolically stable in human hepatocyte suspension.	
Conclusions	[^{14}C]-HMR1726 was metabolically stable in human hepatocyte suspension.

Report HMR014997	**In vivo and in vitro metabolic studies on ^{14}C -HWA486 (leflunomide), ^{14}C -A771726 and ^{14}C -A813226**
Study Design	The in vitro metabolism of ^{14}C-teriflunomide was assessed in human liver microsomes, cytosol, and gastrointestinal subcellular fractions.
Results	**METABOLISM OF ^{14}C-TERIFLUNOMIDE**
After 3 hours of incubation with ^{14}C -teriflunomide, turnover was low with teriflunomide representing 89.9% and 97.0% of radioactivity in microsomes and cytosol, respectively. 4-TFMA oxalinic acid and 4- TFMA glycolanilide were the major metabolites in microsomes (1.2% and 4.4%, respectively) and in cytosol (0.4% and 1.1%, respectively).	
Conclusions	The major metabolites of teriflunomide in microsomes are 4-TFMA oxalinic acid and 4- TFMA glycolanilide (1.2% and 4.4%, respectively).

Report MIH0794	**Estimation of HMR1726 fraction metabolized by cytochrome P450 (CYP) using enzyme kinetic parameters determined in recombinant human enzymes**
Study Design	This study identifies the human drug metabolizing enzymes involved in the oxidative metabolism of teriflunomide, and to estimate the hepatic fraction metabolized by each enzyme using in vitro techniques. **Biological material:** Microsome preparations from insect cells transfected with human recombinant enzymes (Supersomes). **Recombinant human enzymes tested:** Cytochromes P450: CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 and 3A5 Flavin containing monooxygenases: FMOs 3 and 5 **Concentrations used in this study:** 1.5, 15 and 150 µM (0.405, 4.05, 40.5 µg/mL) with or without NADPH at 37°C for 30 min.
Results	**TERFLUNOMIDE METABOLISM BY CYP-450**

Reference ID: 3151674

Recombinant human CYP or FMO enzymes were not directly involved in the metabolism of teriflunomide, or their contribution was negligible. CYP selective substrate control reaction mixtures showed that the Supersome™ preparations were metabolically active.	
Conclusions	CYP or FMO enzymes are not involved in the metabolism of teriflunomide

Report HMR017949	**In vitro metabolism of 4-trifluoromethylalanine, in the human microsomal liver fraction and human hepatocytes**
Study Design	The in vitro metabolism of 4-TFMA (50 µM) was assessed in human liver microsomes and human hepatocytes.
Results	**METABOLISM OF 4-TFMA**
Metabolism was rapid in both systems. 4-TFMA was rapidly and extensively metabolized in both microsomal fractions and hepatocytes. In microsomes, the main metabolites observed were 2-hydroxy-TFMA and an uncharacterized 4-TFMA oxidized derivative at the nitrogen level. In hepatocytes, the main metabolites were 2-hydroxy-TFMA, N-acetyl-TFMA, and 4-TFMA oxalinic acid.	
Conclusions	Main metabolites of TFMA are 2-hydroxy-TFMA, N-acetyl-TFMA, and 4-TFMA oxalinic acid.

INHIBITION POTENTIAL

Report 2005-0097	**In vitro cytochrome P450 2C19 enzyme inhibition study of HMR1726 in human liver microsomes: Determination of IC50 values and screening for metabolism-dependent inhibition**
Study Design	This study was conducted to evaluate the potential of HMR1726 to inhibit CYP2C19 in the pooled human liver microsomes. The activity of CYP2C19 isoform was measured using the probe substrate of S-(+)-mephenytoin. A specific CYP2C19 inhibitor was used as positive control (tranylcypromine). Test System: Pooled human liver microsomes incubated with the CYP2C19 isoform selective substrate with or without HMR1726 or selective inhibitor for 10 min at 37°C, followed by the addition of an NADPH generating system in timed sequence Test Inhibitor: and HMR1726 at multiple concentrations up to 200 µM (0, 0.02, 0.2, 2, 20 or 200 µM) Test Substrate: S-(+)-mephenytoin Control inhibitor: tranylcypromine
Results	**INHIBITION OF CYP2C19 BY HMR 1726**
Incubation of HMR1726 in microsomal mixtures at concentrations up to 200 µM, resulted in inhibition exceeding 80% of CYP2C19 enzyme activity. The IC50 value was 49±15 µM. Pre-incubation of teriflunomide with NADPH as compared to that without NADPH did not result in more than a 16% decrease in enzyme activity for CYP2C19. This suggests that the	

potential for metabolism-dependent inhibition would be minimal.

Percent of remaining activity in HLM:

CYP450 Isoform	HMR1726[1]					Positive Control[2]
	0.02 µM	0.2 µM	2 µM	20 µM	200 µM	
2C19	96.6	86.5	89.2	75.0	16.5	39.3

Conclusions	• The potential for metabolism-dependent inhibition was minimal. • The likelihood of a DDI is given below: Ki: 158 µM, I/Ki=1.1 (I=167 µM or 45.3 µg/ml with 14 mg QD) DDI probability: Likely

Report MIH 0376	**Investigating the potential for HMR1726 to inhibit CYP2B6 using human liver microsomes in vitro**
Study Design	Test System: Microsomes incubated with the CYP2B6 isoform selective substrate, bupropion, with or without HMR1726 or selective inhibitor for 10 min at 37°C, followed by the addition of an NADPH generating system in timed sequence Test Inhibitor: and HMR1726 at multiple concentrations up to 800 µM (50, 100, 150, 200, 400, 800 µM) Test Substrate: bupropion at100 µM Control inhibitor: Ticlopidine To investigate time-dependent inhibition, HMR17268 microsomes and NADPH were pre-incubated at 37□C for 30 min, and then bupropion was added followed by a 30 min incubation period.
Results	**INHIBITION OF CYP2B6 BY HMR 1726**

At 100 µM HMR1726, inhibition of CYP2B6 was < 50%. Assuming the inhibition followed Michaelis-Menten kinetics and HMR1726 was a competitive inhibitor, the estimated apparent Ki value would be 240 µM, whereas if HMR1726 was a noncompetitive inhibitor, the estimated Ki would be 480 µM (130 µg/ml).

CYP Selective Substrate Assay	Percent of Control			
	Concurrent Incubation [a]		Pre-incubation [b]	
	HMR1726 (100 µM)	Ticlopidine (0.2 µM)	HMR1726 (100 µM)	Ticlopidine (0.2 µM)
CYP2B6 Bupropion hydroxylation	104.7	33.9	89.2	23.2

[a] Microsome reaction mixtures were incubated at 37°C with bupropion and an NADPH generating system, concurrently with or

I/Ki ratio was > 0.1, indicating that clinically significant drug interactions due to inhibition of CYP2B6 by HMR1726 are possible.

CYP isoform	Inhibition model (assumed)	Apparent Ki (μM)	HMR1726 plasma concentration 139 μM (37.6 μg/mL) Interaction is possible (I/Ki ≥ 0.1)
CYP2B6	Competitive	240	0.579
	Noncompetitive	480	0.290

MW=270.2

Conclusions	• HMR1726 inhibited CYP2B6. • The likelihood of a DDI is given below: Ki: 240 μM, I/Ki=0.6 (I=167 μM or 45.3 μg/ml with 14 mg QD) DDI probability: Possible

Report MIH 0542	**In vitro CYP2C8 inhibition studies of HMR1726 in human liver microsomes**
Study Design	Test System: Microsomal liver fraction Test Inhibitor: and HMR1726 at multiple concentrations up to 200 μM (μM) Test Substrate: Paclitaxel at 2-20 μM Control inhibitor: Quercetin
Results	**INHIBITION OF CYP2C8 BY HMR 1726**

The following Ki (μmol/L) was found for HMR1726:

Enzyme	Test Substrate	Positive Control	IC50 (μmol/L) HMR1726	Ki(μmol/L) HMR1726	I/Ki
CYP2C8	Paclitaxel		0.219	0.100 competitive	1670
		Quercetin	2.35, 1.69		

I= 167 μM in Phase 3 studies, 139 μM in PK studies

I/Ki ratio was > 1, indicating that clinically significant drug interactions due to inhibition of CYP2C8 by HMR1726 are likely.

Conclusions	• HMR1726 inhibited CYP2C8. • The likelihood of a DDI is given below: Ki: 0.1 μM, I/Ki=1670 (I=167 μM or 45.3 μg/ml with 14 mg QD) DDI probability: Likely

Reference ID: 3151674

Report MIH 0793	Investigating the potential for HMR1726 to inhibit cytochrome P450 (CYP) isoforms using human liver microsomes in vitro
Study Design	Test System: Human liver microsomes. Multiple concentrations of HMR1726 ranging from 0.25 to 200 µM were used Test Inhibitor: and HMR1726 at multiple concentrations up to 200 µM (µM) Test Substrate: See below Control inhibitor: see below

CYP Isoform	HLM protein [a] (mg/mL)	Selective Substrate		Selective Inhibitor		Pre-incubation time (min)	Co-Incubation time (min)
		Name	Conc. (µM)	Name	Conc. (µM)		
CYP1A2	0.1	Phenacetin	10	Furafylline	20	30	30
CYP2C8	0.1	Paclitaxel	5	2C8 mAb [b]	0.05 mg/mL	30	15
CYP2C9	0.1	Tolbutamine	150	Sulfaphenazole	50	30	20
CYP2C19	0.5	S-Mephenytoin	50	Tranylcypromine	100	30	30
CYP2D6	0.1	Bufuralol HCL	10	Quinidine	10	30	30
CYP3A	0.05	Midazolam	3	Ketoconazole	1	30	15
CYP3A	0.05	Testosterone	50	Ketoconazole	1	30	30

[a] Pooled microsomes from 50 human liver donors were used
[b] mAb = monoclonal antibody

IC50 values were determined using both co-incubation conditions (to assess reversible/direct inhibition) and pre-incubation conditions (to assess time/metabolism-dependent inhibition).

Best Available Copy

Results

INHIBITION OF CYP's

HMR1726 reversibly inhibited CYP2C8 and CYP2C9. The apparent Ki and I/Ki values for HMR1726 inhibition of CYP2C8 and CYP2C9 in human liver microsome reaction mixtures are shown below. The other isozymes were not inhibited significantly.

CYP Isoform	Inhibition Model	Apparent K_i (µM)	I/K_i [a]
CYP2C8	Mixed	0.150	927
CYP2C9	Mixed	8.60	16.2

[a] I = 139 µM, mean plasma concentration from study HMR1726D/2001 with 14 mg dose

I/Ki ratio was > 1, indicating that clinically significant drug interactions due to inhibition of CYP2C8 and 2C9 by HMR1726 are likely.

HMR1726 at 100 µM (approximately 27.0 µg/mL) did not inhibit activity of CYPs 1A2, 2C19, 2D6 and 3A by more than 50%. Consequently, assuming competitive inhibition, the estimated Ki values would be greater than 50 µM (14.5 µg/mL) or one half of the IC50.

CYP Isoform	1A2	2C8	2C9	2C19	2D6	3A (M)	3A (T)
IC_{50} Value[a] (µM)	138	0.174	15.4	315	624	313	210

[a] IC_{50} values higher than 200 µM were extrapolated by program used for determination

Reference ID: 3151674

I/Ki for these isoenzymes were >0.1, suggesting interactions are possible, although the relative contribution compared to CYP2C8 would be negligible. Note: Inhibition of CYP2C19 from previous study 2005-0097 shows a different IC50(49 µM vs 315µM)	
Conclusions	• HMR1726 inhibited CYP2C8 and 2C9 • The likelihood of a DDI with 2C8 is given below: Ki: 0.15 µM, I/Ki=1116 (I=167 µM or 45.3 µg/ml with 14 mg QD) DDI probability: Likely • The likelihood of a DDI with 2C9 is given below: Ki: 8.6 µM, I/Ki=19.5 (I=167 µM or 45.3 µg/ml with 14 mg QD) DDI probability: Likely • The relative inhibition of other CYPs is likely to be less pronounced.

Report MIH 0882	**In Vitro Evaluation of HMR1726 as an Inhibitor of CYP2A6 and CYP2E1 in Human Liver Microsomes**
Study Design	Test System: Human liver microsomes. Multiple concentrations of HMR1726 ranging from 0.25 to 200 µM were used. Test Inhibitor: and HMR1726 at multiple concentrations up to 200 µM (µM) Test Substrate: See Table below Control inhibitor: Direct inhibition control for 2A6: Nicotine (30 µM) Metabolism-dependent inhibition control 8-Methoxypsoralen (0.05 µM) Direct inhibition control for 2E1: 4-Methylpyrazole (15µM) Metabolism-dependent inhibition control: 3-Amino-1,2,4-triazole (10,000 µM)

CYP Enzyme	HLM protein (mg/mL)	Selective Substrate		Selective Inhibitor		Pre-incubation time (min)	Co-incubation time (min)
		Name	Conc. (µM)	Name	Conc. (µM)		
CYP2A6	0.0125	Coumarin	0.6	HMR1726	15 – 500 µM	30	5
CYP2E1	0.1	Chlorzoxazone	25	HMR1726	15 – 500 µM	30	5

IC50 values were determined using both co-incubation conditions (to assess reversible/direct inhibition) and pre-incubation conditions (to assess time/metabolism-dependent inhibition).

Results	**INHIBITION OF CYP2A6 and CYP2E1**

Co-incubation: Under the experimental conditions examined, HMR1726 directly inhibited CYP2A6 and CYP2E1, as approximately 40% and 19% inhibition, respectively, was observed at the highest concentration of HMR1726 evaluated (i.e., 500 µM). This concentration is much higher than the therapeutic concentration (139µM). The IC50 values for HMR1726 reversible inhibition of CYP2A6 and CYP2E1 were > 500 µM and ≥ the limit of solubility in this test system. Therefore, apparent *Ki* values were not determined. Assuming competitive inhibition, the estimated *Ki* values would be greater than 250 µM (68 µg/mL) for these enzymes.

Best Available Copy

Pre-incubation: Similar inhibition profiles were observed using co-incubation and pre-incubation conditions, suggesting that HMR1726 is not a time- or metabolism-dependent inhibitor of CYP2A6 or CYP2E1.	
Conclusions	HMR1726 did not inhibited CYP2A6 and 2E1 at therapeutic concentrations, hence in vivo drug interactions are unlikely,

INDUCTION POTENTIAL

Report MIH 0318	**Assessment of in vitro P450 induction potential of HMR1726 in primary cultures of human hepatocytes**
Study Design	Test System: Fresh human hepatocytes in primary culture Test Inducer: HMR1726 at multiple concentrations up to 139 µM (5.1, 15.4, 46.3, and 139 µM) Probe Substrate: □ CYP1A2: 4-acetamidophenol (phenacetin) □ CYP2C9: 4'-hydroxydiclofenic (diclofenac) □ CYP3A: 6β-hydroxytestosterone (testosterone) Control inducer: Rifampin and omeprazole Rifampin (25 µM, a moderate inducer for CYP2C9 and a potent inducer for CYP3A4) Omeprazole (25 µM, a potent inducer for CYP1A2) Measurement of mRNA expression levels by real time RT-PCR with specific primers and probes for CYP1A2, CYP2C9, and CYP3A4
Results	**INDUCTION OF CYP1A2, 2C9 and 3A4**
Omeprazole treatment produced an increase in CYP1A2 activity of approximately 14- to 49-fold, which was associated with increases in mRNA expression of 37- to 645-fold. Rifampin treatment resulted in moderate increases in CYP2C9 enzyme activity and mRNA expression of approximately 2- to 12-fold and 2-fold, respectively. Rifampin treatment produced an increase in CYP3A enzyme activity of approximately 8- to 59-fold, which was associated with increases in its mRNA expression of approximately 34- to 41-fold. These results demonstrated that the test system of three human hepatocyte cultures was functional. HMR1726 was considered an inducer if it caused an increase in a selective enzyme activity greater than 40% of the activity increase observed with a selective positive control (omeprazole or rifampin). Treatment with HMR1726, with a concentration range of 5.1 to 139 µM, resulted in: • no induction of CYP1A2 for all three donors (any response < 40% of positive control) • induction of CYP2C9 observed with ≥ 15.4 µM for two donors (≥ 40% response relative to positive control) • induction of CYP3A observed with ≥ 139 µM for one donor (≥ 40% response relative to positive control)	
Conclusions	• Induction of CYP2C9 and CYP3A by HMR1726 is considered possible. • HMR1726 did not induce CYP1A2

Reference ID: 3151674

Best Available Copy

TRANSPORTER STUDIES

Report AIV0202	**Apparent permeability coefficient, pH and BSA influence, P-glycoprotein involvement and inhibition studies of HMR1726 using Caco-2-TC7 cells as in vitro model**
Study Design	Test System: Caco-2-TC7 cells

Compound	Concentration	Apical to basal transport P_{app} x 10^{-7} ($cm.s^{-1}$) ± SD
HMR1726, (BCS standard conditions)	20 µM	213 ± 82
HMR1726, pH effect (apical pH 7.4)	20 µM	111 ± 7
HMR1726, BSA effect (apical 5% BSA)	20 µM	47.8 ± 0.5
HMR1726 + 10 µM Cyclosporine A	20 µM	179 ± 16
Low permeability reference: Mannitol	20 µM	1.33 ± 0.08
High permeability reference: Testosterone	20 µM	304 ± 19

Probe Substrates: Digoxin and Vinblastine for P-gp
Estrone-3-sulfate for BCRP
Probe Inhibitor: Cyclosporine A and PSC833 for P-gp
Fumitremorgin C for BCRP

Results	**P-gp and BCRP TRANSPORTER (substrate and inhibitor)**

At apical pH = 6.5, the P_{app} of [^{14}C]HMR1726 (20 µM) was 213 ± 82 x 10^{-7} cm/s. As expected, permeability coefficient of [^{14}C]Mannitol (20 µM), a low permeability probe compound, was 1.33 ± 0.08 x 10^{-7} cm/s and permeability coefficient of [^{14}C]Testosterone, a high permeability probe compound, was equal to 304 ± 19 x 10^{-7} cm/s.

At apical pH = 7.4, the P_{app} of [^{14}C]HMR1726 (20 µM) was significantly decreased to 111 ± 7 x 10^{-7} cm/s.
In the presence of the unspecific P-gp inhibitor Cyclosporine A (10 µM), the P_{app} of [^{14}C]HMR1726 (20 µM) was 179 ± 16 x 10^{-7} cm/s.

Therefore HMR 1726 is a high permeability compound
The measured amount of [^{14}C]HMR1726 transported across the monolayer from apical to basal (absorption direction) increased almost linear with [^{14}C]HMR1726 concentration from 0.180 ± 0.017 to 11.8 ± 0.3 pmol/min/cm² for 1 to 20 µM [^{14}C]HMR1726, respectively. The measured amount of [^{14}C]HMR1726 transported across the monolayer from basal to apical (secretion direction) increased almost linear from 1.66 ± 0.09 to 12.4 ± 0.2 pmol/min/cm² for 1 to 20 µM [^{14}C]HMR1726, respectively. The secretion to absorption ratio was > 9-fold for 1 µM [^{14}C]HMR1726 and decreased with increasing concentrations of HMR1726, indicating an asymmetric transport process, which is saturated at 20 µM. [^{14}C]HMR1726 transport across a Caco-2-TC7 cell monolayer was clearly asymmetric in absorption and secretion direction. Therefore, HMR1726 is identified as a substrate of efflux transporters in Caco-2-TC7 cells.

Asymmetric transport [^{14}C]HMR1726 across the Caco-2-TC7 cell monolayer was only slightly reduced in the presence of the P-gp inhibitor PSC833, moderately reduced in the presence of the unspecific inhibitor Cyclosporine A and completely reduced in the presence of the BCRP inhibitor Fumitremorgin C. Therefore HMR1726 is identified as a substrate of BCRP in Caco-2-TC7 cells.

Reference ID: 3151674

Best Available Copy

Digoxin is used as a substrate for P-gp dependent transport in Caco-2-TC7 cells. The net transport of [^{3}H]Digoxin (5 µM) was not inhibited in the presence of increasing concentrations of HMR1726 (up to 300 µM) , but was 99% inhibited by the positive control verapamil. The results show that HMR1726 was not an inhibitor of P-gp mediated Digoxin transport in Caco-2-TC7 cells.

Transporter involvement				
Experimental conditons: BSA 0.5 % and pH 7.4				
Compound	**Concentration (µM)**	**Apical to basal transport**	**Basal to apical transport**	**Ratio**
		P_{app} x 10^{-7} (cm.s^{-1})	P_{app} x 10^{-7} (cm.s^{-1})	$\frac{Papp_{\ basal\ to\ apical}}{Papp_{\ apical\ to\ basal}}$
		Control		
Test compound: HMR1726	1	**28.9** ± 0.8	**271** ± 12	**9.37**
Positive control: Digoxin	5	**6.40** ± 0.86	**240** ± 5	**37.5**
Positive control: estrone-3-sulfate	0.01	**16.2** ± 2.4	**48.4** ± 1.4	**2.99**
		+ Cyclosporine A (10 µM)		
Test compound: HMR1726	1	**88.4** ± 24.3	**176** ± 3	**1.99**
Positive control: Digoxin	5	**58.8** ± 2.1	**66.3** ± 0.6	**1.13**
		+ PSC833 (1 µM)		
Test compound: HMR1726	1	**33.6** ± 3.5	**211** ± 11	**6.28**
Positive control: Digoxin	5	**66.7** ± 9.5	**85.1** ± 3.9	**1.28**
		+ Fumitremorgin C (10 µM)		
Test compound: HMR1726	1	**83.4** ± 7.5	**71.9** ± 4.5	**0.862**
Positive control: Estrone-3-sulfate	0.01	**13.0** ± 0.9	**15.1** ± 0.8	**1.16**

Conclusions	• HMR1726 is a high permeability compound regarding BCS classification. • HMR1726 is a substrate of efflux transporters, most obviously BCRP. The net flux ratio is 9.37/0.862=10.87. Since this ratio is greater than 2, suggests further in vivo studies must be conducted with a BCRP inhibitor. • HMR1726 is a not an inhibitor of P-gp.

Report TRE 0034	**Evaluation of the uptake of HMR1726 into human cryopreserved hepatocytes in suspension**
Study Design	Test System: 4 donor pool (2 of each female and male) of human cryopreserved hepatocytes HMR1726 was incubated with human hepatocytes at 37°C in the presence and in the absence of an inhibitor cocktail and at 4°C. The inhibitor cocktail was composed of the potent transporter inhibitors Cyclosporine A (20 µM), Rifampicin (20 µM) and Quinine (100 µM). Hepatocytes were separated by a rapid centrifugation method through a layer of mineral oil. Probe Substrates: OATPs: 1 µM [^{3}H]E17βG (1, 2, 3 min), 2 µM[^{3}H]Estrone-3-sulfate (1, 2, 3 min) OCTs: 25 µM [^{14}C]TEA (1, 2, 3 min), 1 µM [^{3}H]MPP+ (0.5, 1, 1.5 min) NTCP: 1 µM [^{3}H]Taurocholic acid (1, 2, 3 min) Probe Inhibitor Cocktail : 20 µM Rifampicin (inhibitor of OATPs and

Reference ID: 3151674

	NTCP), 100 µM Quinine (inhibitor of OCTs) and 20 µM Cyclosporine A (inhibitor of OATPs and NTCP)
Results	**OATPs, OCT and NTCP TRANSPORTER (substrate)**
In human hepatocytes, uptake of HMR1726 (both 1 and 5 µM) at 37°C was indistinguishable in the absence and in the presence of a potent transporter 'inhibitor cocktail' for OATP-, OCT-, and NTCP-dependent uptake. Uptake of HMR1726 in human hepatocytes was clearly reduced at 4°C. Uptake of HMR1726 in human hepatocytes was clearly reduced at 4°C, which might be due to a decreased passive permeation or an undefined active transporter, which was not inhibited by the inhibitor cocktail.	
Conclusions	• HMR1726 was not identified as a substrate of the most important hepatic uptake transporters OATPs, OCTs and NTCP.

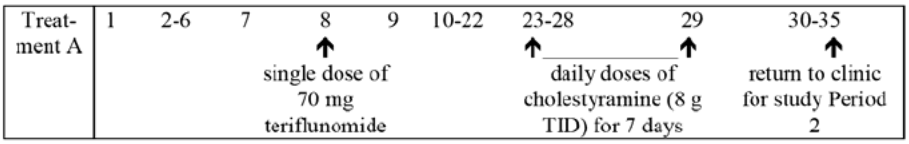
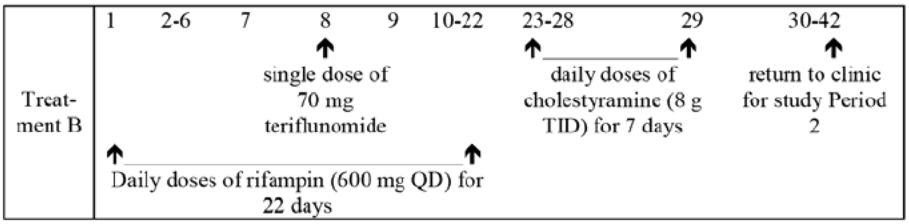
Best Available Copy

Report TRE 0029	**Evaluation of HMR1726 as inhibitor of uptake transporters hOAT3, hOCT2 (renal uptake), hOATP1B1 (hepatic uptake) and efflux transporter hBCRP (intestinal, hepatic and renal efflux)**
Study Design	Cell lines / Probe substrate [concentration] / Probe inhibitor [concentration] / Incubation time CHO^{Fl} and CHO^{Fl}-hOAT3 / Estrone-3-sulfate [0.05 µM] / Probenecid [10 and 50µM] / 0.5 min CHO^{Fl} and CHO^{Fl}-hOCT2 / Metformin [25 µM] / Cimetidine [100 and 500 µM] / 1 min HEK^{TR} and HEK^{TR}-hOATP1B1 / Estradiol-17β-glucuronide [1 µM] / Rifampicin [2 and 10 µM] / 15 min hBCRP membrane vesicles / Methotrexate [100 µM] / FumitremorginC [10 µM] / 3 min HMR1726 concentrations: 0, 0.1, 0.3, 0.7, 1, 3, 7, 10, 30, 70, 100 µM
Results	**INHIBITOR OF OAT3, OCT2, OATP1B1 and BCRP TRANSPORTER**
HMR1726 as an inhibitor of hOAT3 mediated ES uptake In three independent experiments the net uptake of [^{3}H]ES was inhibited in the presence of increasing concentrations of HMR1726 (up to 100 µM) with IC_{50} values of 0.674, 1.63 and 0.785 µM, respectively. Therefore HMR1726 was identified as an inhibitor of OAT3 mediated ES uptake with a mean IC_{50} value of 1.03 ± 0.3 µM. **HMR1726 as an inhibitor of hOCT2 mediated Metformin uptake** Three independent experiments were performed with up to 100 µM HMR1726. In two experiments HMR1726 was not an inhibitor of OCT2 mediated net uptake of [^{14}C]Metformin. In one experiment OCT2 mediated net uptake was slightly inhibited and an IC_{50} value of 33.3 µM was determined. In this experiment also the control inhibitor Cimetidine showed a more pronounced inhibition at the concentration of 100 µM. HMR1726 is a very weak inhibitor of OCT2 *in vitro* with an IC_{50} value > 100 µM **HMR1726 as an inhibitor of hOATP1B1 mediated E17βG uptake** In two independent experiments the net uptake of [^{3}H]E17βG was inhibited in the presence of increasing concentrations of HMR1726 (up to 100 µM) with IC_{50} values of 9.32 and 4.95 µM, respectively. Therefore HMR1726 was identified as an inhibitor of OATP1B1 mediated	

E17βG uptake with a mean IC_{50} value of 7.14 ± 2.19 µM. **HMR1726 as an inhibitor of hBCRP mediated Methotrexate transport** In two independent experiments the net uptake of [^{3}H]Methotrexate was inhibited in the presence of increasing concentrations of HMR1726 (up to 100 µM) with IC_{50} values of 0.213 and 0.0797 µM, respectively. Therefore HMR1726 was identified as an inhibitor of BCRP mediated Methotrexate transport with a mean IC_{50} value of 0.146 ± 0.067 µM.	
Conclusions	• *In vitro*, HMR1726 was an inhibitor of hOAT3 mediated ES uptake with a mean IC_{50} value of 1.03 ± 0.3 µM. • *In vitro*, HMR1726 was a very weak inhibitor of hOCT2 mediated Metformin uptake with an IC_{50} value > 100 µM. • *In vitro*, HMR1726 was an inhibitor of hOATP1B1 mediated E17βG uptake with a mean IC_{50} value of 7.14 ± 2.19 µM. • *In vitro*, HMR1726 was an inhibitor of hBCRP mediated Methotrexate transport with a mean IC_{50} value of 0.146 ± 0.067 µM.

Appears This Way On Original

EXTRINSIC FACTORS

Study INT6039	**A phase I, single dose, open-label, randomized, two-way crossover drug interaction study of HMR1726 (Teriflunomide) and rifampin in healthy male subjects**
Rationale	To determine the effect of multiple doses of rifampin (potent nonspecific CYP inducer and Pglycoprotein inducer) on single dose pharmacokinetics of teriflunomide in healthy male subjects. Concomitant administration of leflunomide and rifampin to healthy subjects showed an increase of about 40% in the Cmax of teriflunomide, possibly caused by an intensified conversion of leflunomide to teriflunomide. However, a reduction in the elimination of teriflunomide could not be ruled out.
Study Design	Single center, single-dose, open-label, randomized, two-way crossover study in 20 healthy male subjects with a washout period of 35 days between two teriflunomide treatments in each of the two periods  
Study Population	N=21 Healthy subjects, treatment A=20; treatment B =19 Age: 18-55 years Gender: All males Race: 16 white, 3 Black, 2 Other
Treatment Groups	Treatment A: teriflunomide, 70 mg SD on Day 8 Treatment B: teriflunomide 70 mg SD on Day 8 + Rifampin (600 mg QD Day 1-22) Administration of rifampin (600 mg QD) started 7 days prior to the administration of teriflunomide and was continued throughout the 360-hour serial plasma sampling period to ensure that liver enzymes would be maximally induced. After each treatment period, cholestyramine (8 g TID) was administered for seven consecutive days in order to increase the clearance of teriflunomide from plasma. Batch No(s): 1629 Washout between periods: 21 days Comments:

Reference ID: 3151674

<table>
<tr><td></td><td>

Teriflunomide exposure following this dose was expected to be lower than the steady state exposure in multiple sclerosis patients administered 7 mg and 14 mg once daily for 9 months. A loading dose to ensure steady state levels was not administered in this study
Rifampin dose is acceptable.

</td></tr>
<tr><td>Dosage and Administration</td><td>Teriflunomide with 240 mL of water at about 8 AM following an overnight fast. No food till 4 hours post dose.
Rifampin was administered at about 8 AM on study Days 1 through 22 (inclusive) following an overnight fast. No food till 2 hours post dose.
A single dose of 70 mg teriflunomide was selected as in previous clinical studies teriflunomide dosages up to 100 mg had been well tolerated in healthy subjects.</td></tr>
<tr><td>Sampling: Blood</td><td><u>For plasma terflunomide and TFMA concentrations:</u>
Serial plasma sampling for 360 hours (15 days) and additional at 528 (teriflunomide only) following teriflunomide dosing was considered adequate to demonstrate any pharmacokinetic drug interaction between rifampin and teriflunomide because of the linear elimination characteristics of teriflunomide</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td><u>Plasma HMR1726 and TFMA:</u>
<table>
<tr><td></td><td><u>HMR1726</u></td><td>TFMA</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>Capillary GC (b) (4)</td></tr>
<tr><td>Linear Range</td><td>0.1-100 µg/ml
0.01-1</td><td>0.5-50 (ng/ml)</td></tr>
<tr><td>LLOQ</td><td>0.1 and 0.01</td><td>0.5</td></tr>
<tr><td>QCs</td><td>0.3, 20, 75</td><td>1.5,7.5, 35</td></tr>
<tr><td>Interday precision</td><td>% CV <8.3</td><td>% CV <10.2</td></tr>
<tr><td>Intraday precision</td><td>% CV <2.4</td><td>-</td></tr>
</table></td></tr>
<tr><td>PK Assessment</td><td>Cmax, Tmax, AUC0-t, AUC0-∞, CL/F, t½,</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic Results:</td><td>TERFLUNOMIDE + RIFAMPIN</td></tr>
<tr><td colspan="2">Table- Geometric means, ratio estimates, and 90% confidence interval of teriflunomide pharmacokinetic parameters</td></tr>
</table>

Parameter	Geometric Means		Ratio Estimates	90% Confidence Intervals (CIs)
	Treatment A[a] (Reference)	Treatment B[a] (Test)		
C_{max} (µg/mL)	10.1	11.8	117	111 - 122
$AUC_{(0\text{-}360h)}$ (µg*h/mL)	1790	1430	79.7	76.0 - 83.5
$AUC_{(0\text{-}\infty)}$ [b] (µg*h/mL)	3110	1890	60.8	55.2 - 66.9
$t_{1/2}$ (h)	279	169	--	--

[a] Treatment A: teriflunomide alone; Treatment B: concomitant treatment with teriflunomide and rifampin.

[b] In 14/20 subjects receiving Treatment A and in 3/19 subjects receiving Treatment B, the extrapolated portion of $AUC_{(0\text{-}\infty)}$ was ≥ 30%. All were included in the calculations.

Comment: Since in many subjects the % AUC extrapolated was >30% (12.5-58.8%), AUC0-360 would be more appropriate for comparisons of exposure.

Safety	The study did not produce evidence of any new findings with regard to the safety and tolerability of teriflunomide.
Conclusion	• Co-administration of a single 70 mg teriflunomide dose with multiple rifampin 600 mg doses reduced plasma $AUC_{(0\text{-}360h)}$ of teriflunomide (-20%) and $AUC_{(0\text{-}inf)}$ (-39%). Teriflunomide was not at steady state in this study. • Mean Cmax was slightly increased (+17%) after concomitant administration of teriflunomide and rifampin. • Plasma TFMA concentrations were below the lower limit of quantitation after both treatments (teriflunomide alone and combined treatment with teriflunomide and rifampin). • Median t_{max} values were 2.0 h and 1.5 h after teriflunomide alone and combined teriflunomide and rifampin treatment, respectively.
Dosage Adjustment	Patients on rifampin and other inducers should be monitored for effectiveness. The decrease in mean AUC was between 20-39%. Comment: Given the large amount of % extrapolated in the calculation of AUCinf, it appears that the decrease in exposure in minimal. This was also observed in the case of ARAVA. No dose adjustment is necessary.

Study 1932	**An open-label, two treatment, pharmacokinetic interaction study of repeated oral doses of teriflunomide on a single oral dose of repaglinide in healthy male subjects**
Rationale	Teriflunomide is an inhibitor of CYP2C8 in vitro. Repaglinide is extensively metabolized by CYP2C8 and CYP3A and appears to be a substrate for OATP1B1 (organic anion transporting protein).
Study Design	Single center, open-label, non-randomized, single sequence, 2-period, 2-treatment PK interaction study
Study Population	N=20 Healthy subjects (Two subjects discontinued the study treatment: 1 subject on teriflunomide alone discontinued due to a TEAE (neutropenia) after 7 days of teriflunomide treatment, and 1 subject discontinued for family reasons) Age: 18-45 years Gender: All males Race: All White
Treatment Groups	Treatment A: Teriflunomide in Period 2, 70 mg QD for 4 days followed by 14 mg QD day for 8 days Treatment B: Repaglinide: single dose of 2.5 mg (1/2 tablet) on Day 1 Period I and Day 12 Period 2 Batch No(s): FRA- 01179 Comment: • A low dose of Repaglinide has been tested in this study (recommended dose is 0.5-16 mg). The magnitude of effect seen could be greater than that observed in this study Washout between periods: 21 days
Dosage and Administration	Teriflunomide: Oral, in fed conditions except on the day of co-administration with repaglinide, where it was given in fasted conditions Repaglinide: Oral, in fasted conditions Cholestyramine: (4 g 3 times daily) following teriflunomide administration administered in Period 2 from Day 15 to Day 28 (14 days). Additional cholestyramine may have been given when teriflunomide plasma concentrations were >0.02 µg/mL at the end of second period.
Sampling: Blood	For plasma Repaglinide concentrations: At predose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours postdose on Day 1 of Period 1 and on Day 12 of Period 2. For plasma teriflunomide concentrations: At predose on Days 1, 10, 11, 12, and at 24 and 48 hours after the last teriflunomide dose on Day 12 and post cholestyramine treatment on Day 25 in Period 2.
Urine	none
Feces	none

<table>
<tr><td>Analysis</td><td>Plasma HMR1726 and Repaglinide:
<table>
<tr><td></td><td>HMR1726</td><td>Repaglinide</td></tr>
<tr><td>Method</td><td>LC-MS-MS</td><td>LC-MS-MS</td></tr>
<tr><td>Linear Range</td><td>0.1-100
0.01-3 µg/ml</td><td>99.2-9920 pg/ml</td></tr>
<tr><td>LLOQ</td><td>0.1 and 0.01 µg/ml</td><td>99.2 pg/ml</td></tr>
<tr><td>QCs</td><td>0.3, 30, 75 µg/ml
0.02, 0.5, 2.5, 60 µg/ml</td><td>299,3480, 7460, 1490 pg/ml</td></tr>
<tr><td>Interday precision</td><td>% CV <6.79%</td><td>% CV <2.64</td></tr>
</table></td></tr>
<tr><td>PK Assessment</td><td>Cmax, Tmax, AUC0-t, AUC0-∞, CL/F, t½,</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic Results:</td><td>TERFLUNOMIDE + REPAGLINIDE</td></tr>
</table>

Terifluniomide was at steady state by Day 12.

Mean + SD (Geometric Mean) [CV%] of repaglinide pharmacokinetic parameters

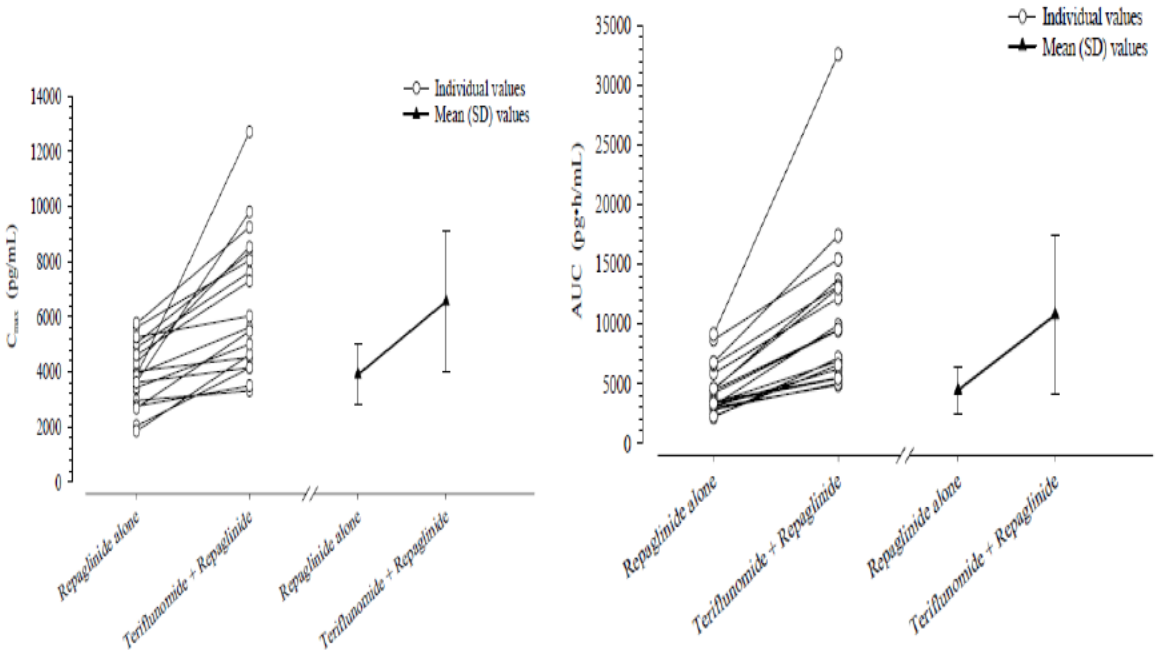
PK parameters	Repaglinide alone	Teriflunomide + Repaglinide
N	20	18
C_{max} (pg/mL)	3910 ± 1120 (3740) [28.5]	6550 ± 2550 (6110) [38.9]
t_{max}[a] (h)	0.50 (0.50 - 1.00)	0.50 (0.50 - 1.00)
AUC_{last} (pg•h/mL)	4220 ± 1870 (3890) [44.2]	10200 ± 6370 (8850) [62.7]
AUC (pg•h/mL)	4420 ± 1980 (4060) [44.9]	10700 ± 6680 (9360) [62.1]
$t_{1/2z}$ (h)	0.986 ± 0.793 (0.776) [80.4]	2.81 ± 1.83 (2.27) [65.1]
t_{last}[a] (h)	3.50 (2.00 - 8.00)	8.00 (5.00 - 24.00)

Estimate of treatment ratios with 90% confidence interval for repaglinide

Best Available Copy

Parameter	Comparison	Estimate	90% CI
Cmax	Teriflunomide + Repaglinide vs. Repaglinide alone	1.64	(1.44 to 1.87)
AUClast	Teriflunomide + Repaglinide vs. Repaglinide alone	2.25	(2.01 to 2.52)
AUC	Teriflunomide + Repaglinide vs. Repaglinide alone	2.28	(2.04 to 2.54)

The variability in the data is shown in the following stick plot:



Comment: Two subjects (#1011, 1012 and 1017) AUC ratio was 3.31, 3.18 and 3.57, These subjects also had a higher Cmax ratio of 2.5, 2.71 and 3.31. But these were not the subjects that showed a significant AE in the study.

Safety	1 subject (#1004) on teriflunomide alone discontinued due to a TEAE (neutropenia) after 7 days of teriflunomide treatment
Conclusion	• Teriflunomide administration of 70 mg once a day for 4 days followed by 14 mg once a day for 8 days orally resulted in an increase in mean AUClast and AUC of repaglinide after a single dose of 0.25 mg repaglinide by 2.25 and 2.28 fold (90% CI 2.04-2.54), respectively. • Since the recommended dose of repaglinide is 0.5-16 mg, the increase in repaglinide concentrations could be higher at higher dose.
Dosage Adjustment	Monitoring for glucose levels should be recommended to adjust the dose.

Study INT11932	**An open-label, nonrandomized, two-period, two-treatment, single-sequence pharmacokinetic interaction study of repeated oral doses of teriflunomide on a single oral dose of bupropion in healthy male subjects.**
Rationale	In vitro, teriflunomide inhibited the activity of human CYP2B6 with a ratio I/Ki >0.1 (Ki ~ 240 µM and I ~ 139 µM; I = steady-state concentration of 37.6 µg/mL following 14 mg daily oral dosing and Ki: enzyme inhibition constant. Bupropion, an antidepressant, is a substrate of CYP2B6
Study Design	Single center, open-label, non-randomized, single sequence, 2-period, 2-treatment PK interaction study
Study Population	N=17 Healthy subjects Age: 23-44 years Gender: All males Race: 11 white, 3 Black, 3 Other
Treatment Groups	Treatment A: teriflunomide in Period 2, 70 mg QD for 4 days followed by 14 mg QD day for 10 days Treatment B: Bupropion: single dose of 150 mg on Day 1 Period I and Day 12 Period 2 Washout: ≥ 3 days between periods Batch No(s): FRA-01431 The recommended dose of bupropion is 300mg/day, with an initial dose of 200 mg/day and maximum of 400 mg/day
Dosage and Administration	Oral route in fed state for both teriflunomide and bupropion (except Period 2, day 12 where administration was performed in fasted state) Cholestyramine: (4 g 3 times daily) following teriflunomide administration administered in Period 2 from Day 15 to Day 28 (14 days). Additional cholestyramine may have been given when teriflunomide plasma concentrations were >0.02 µg/mL at the end of second period.
Sampling: Blood	For plasma Bupropion and hydroxybupropion concentrations: At predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48 and 72 hours following bupropion administration on Day 1 of Period 1 and on Day 12 of Period 2. For plasma teriflunomide concentrations: At predose on Days 1, 10, 11, 12, 13, 14 and 15 of Period 2. For safety, two additional samples were taken after the washout procedure at Days 29 and 35.
Urine	none
Feces	none
Analysis	Plasma HMR1726 and Bupropion:

		HMR1726	Bupropion	Hydroxybupropion	
	Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	
	Linear Range	0.1-100 0.01-3 µg/ml	1-201 ng/ml	2-804 ng/ml	
	LLOQ	0.1 and 0.01	1	2	
	QCs	0.3, 20, 75 0,025, 0.5, 2.5	3, 16, 70 ,151	5.97, 63.7, 279, 597	
	Interday precision	% CV<11.2%	% CV <3.13%	% CV <4.39%	
PK Assessment	Cmax, Tmax, AUC0-t, AUC0-∞, CL/F, t½,				
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs				
PD Assessment	none				
Pharmacokinetic Results:	**TERFLUNOMIDE + BUPROPION**				

Terifluniomide was at steady state by Day 12 when bupropion was administered as shown by the trough concentrations taken from Day 10-15.

Mean ± SD (Geometric Mean) [CV%] of bupropion pharmacokinetic parameters

	Bupropion alone	Teriflunomide+Bupropion
N	17	17
C_{max} (ng/mL)	111 ±35.2 (106) [31.8]	112 ±26.9 (109) [24.1]
t_{max}[a] (h)	2.00 (1.00 - 3.00)	3.00 (1.00 - 4.00)
$t_{1/2z}$ (h)	16.7 ±5.80 (15.7) [34.7]	15.6 ±6.01 (14.5) [38.4]
AUC_{last} (ng.h/mL)	990 ±315 (944) [31.8]	899 ±223 (875) [24.8]
AUC (ng.h/mL)	1030 ±331 (983) [32.0]	936 ±236 (910) [25.2]

Mean ± SD (Geometric Mean) [CV%] of hydroxybupropion pharmacokinetic parameters

Reference ID: 3151674

	Bupropion alone	Teriflunomide+Bupropion
N	17	17
C_{max} (ng/mL)	270 ±118 (247) [44.0]	342 ±102 (328) [29.7]
t_{max}[a] (h)	6.00 (4.00 - 8.00)	5.00 (4.00 - 8.00)
$t_{1/2z}$ (h)	25.9 ±6.10 (25.3) [23.5]	22.7 ±5.37 (22.2) [23.6]
AUC_{last} (ng.h/mL)	10300 ±4400 (9320) [42.9]	12300 ±4290 (11600) [34.9]
AUC (ng.h/mL)	12300 ±5530 (11100) [45.0]	14200 ±5650 (13300) [39.9]

Table- Treatment ratio estimates with 90% CI (teriflunomide + bupropion versus bupropion alone)

Compound	Parameter	Estimate	90% CI
Bupropion	C_{max}	1.03	(0.94 to 1.12)
	AUC_{last}	0.93	(0.87 to 0.99)
	AUC	0.93	(0.87 to 0.99)
Hydroxybupropion	C_{max}	1.33	(1.19 to 1.48)
	AUC_{last}	1.25	(1.10 to 1.42)
	AUC	1.20	(1.05 to 1.36)

Phase 2 metabolism through UDT's and not Phase 1 metabolism via CYP2B6 is more important for hydroxybuproioin clearance; hence the effect seen on hydroxybuproioin may be related to UGT rather than CYP2B6, though not completely understood. The clinical relevance of a 25% increase in AUC of hydroxybupropion may not be significant.

Safety	• Potential clinically significant abnormalities (PCSA) for laboratory values were infrequent • An increase in eosinophil (>0.5 Giga/L) during both teriflunomide and cholestyramine treatment periods (0.8Giga/L) and Period 2 Day 15 (0.9 Giga/L) in a subject who had an abnormal baseline (0.7Giga/L) was observed. • An elevated creatinine phosphokinase (>3 ULN) at Period 2 Day 11 (9.8ULN versus 0.7 ULN baseline), which returned to normal range (0.7 ULN) at the EOS. The elevated creatinine phosphokinase was exercised induced. • A transient neutropenia at Period 2 Day 15 (1.4 Giga/L) versus 2.6 Giga/L at baseline. • An increase in ALT >3 ULN (maximum value 3.4 ULN) at Period 2 Day 28 (14 days after end of teriflunomide treatment, at the end of cholestyramine treatment), which decreased to normal values 12 days later
Conclusion	• Coadministration of repeated teriflunomide doses (70 mg QD for 4 days, followed by 14 mg QD for 10 days) with a single dose of

	bupropion 150 mg (sustained release formulation) resulted in no effect on the geometric mean AUClast and AUC of bupropion (CYP2B6 substrate). • Hydroxybuprion AUC was increased by 25% (90% CI 10-42%)
Dosage Adjustment	none

Appears This Way On Original

Study INT6040	**A study investigating a potential pharmacodynamic and pharmacokinetic interaction between HMR1726 (teriflunomide) and warfarin in healthy male subjects**
Rationale	Teriflunomide has been shown to inhibit CYP2C9 in vitro with a Ki = 46 µM. Teriflunomide also inhibits CYP2C19 in vitro with an IC50 of 49 µM (assumed competitive inhibition Ki of 25 µM against S-(+)-metphenytoin). R warfarin is metabolized by cytochrome P450 (CYP)1A2, 3A4, 2C19 and S warfarin by 2C9. Teriflunomide at high concentrations could interact with warfarin both pharmacokinetically and pharmacodynamically. After once-daily doses of 14 mg for 36 weeks, mean concentrations of teriflunomide (Cmin) in plasma were ~40 µg/L (148 µM). Therefore, there is a possibility of an interaction between teriflunomide and warfarin (I/Ki ≥0.1)
Study Design	Open, nonrandomized, single sequence, 2-treatment, 2-period design
Study Population	N=14 Healthy subjects, treatment A=14; treatment B =12 Age: 19-45 years Gender: All males Race: All White
Treatment Groups	Treatment A: Warfarin alone (25 mg on Day 1) Treatment B: teriflunomide 70 mg QD on Days 1-3, 14mg QD for 8 Days+ Warfarin (25 mg SD on Day 5) Washout period: 7 days Batch No(s): FRA-00436
Dosage and Administration	Warfarin doses (25 mg) were administered with 240 mL of noncarbonated water under fasted conditions. The observed INR values at this dose correspond to the recommended therapeutic activity of warfarin. Teriflunomid dose (14 mg) was administered with 240 mL of noncarbonated water under fed conditions except on Day 5 in fasted conditions. Cholestyramine: 8 g TID from Days 12 to 22
Sampling: Blood	For plasma S and R-Warfarin concentrations: at predose, and at 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours post warfarin dosing. Teriflunomide: Trough blood samples were collected after a daily single oral dose of teriflunomide for 11 days. Blood samples were also collected at the follow-up visit after the cholestyramine treatment.

<table>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>Plasma HMR1726 and Warfarin:
<table>
<tr><td></td><td>HMR1726</td><td>Warfarin</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range</td><td>0.1-100 µg/ml
0.01-5 µg/ml</td><td>5-1500 ng/ml for both –S and -R</td></tr>
<tr><td>LLOQ</td><td>0.1 and 0.01 µg/ml</td><td>5 ng/ml</td></tr>
<tr><td>QCs (µg/ml)</td><td>ml 0.3, 10, 20 and 50 µg/ml</td><td>15, 35, 1250 ng/ml</td></tr>
</table>
<table>
<tr><th>Method</th><th>Accuracy</th><th>Precision</th></tr>
<tr><td>LC/MS/MS (R-warfarin)</td><td>-3.3-0.8%</td><td>2.8-14.2%</td></tr>
<tr><td>LC/MS/MS (S-warfarin)</td><td>-2.4-0.8%</td><td>2.2-14.1%</td></tr>
<tr><td>LC/MS/MS (HMR1726 - trough samples, Method DOH0590)</td><td>-7.9-2.0%</td><td>4.7-9.9%</td></tr>
<tr><td>LC/MS/MS (HMR1726 - after cholestyramine treatment)</td><td>-2.3-0.7%</td><td>3.5-7.7%</td></tr>
</table></td></tr>
<tr><td>PK Assessment</td><td>Warfarin
• Primary pharmacokinetics variables: Cmax, AUClast (AUC0-168 h), and AUC of S-warfarin
• Secondary pharmacokinetics variables: tmax and t1/2z of S-warfarin, Cmax, AUClast (AUC0-168 h), AUC, tmax, and t1/2z of R-warfarin
Teriflunomide
• HMR1726 on Days 2 (24 h) to 12
• Plasma HMR1726 concentrations on Day 23 after cholestyramine treatment</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>Warfarin effect on International Normalized Ratio (INR) (0-168 hour profile in Period 1 and 2): at predose, and 8, 12, 16, 24, 36, 48, 72, 96, 120, 144 and 168 hours after warfarin administration

Peak value, time to peak, and the overall hourly average over 168 hours (AUC[0-168]/168)</td></tr>
<tr><td>Pharmacokinetic Results:</td><td>TERFLUNOMIDE + WARFARIN</td></tr>
</table>

Reference ID: 3151674

Mean (SD) pharmacokinetic parameters of warfarin following a single oral administration of 25 mg warfarin and combined treatment with teriflunomide

PK parameter	S-warfarin		R-warfarin	
	Warfarin alone	Warfarin + HMR1726	Warfarin alone	Warfarin + HMR1726
C_{max} (ng/mL)	1280±215 (17) [1260]	1360±195 (14) [1350]	1260±210 (17) [1250]	1370±192 (14) [1360]
t_{max} (h)	2.00 (0.75-6.00)	2.00 (0.50-6.00)	2.50 (0.50-8.00)	3.00 (0.50-6.00)
$AUC_{0\text{-}168\ h}$ (ng.h/mL)	42200±10800 (26) [41000]	45300±11400 (25) [44200]	69800±19200 (27) [67500]	68700±15900 (23) [67200]
AUC (ng.h/mL)	44100±12000 (27) [42700]	47500±12800 (27) [46200]	78800±25500 (32) [75300]	74800±19300 (26) [72700]
$t_{1/2z}$ (h)	37.6±5.72 (15) [37.2]	38.2±3.77 (10) [38.0]	50.8±9.87 (19) [50.0]	45.1±5.66 (13) [44.7]

The effect of coadministration on S-warfarin PK parameters (90% CI)

Comparison	Parameter	Ratio estimate	90% CI
Warfarin+HMR1726/warfarin alone	C_{max} (ng/mL)	1.08	(1.00, 1.16)
	$AUC_{0\text{-}168\ h}$ (ng.h/mL)	1.11	(1.08, 1.14)
	AUC (ng.h/mL)	1.12	(1.08, 1.15)
	$t_{1/2z}$ (h)	1.03	(0.98, 1.09)

The effect of coadministration on R-warfarin PK parameters

Comparison	Parameter	Ratio estimate	90% CI
Warfarin+HMR1726/warfarin alone	C_{max} (ng/mL)	1.10	(1.04, 1.17)
	$AUC_{0\text{-}168\ h}$ (ng.h/mL)	1.02	(0.98, 1.06)
	AUC (ng.h/mL)	1.00	(0.95, 1.05)
	$t_{1/2z}$ (h)	0.92	(0.87, 0.98)

Reference ID: 3151674

Pharmacodynamic Results:	**TERFLUNOMIDE + WARFARIN**

Treatment ratios (warfarin + HMR1726)/warfarin with 90% CIs for INR activity parameters

Parameter	Ratio estimate	Estimate Standard error	p-value	90% CI
Peak level INR activity	0.753	0.07144	0.0022	[0.66 ; 0.856]
Overall hourly average over 168 h	0.874	0.02036	<.0001	[0.843 ; 0.907]
Time to peak level activity	1.157	0.1192	0.2432	[0.935 ; 1.432]

Compared to warfarin alone, coadministration of HMR1726 and warfarin reduced peak level INR activity by 25%. For time to peak level activity, the lack of interaction was not demonstrated due to the relatively large variability. For overall hourly INR activity over 168 hours, the lack of interaction was demonstrated by the 90% CI of treatment ratio fully contained in the bioequivalence reference interval (0.80, 1.25).

Safety	Most of the reported TEAEs occurred during the cholestyramine + HMR1726 treatment period. One subject was discovered with an elevated alanine aminotransferase (ALT) level >5 times the upper limit of normal (ULN) (329 IU/L) and an aspartate aminotransferase (AST) level >3 x ULN (160 IU/L) during the cholestyramine + HMR1726 treatment period. The ALT and AST values returned to normal ranges within 40 days.
Conclusion	• As compared with warfarin alone, lack of interaction was shown on overall hourly INR over 168h, but not on peak INR activity which was decreased by 25% when HMR1726 was coadministered with warfarin. • As compared to treatment with warfarin alone, coadministration of multiple HMR1726 doses showed no interaction potential on the pharmacokinetics of warfarin, since the 90% CI values for Cmax, AUC0-168 h, AUC, and t1/2z for S-warfarin and R-warfarin were all within the pre-specified bioequivalence limits of 0.80 to 1.25. • Considering the lack of PK interaction, the effect of coadministration on peak INR is unclear, but of limited extent.
Dosage Adjustment	INR monitoring is recommended.

Study INT10563	**An open-label, non-randomized, two-period, two-treatment, single-sequence pharmacokinetic interaction study of 14-day repeated oral doses of teriflunomide on a single oral dose of midazolam in healthy male subjects**
Rationale	HMR1726 induced cytochrome P450 3A (CYP3A) activity (≥40%) in vitro at concentrations greater than or equal to 139 µM. After once-daily doses of 14 mg for 36 weeks administered to subjects with multiple sclerosis, mean plasma concentration of HMR1726 (Cmin) was ~40 µg/mL (148 µM). Therefore, HMR1726 may induce CYP3A enzyme activity. Midazolam is a CYP3A4 probe. Thus, the aim of this study was to assess the effect of repeated administrations of HMR1726 on the pharmacokinetic profile of a single dose of midazolam in healthy male subjects.
Study Design	Open-label, nonrandomized, single-sequence, 2-period, 2-treatment, repeat dose for HMR1726, single dose for midazolam
Study Population	N=26 Healthy subjects, treatment A=26; treatment B =25 2 subjects completed all 4 treatments, but refused to attend their end-of-study appointments and were reported lost to follow-up and 1 subject discontinued the study due to other reason Age: 18-45 years Gender: All males Race: 19 White, 6 Black, 1 Other
Treatment Groups	Treatment A: Midazolam alone (2mg) Treatment B: teriflunomide 70 mg SD for 3 Days followed by 14 mg QD for 11 Days + Midazolam(2 mg) Batch No(s): FRA-00436 Washout between periods: 2-4 days
Dosage and Administration	Terflunomide: Oral route at 08:00 a.m. with 240 mL of noncarbonated water Fed for all administrations except the Period 2, Day 14 dose Midazolam: 5-mL vials containing 1 mg/mL solution for injection mixed with 120 mL of 5% glucose in water Oral route at 08:00 a.m. with 240 mL of noncarbonated water 10-hr overnight fast (food was not allowed for at least 4 hours and water for 2 hours after drug administration) Cholestyramine: 8 g, 3 times a day for 11 days (ie, total of 24 g per day): Day 15-25:

<table>
<tr><td>Sampling: Blood</td><td><u>For plasma teriflunomide concentrations:</u>
predose, on Days 1, 12, 13, and 14 and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours on Day 14 in Period 2 (midazolam + HMR1726).
<u>For plasma midazolam</u>
predose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours after midazolam administration on Day 1 in Period 1 (midazolam alone) and on Day 14 in Period 2 (midazolam + HMR1726).</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td><u>Plasma HMR1726 and midazolam: (active metabolite not measured)</u>
<table>
<tr><td></td><td>HMR1726</td><td>Midazolam</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range</td><td>0.1-100
0.01-1 µg/ml</td><td>0.1 ng/ml</td></tr>
<tr><td>LLOQ</td><td>0.1 and 0.01</td><td>0.1 ng/ml</td></tr>
<tr><td>QCs</td><td>0.3, 3.75, 20, 75 and
0.0250, 0.500, 2.50</td><td>0.2, 0.4, 80</td></tr>
<tr><td>Interday precision</td><td>% CV <6.41 and <8.33</td><td>% CV <5.7</td></tr>
</table></td></tr>
<tr><td>PK Assessment</td><td>Midazolam (Period 1 and 2): Cmax, AUClast , and AUC
Midazolam (Period 1 and 2): tmax and t1/2z
HMR1726 (Period 2): Cmax, tmax, Ctrough, and AUC0-24 and plasma HMR1726 concentrations after cholestyramine treatment</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic Results:</td><td>TERFLUNOMIDE + MIDAZOLAM</td></tr>
<tr><td colspan="2"><u>Teriflunomide:</u>
Mean trough concentrations of HMR1726 ranged from 27.9 to 29.1 µg/mL on Day 12, Day 13 and on Day 14 when coadministered with midazolam
Table - Descriptive statistics of plasma trough concentrations (µg/mL) of HMR1726 (N=25)
<table>
<tr><th>Day 1</th><th>Day 12 (predose)</th><th>Day 13 (predose)</th><th>Day 14 (predose)</th><th>Day 14 (24 h postdose)</th></tr>
<tr><td><LLOQ</td><td>28.0±7.03
(25) [27.2]</td><td>29.1±7.25
(25) [28.3]</td><td>27.9±6.33
(23) [27.2]</td><td>28.7±6.69
(23) [27.9]</td></tr>
</table>
Descriptive statistics of HMR1726 pharmacokinetic parameters on Day 14 are presented in the following Table:

Table - Pharmacokinetic parameters of HMR1726 on Day 14 (N=25)</td></tr>
</table>

PK parameter	Midazolam + HMR1726 arm
Cmax (µg/mL)	34.4 ±6.64 (19) [33.8]
Tmax (h)	4.00 (0.50-12.00)
AUC0-24 (µg.h/mL)	720 ±145 (20) [706]

Midazolam:

Descriptive statistics of midazolam pharmacokinetic parameters are provided in the following Table:

Table - Pharmacokinetic parameters of midazolam

PK parameter	Midazolam alone (N=26)			Midazolam + HMR1726 (N=25)		
C_{max}	9.63	±	4.84	10.5	±	3.10
(ng/mL)	(50)		[8.95]	(29)		[10.1]
t_{max}		0.50			0.50	
(h)	(0.50	,	1.00)	(0.25	,	1.00)
$t_{1/2z}$	3.48	±	1.25	4.12	±	1.71
(h)	(36)		[3.31]	(42)		[3.81]
AUC_{last}	21.1	±	12.2	26.3	±	11.8
(ng.h/mL)	(58)		[19.4]	(45)		[24.5]
AUC	22.3	±	12.8	27.8	±	12.8
(ng.h/mL)	(58)		[20.5]	(46)		[25.9]

Table - Treatment ratio estimates for midazolam with 90% confidence interval (N=25)

PK parameter	[Midazolam + HMR1726] vs [Midazolam alone] ratio	
	Estimate	90%CI
C_{max}	1.13	(1.00 to 1.28)
AUC_{last}	1.27	(1.14 to 1.42)
AUC	1.27	(1.15 to 1.42)

Safety	One subject experienced an elevated ALT level (>3 x ULN) during the HMR1726 + cholestyramine treatment period. The ALT value returned to normal range after 28 days.
Conclusion	On the basis of a small 27% increase in midazolam exposure, the administration of HMR1726 may result in weak inhibition of CYP3A
Dosage Adjustment	none

Reference ID: 3151674

Study INT10564	**Pharmacokinetic interaction of repeated oral doses of teriflunomide on oral contraceptive steroids (ethinylestradiol and levonorgestres) in young healthy females**
Rationale	Oral contraceptive steroids, ethinylestradiol and levonorgestrel are substrates of several enzymes including CYP3A4, CYP2C9, UDP-glucuronosyltransferases (UGT1A1) and sulfonyltransferases (SULT1E1). In vitro, teriflunomide induces CYP3A activity at concentrations ≥139 µM (approximately 38 µg/mL) and CYP2C9 activities at concentration of 15.4 µM. However, in 2 clinical studies in healthy subjects, teriflunomide weakly inhibited CYP3A as shown by a 1.27 fold increase in midazolam (a CYP3A4 substrate) mean exposure and had no effect on pharmacokinetics (PK) of warfarin (a CYP2C9 substrate) after administration of repeated doses of teriflunomide. This study will evaluate the effect of teriflunomide on other pathways such as the UGT1A1 or SULT1E1 involved in the metabolism of OCs.
Study Design	Open-label, single center, 2-period, 2-treatment, single-sequence study with 7-day washout period between Period 1 and 2. • Screening: 2 to 44 days with a run-in period under Minidril® starting on Day -28 (Cycle 1), • Period 1 and 2: 22 days including 21 treatment days, (Cycle 2 and 3) • Wash-out period between Period 1 and Period 2: 7 days • A fourth cycle of Minidril® of 28 days • End of study: 2 days after the end of the fourth cycle
Study Population	N=24 Healthy subjects, treatment A=24; treatment B =23 (1 discontinued) Age: 18-45 years Gender: All females Race: All White
Treatment Groups	Treatment A: repeated oral administrations of Minidril® for 21 days (Day 1 to Day 21) Treatment B: repeated oral administrations of Minidril® for 21 days (Day 1 to Day 21) +teriflunomide for 14 days (Day 8 to Day 21) All study medication was administered under fed conditions with a moderate fat breakfast (both drugs can be taken under fed conditions) Batch No(s): FRA-01179 Washout between periods: 7days
Dosage and Administration	Teriflunomide: Oral route (at 8:00 a.m. with 240 mL of noncarbonated water)

<table>
<tr><td></td><td>Oral Contraceptive:
Minidril® (tablet containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel), Oral route (at 8:00 a.m. with 240 mL of noncarbonated water)

Cholestyramine: 4 g, 3 times a day for 11 days: Day 22</td></tr>
<tr><td>Sampling: Blood</td><td>For plasma teriflunomide concentrations:
Predose on Day 1 and Day 19 to Day 21. On Day 21, samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours post-dose.

For plasma Ethinylestradiol and levonorgestrel:
At predose on Day 1 and Day 19 to Day 21.
On Day 21, samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours post-dose</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>Plasma HMR1726 and oral contraceptive:
<table>
<tr><td></td><td>HMR1726</td><td>Ethinylestradiol (E) and levonorgestrel (L)</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range</td><td>0.1-100
0.01-1 µg/ml</td><td>0.005-0.5 ng/ml E and
0.1-20 ng/ml L</td></tr>
<tr><td>LLOQ</td><td>0.1 and 0.01 µg/ml</td><td>0.005 and 0.1 ng/ml</td></tr>
<tr><td>QCs</td><td>0.3, 3.75, 20 and
0.0250, 0.500, 2.50</td><td>0.0100, 0.250, 0.500 E and
of 0.250, 10.0, 20.0 L</td></tr>
<tr><td>Interday precision</td><td>% CV <22.38 and < 10.25</td><td>% CV <5.55 E
% CV <6.93 L</td></tr>
</table></td></tr>
<tr><td>PK Assessment</td><td>Ethinylestradiol and levonorgestrel: Cmax, AUC, Tmax</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic Results:</td><td>TERIFLUNOMIDE + ORAL CONTRACEPTIVE</td></tr>
<tr><td colspan="2">Subject 1030 did not receive the planned teriflunomide dose of 14 mg on Day 15 in Period 2, but received 28 mg of teriflunomide (instead of 14 mg) on Day 16 in Period 2. This subject was included in the PK population since teriflunomide predose concentration in this subject (47.4 µg/mL) on Day 21 in Period 2 when Minidril® was coadministered was in the range of the concentrations observed in the rest of the subjects (25.3-59.8 µg/mL).

Ethinylestradiol:
Mean ± SD (Geometric Mean) [CV%] of ethinylestradiol pharmacokinetic parameters on Day</td></tr>
</table>

21

PK parameter	Minidril® alone	Minidril® + Teriflunomide
N	24	22
C_{max}	0.0785 ± 0.0198	0.124 ± 0.0389
(ng/mL)	(0.0763) [25.2]	(0.120) [31.3]
t_{max}[a]	3.54	3.00
(h)	(1.50 - 6.00)	(0.50 - 6.07)
AUC_{0-24}	1.02 ± 0.299	1.59 ± 0.498
(ng•h/mL)	(0.986) [29.3]	(1.52) [31.4]

[a] Median (Min - Max)

Estimates of treatment ratios with 90% CIs – ethinylestradiol

Parameter	Comparison	Estimate	90% CI
C_{max}	Minidril® + teriflunomide vs. Minidril® alone	1.58	(1.48 to 1.68)
AUC_{0-24}	Minidril® + teriflunomide vs. Minidril® alone	1.54	(1.46 to 1.63)

Levonorgestrel

Mean ± SD (Geometric Mean) [CV%] of levonorgestrel pharmacokinetic parameters on Day 21

Parameter	Minidril® alone	Minidril® + Teriflunomide
N	24	22
C_{max}	7.23 ± 1.30	9.60 ± 2.10
(ng/mL)	(7.12) [18.0]	(9.39) [21.9]
t_{max}[a]	3.00	2.00
(h)	(1.00 - 6.00)	(0.50 - 4.05)
AUC_{0-24}	108 ± 24.7	151 ± 36.0
(ng•h/mL)	(106) [22.8]	(148) [23.8]

[a] Median (Min - Max)

Table - Estimates of treatment ratios with 90% CIs – levonorgestrel

Parameter	Comparison	Estimate	90% CI
C_{max}	Minidril® + teriflunomide vs. Minidril® alone	1.33	(1.24 to 1.42)
AUC_{0-24}	Minidril® + teriflunomide vs. Minidril® alone	1.41	(1.34 to 1.49)

The 90% CIs for both ethinylestradiol and levonorgestrel AUC0-24 ratios were entirely outside the protocol-specified boundaries of 0.80-1.25, indicating a pharmacokinetic interaction with teriflunomide. Stick plots showed that all subjects showed an increase in

Reference ID: 3151674

AUC and Cmax of ethinylestradiol and levonorgestral upon coadministration with teriflunomide.

Teriflunomide:

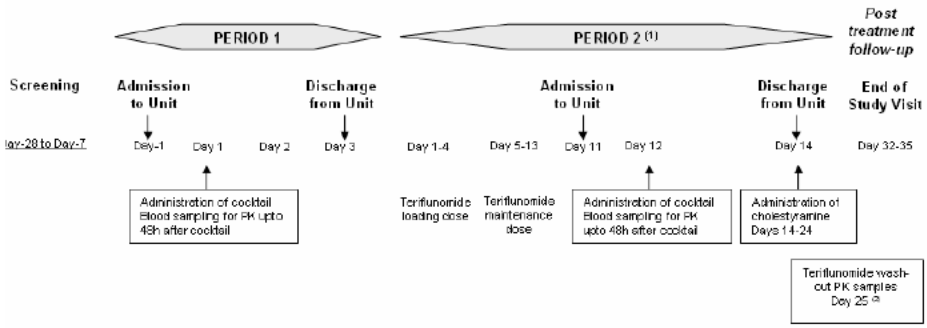
Mean ± SD (Geometric Mean) [CV%] of teriflunomide pharmacokinetic parameters on Day 21

Parameter	Minidril® + Teriflunomide
N	22
C_{max}	46.3 ± 10.2
(µg/mL)	(45.2) [22.0]
t_{max}[a]	12.0
(h)	(0.00 - 24.1)
AUC_{0-24}	983 ± 214
(µg•h/mL)	(961) [21.8]
C_{trough}	41.3 ± 9.96
(µg/mL)	(40.2) [24.1]

[a] Median (Min - Max)

Safety	There were 5 subjects who had asymptomatic ALT increased (declared as TEAE when >2ULN) during the study: one subject (Subject No. 1030) during the teriflunomide + Minidril® period, 2 subjects (Subject No. 250001009 and 250001015) in the "cholestyramine after Minidril® + teriflunomide" treatment period, and 2 subjects (Subject No. 1021 and 1004) in the cholestyramine + Minidril® treatment.
Conclusion	Teriflunomide administration of 70 mg once a day for 4 days followed by 14 mg once a day for 10 days orally resulted in an increase in ethinylestradiol and levonorgestrel exposure after administration of repeated doses of Minidril® (containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel). • Cmax increased on average of 1.58-fold for ethinylestradiol and 1.33- fold for levonorgestrel. • AUC0-24 increased on average of 1.54-fold for ethinylestradiol and 1.41-fold) for levonorgestrel.
Dosage Adjustment	Caution towards type and dose of oral contraceptives.

Best Available Copy

Study INT10564	**An open label, single sequence, two period crossover study to assess the effect of repeated doses of teriflunomide (HMR1726) upon the single dose pharmacokinetics of caffeine, omeprazole and metoprolol given as a cocktail as probe substrates for CYP1A2, CYP2C19 and CYP2D6 activities, respectively, in healthy male subjects**
Rationale	To investigate the effect of repeated doses of teriflunomide upon the pharmacokinetics (PK) of caffeine, omeprazole and metoprolol used as probe substrates for their respective CYP1A2, CYP2C19 and CYP2D6 activities.
Study Design	
Study Population	N=36 Healthy subjects excluding poor metabolizers of 2C19, 2D6. treatment A=24; treatment B =23 (Two subjects out of the 36 included discontinued the study, one after receiving the cocktail in Period 1 (consent withdrawn due to personal reason) and one was withdrawn during teriflunomide treatment due to urticaria.) Age: 18-45 years Gender: All males Race: 32 White, 3 Black and 1 Asian
Treatment Groups	Treatment A: Teriflunomie to steady state Treatment B: Caffeine or Omeprazole or Metoprolol single dose
Dosage and Administration	Treatment A: Dose: 70 mg (5 x 14 mg tablets) dose once daily for 4 days followed by doses of 14 mg (1 tablet) once daily for 9 days in Period 2 Administration: Oral route in fed condition (except on Day 12 when given fasted with the cocktail probes) Batch number: FRA-01179 Treatment B: Caffeine: single dose of 100 mg on Day 1 in Period 1 and Day 12 in Period 2 Omeprazole: single dose of 20 mg on Day 1 in Period 1 and Day 12 in Period 2 Metoprolol: single dose of 100 mg on Day 1 in Period 1 and Day 12 in

<table>
<tr><td></td><td>Period 2

Administration: Caffeine: Oral route in fasted condition
Omeprazole: Oral route in fasted condition
Metoprolol: Oral route in fasted condition

<u>Cholestyramine:</u> 4 g, 3 times a day for 11 days: Day 22</td></tr>
<tr><td>Sampling: Blood</td><td><u>For plasma teriflunomide concentrations:</u>
Plasma samples were collected at predose on Day 1, 10, 11, 12, 13 and 14 of Period 2. An additional sample was collected at Day 25 after the washout procedure

<u>For plasma cocktail probe drugs:</u>
At predose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24 and 48 hours following cocktail administration on Day 1 of Period 1 and on Day 12 of Period 2</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td><u>Plasma HMR1726 and probe drugs:</u>
<table>
<tr><td></td><td>HMR1726</td><td>Probe drugs
Caffeine (C), paraxanthine (P), omeprazole (O), metoprolol (M)</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range</td><td>0.1-100 and
0.01-1 µg/ml</td><td>25.0 to 20000 ng/mL C P
5.00 to 2500 ng/mL O M</td></tr>
<tr><td>LLOQ</td><td>0.1 and 0.01</td><td>25, 25, 5, 5 ng/ml resp.</td></tr>
<tr><td>QCs</td><td>0.3, 3.75, 20, 75 and
0.0250, 0.500, 2.50</td><td>75.0, 500, 4000, and 15000 C P
15.0, 60.0, 200, and 1880 O M</td></tr>
<tr><td>Interday precision</td><td>% CV <8.92</td><td>% CV <8.6 % C P
% CV <9.3% O M</td></tr>
</table></td></tr>
<tr><td>PK Assessment</td><td>Cmax, AUC, Tmax, t1/2</td></tr>
<tr><td>Safety Assessment</td><td>Vital signs, ECG , Clinical laboratory, AEs</td></tr>
<tr><td>PD Assessment</td><td>none</td></tr>
<tr><td>Pharmacokinetic Results:</td><td>TERIFLUNOMIDE
+
CAFFIENE, OMEPRAZOLE, METAPROLOL</td></tr>
</table>

Reference ID: 3151674

Trough concentrations of teriflunomide showed that steady state had reached.
The PK parameters of cocktail probes/analytes were summarized as below:

Mean ± SD (Geometric Mean) [CV%] of caffeine pharmacokinetic parameters

PK parameter	Cocktail alone (N= 36)	Teriflunomide + Cocktail (N= 34)
C_{max} (ng/mL)	2210 ± 366 (2180) [16.5]	1820 ± 403 (1780) [22.1]
t_{max} [a] (h)	1.00 (0.50 – 2.00)	0.50 (0.47 – 2.00)
AUC_{last} (ng.h/mL)	18900± 7520 (17500) [39.8]	8580 ± 4010 (7910) [46.8]
AUC (ng.h/mL)	19900 ± 8110 (18500) [40.7]	8930 ± 4160 (8220) [46.5]
$t_{1/2z}$ (h)	5.45 ± 2.43 (5.04) [44.7]	2.65 ± 0.794 (2.55) [29.9]

Mean ± SD (Geometric Mean) [CV%] of paraxanthine pharmacokinetic parameters

PK parameter	Cocktail alone (N= 36)	Teriflunomide + Cocktail (N= 34)
C_{max} (ng/mL)	623 ± 88.3 (616) [14.2]	658 ± 79.3 (653) [12.1]
t_{max} [a] (h)	7.00 (1.00 – 12.00)	3.00 (1.00 – 8.00)
AUC_{last} (ng.h/mL)	11000 ± 2820 (10700) [25.7]	6540 ± 1930 (6280) [29.5]
AUC (ng.h/mL)	12100 ± 3240 (11700) [26.7]	7080± 1920 (6850) [27.1]
$t_{1/2z}$ (h)	8.69 ± 2.87 (8.21) [33.0]	4.69 ± 2.64 (4.27) [56.4]

Mean ± SD (Geometric Mean) [CV%] of omeprazole pharmacokinetic parameters

PK parameter	Cocktail alone (N=36)	Teriflunomide + Cocktail (N=34)
C_{max} (ng/mL)	193 ± 132 (160) [68.7]	188 ± 113 (154) [60.2]
t_{max} [a] (h)	2.00 (1.00 – 5.00)	2.00 (0.92 – 4.00)
AUC_{last} (ng.h/mL)	425 ± 333 (330) [78.2]	394 ± 311 (302) [78.9]
AUC (ng.h/mL)	458 ± 337 (371) [73.6]	418 ± 315 (330) [75.3]
$t_{1/2z}$ (h)	0.876 ± 0.305 (0.835) [34.8]	0.825 ± 0.217 (0.800) [26.4]

Reference ID: 3151674

Mean ± SD (Geometric Mean) [CV%] of metoprolol pharmacokinetic parameters

PK parameter	Cocktail alone (N=36)	Teriflunomide + Cocktail (N=34)
C_{max} (ng/mL)	103 ± 44.0 (91.6) [42.7]	107 ± 53.6 (94.6) [50.1]
t_{max} [a] (h)	2.00 (1.00 – 4.00)	2.00 (0.50 – 4.00)
AUC_{last} (ng.h/mL)	636 ± 405 (515) [63.7]	603 ± 447 (482) [74.1]
AUC (ng.h/mL)	721 ± 422 (612) [58.6] [b]	681 ± 478 (556) [70.2] [b]
$t_{1/2z}$ (h)	3.41 ± 1.04 (3.28) [30.6]	3.30 ± 0.826 (3.21) [25.1]

Treatment ratio estimates with 90% CI (teriflunomide + cocktail vs. cocktail alone) for probe drugs/analyte

Drug	Comparison	Parameter	Estimate	90% CI
Caffeine	Teriflunomide + Cocktail /Cocktail	C_{max}	0.82	(0.77 to 0.87)
	Teriflunomide + Cocktail/ Cocktail	AUC_{last}	0.45	(0.41 to 0.50)
	Teriflunomide + Cocktail/ Cocktail	AUC	0.45	(0.40 to 0.50)
Paraxanthine	Teriflunomide + Cocktail/ Cocktail	C_{max}	1.06	(1.03 to 1.10)
	Teriflunomide + Cocktail/ Cocktail	AUC_{last}	0.59	(0.55 to 0.63)
	Teriflunomide + Cocktail/ Cocktail	AUC	0.58	(0.55 to 0.63)
Metoprolol	Teriflunomide + Cocktail/ Cocktail	C_{max}	1.06	(0.97 to 1.17)
	Teriflunomide + Cocktail/ Cocktail	AUC_{last}	0.98	(0.91 to 1.05)
	Teriflunomide + Cocktail/ Cocktail	AUC	0.99	(0.91 to 1.06)
Omeprazole	Teriflunomide + Cocktail/ Cocktail	C_{max}	0.93	(0.82 to 1.05)
	Teriflunomide + Cocktail/ Cocktail	AUC_{last}	0.87	(0.79 to 0.95)
	Teriflunomide + Cocktail/ Cocktail	AUC	0.90	(0.82 to 0.98)

Safety	ALT>5 ULN was seen in the cholestyramine after the teriflunomide phase in 1 subjects and >3ULN in 4 subjects.
Conclusion	The current study of coadministration of repeated doses of teriflunomide with a single dose cocktail containing caffeine (100 mg), omeprazole (20 mg) and metoprolol (100 mg) resulted in the following conclusions: • geometric mean AUC of caffeine decreased by 55 % after a single dose of caffeine and AUC of paraxanthine decreased by 41% • no effect on the geometric mean AUC of omeprazole after a single dose of omeprazole • no effect on the geometric mean AUC of metoprolol
Dosage Adjustment	Monitor with concomitant use of drugs metabolized by CYP1A2 as there may be reduced efficacy

INTRINSIC FACTORS

<table>
<tr><td>Study POP11432</td><td>An open-label pharmacokinetic and tolerability study of teriflunomide given as a single 14 mg dose in subjects with severe renal impairment, and in matched subjects with normal renal function</td></tr>
<tr><td>Rationale</td><td>Contribution of renal elimination of unchanged teriflunomide in the overall compound clearance is small. However, in patients with renal impairment, even when a low percentage of the drug is excreted by renal route as unchanged, the pharmacokinetics (PK) of the drug may be modified. This could be due to the decrease of protein binding (ie, corresponding increase of the drug free fraction) and/or other factors. Renal impairment may also adversely affect the hepatic metabolism of drugs and thus their exposure. In particular, uremia may affect some specific pathway of hepatic/gut metabolism to a significant extent.</td></tr>
<tr><td>Study Design</td><td>Single-center, open-label, single oral dose study</td></tr>
<tr><td>Study Population</td><td>N=8 Severe RI and 8 healthy
Gender: males (age 18-75) post menopausal females (Age 45-75)
Race: 32 White, 3 Black and 1 Asian</td></tr>
<tr><td>Treatment Groups</td><td>Group 1: Severe RI (CrCL <30 mL/min, not requiring dialysis)
(MDRD: GFR 15-29 mL/min/1.73m^2)
$GFR = 186 \times (sCr)^{-1.154} \times (age)^{-0.203} \times (1.212\ if\ black) \times (0.742\ if\ female)$
Group 2: Healthy Subjects</td></tr>
<tr><td>Dosage and Administration</td><td>Teriflunomide Dose: 14 mg single dose
Administration: Oral, fasting
Batch number: FRA - 01179

<u>Cholestyramine:</u> 4 g, 3 times a day for at least 2 days</td></tr>
<tr><td>Sampling: Blood</td><td><u>For plasma teriflunomide concentrations:</u>
At predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 120, 168, 312, 480, 984, and 1272 hours after dose.

Additionally at predose and at 2 and 24 hours after dose for unbound drug concentrations following protein binding assessment by equilibrium dialysis</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td><u>Plasma HMR1726:</u>
<table>
<tr><td></td><td>HMR1726</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range µg/ml</td><td>0.01-3</td></tr>
<tr><td>LLOQ µg/ml</td><td>0.1 and 0.01</td></tr>
<tr><td>QCs µg/ml</td><td>0.00025, 0.01 and 0.04</td></tr>
</table></td></tr>
</table>

Reference ID: 3151674

		0.0250, 0.500 and 2.50
	Interday precision	% CV < 8.33 and <6.64%
PK Assessment	Cmax, AUClast, AUC, unbound Cmax (Cmax,u) and unbound AUC (AUCu), t1/2 eff (effective half life) and Rac, pred (predicted accumulation ratio)	
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs	
PD Assessment	none	
Pharmacokinetic Results:	**SEVERE RENAL IMPAIRMENT**	

Pharmacokinetic parameters were similar between SRI subjects and matched subjects with normal renal function after a 14 mg single dose.

Mean ± SD (Geometric Mean) [CV%] of teriflunomide PK parameters

	Severe Renal Impairment (N=8)	Healthy (N=8)
C_{max}	1.57 ± 0.137	1.33 ± 0.225
(µg/mL)	(1.56) [8.7]	(1.32) [16.9]
t_{max}	2.00	1.75
(h)	(0.50 - 48.07)	(1.00 - 4.00)
$t_{1/2z}$	297 ± 121	306 ± 77.4
(h)	(274) [40.7]	(296) [25.3]
AUC_{last}	480 ± 195	456 ± 130
(h•µg/mL)	(440) [40.6]	(438) [28.5]
AUC	525 ± 242	495 ± 162
(h•µg/mL)	(472) [46.0]	(470) [32.8]
CL/F	33.6 ± 19.8	31.5 ± 11.9
(mL/h)	(29.6) [59.0]	(29.8) [37.7]
Vss/F	11.3 ± 2.00	12.5 ± 1.48
(L)	(11.1) [17.8]	(12.4) [11.9]
$t_{1/2eff}$	315 ± 185	314 ± 94.8
(h)	(273) [58.8]	(302) [30.2]
$R_{ac,pred}$	19.4 ± 11.1	19.4 ± 5.70
	(17.0) [57.2]	(18.7) [29.4]

Estimates of group ratio with 90% CI for teriflunomide (based on C-G)

Comparison	Parameter	Estimate	90% CI
Severe Renal Impairment vs. Healthy	C_{max}	1.16	(0.97 to 1.39)

	AUC_{last}	1.02	(0.63 to 1.66)
	AUC	1.03	(0.61 to 1.74)
	$t_{1/2z}$	0.99	(0.65 to 1.52)
	CL/F	0.97	(0.57 to 1.64)
	Unbound C_{max}	1.15	(0.93 to 1.42)
	Unbound AUC_{last}	1.01	(0.64 to 1.60)
	Unbound AUC	1.02	(0.62 to 1.66)

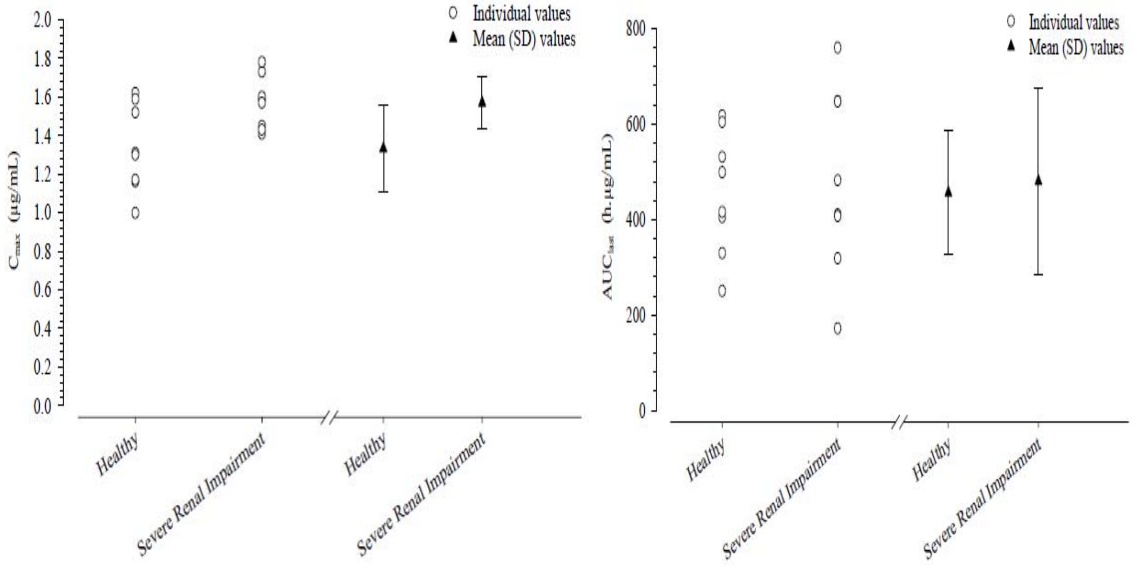
The fraction unbound in healthy subjects (0.25%) was similar to that in patients with severe renal impairment (0.25%).

Estimates of group ratio with 90% CI for teriflunomide (based on MDRD)

Comparison	Parameter	Estimate	90% CI
Severe Renal Impairment vs. Healthy	C_{max}	1.13	(0.98 to 1.46)
	AUC_{last}	0.76	(0.40 to 1.44)
	AUC	0.72	(0.36 to 1.41)
	$t_{1/2z}$	0.75	(0.0.53 to 1.30)
	CL/F	1.38	(0.71 to 2.7)
	Unbound C_{max}	1.21	(0.90 to 1.62)
	Unbound AUC_{last}	0.81	(0.44 to 1.50)
	Unbound AUC	0.77	(0.40 to 1.46)

Individual and Mean parameters are shown in the following Figure (C-G):

Best Available Copy



Comment: The effective half life and predicted accumulation ratio is similar in both severe renal impaired group and the healthy subjects. Hence, significant changes in steady exposure are not expected in the severe renal impaired group.

There was one subject (#1007) in the severe group that had a different profile with drug

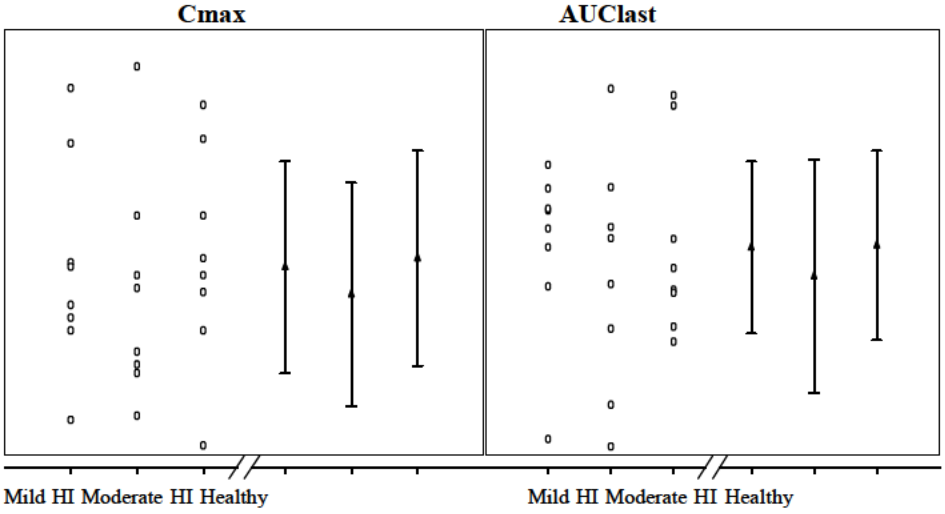
peaking at 48 hours and AUC higher than the rest of the population (917 µg.h/ml). This subject was on Actrapid, Protophan, ASS100, Simvastain, Bondiol, Allopurinol, Bisoprlol, Telmisartan (Micardis). This subject also had a high predicted accumulation ratio of 42.34. This subject did not have any significant AE (note: simvastatin is an OATP1B1 substrate). AUC of 745 µg.h/ml was the second highest AUC observed. Subject #1003 in the severe group had the lowest AUC (181 µg.h/ml). This subject was on Pravastatin. No obvious relationship was found in either case. (note: pravastatin is an OATP1B1 substrate).	
Safety	Between the 2 population groups (SRI or healthy subjects), no clinically meaningful differences in categories, intensity or incidence of AEs were observed during the teriflunomide alone period. An increase in gastrointestinal disorders (abdominal pain upper, nausea, vomiting) was noticeable in SRI subjects during the cholestyramine after teriflunomide period compared to that during teriflunomide alone (5/8 versus 1/8).
Conclusion	Pharmacokinetic parameters were similar between SRI subjects and matched subjects with normal renal function after a single oral dose of teriflunomide at 14 mg. High variability was observed, as seen by the 90% confidence intervals for the PK parameters. Note: Patients with moderate and severe renal impairment were excluded from the Phase 2 and 3 studies.
Dosage Adjustment	none

Study POP6505	**An open-label study on the pharmacokinetics and tolerability of a 14-mg single dose of Teriflunomide in male and post-menopausal female subjects with mild and moderate hepatic impairment and in matched subjects with normal hepatic function**
Rationale	Since HMR1726 is metabolized moderately in the liver, excreted via bile, undergoes enterohepatic recycling, and is highly bound to plasma protein, this study was designed to investigate the pharmacokinetics of HMR1726 in subjects with hepatic impairment compared with the matched healthy subjects in the same study.
Study Design	Open-label, single-dose, parallel design in 3 groups of subjects
Study Population	Planned: 24 subjects (8 subjects in each group) Included: 25 subjects (mild HI: 9; moderate HI: 8, and healthy subjects: 8) Gender: 19 males (25-6 yrs) and 6 post menopausal females(up to 65 yrs) Race: All White
Treatment Groups	Group 1: mild HI (Child-Pugh rating score 5-6) Group 2: moderate HI (Child-Pugh rating score 7-9) Group 3: Healthy subjects with normal hepatic function, sex, age, and weight globally matched (Comment: Individual subject Child Pugh Scores not provided, since there was no significant effect, this information was not requested from the sponsor)
Dosage and Administration	Teriflunomide: One single dose of 14 mg at Day 1 Administration: Oral Batch number(s): FRA-0436 Activated Charcoal: 50 g, 4 times daily for 2 days (Day 54 and Day 55) to accelerate the elimination of HMR1726 after the last pharmacokinetic blood sample collection at Day 54. If necessary, in case the HMR1726 concentration after charcoal treatment was still >0.02 µg/mL, additional charcoal treatment could be given (cholestyramine is contraindicated in hepatic impairment)
Sampling: Blood	For plasma teriflunomide concentrations: At predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 120, 168, 312, 480, 984, and 1272 hours after dose. Additionally at predose and at 1, 1.5, 2, 3, 8, and 24 hours after dose for unbound drug concentrations following protein binding assessment by equilibrium dialysis
Urine	none
Feces	none
Analysis	Plasma HMR1726:

Reference ID: 3151674

	HMR1726 Method: LC/MS/MS Linear Range: 0.01-1 µg/ml LLOQ (µg/ml): 0.1 and 0.01 QCs (µg/ml): 0.025, 0.10, and 4.0 Interday precision: % CV < 5.09 and <6.72
PK Assessment	Cmax, AUClast, AUC, unbound Cmax (Cmax,u) and unbound AUC (AUCu), t1/2 eff (effective half life) and Rac, pred (predicted accumulation ratio)
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs, Given the risk of hepatic toxicity with HMR1726, ALT was regularly monitored.
PD Assessment	none
Pharmacokinetic Results:	**MILD AND MODERATE HEPATIC IMPAIRMENT**

Individual and mean (standard deviation) Cmax and AUClast values of HMR1726 after a single oral dose of 14 mg



HMR1726 pharmacokinetics parameters (total and unbound) after a single oral dose of 14 mg HMR1726

parameter	Mild HI (N = 8)	Moderate HI (N = 8)	Healthy (N = 8)
C_{max} (µg/mL)	1.64 ± 0.249 (15) [1.62]	1.58 ± 0.263 (17) [1.56]	1.66 ± 0.253 (15) [1.64]
t_{max} (h)	1.75 (0.50 , 2.50)	1.25 (0.50 , 8.00)	2.00 (1.00 , 4.00)
$t_{1/2z}$ (h)	259 ± 73.1 (28) [246]	239 ± 104 (44) [220]	261 ± 106 (41) [244]
AUC_{last} (µg.h/mL)	441 ± 141 (32) [407]	393 ± 192 (49) [343]	444 ± 156 (35) [422]
AUC (µg.h/mL)	463 ± 153 (33) [426]	418 ± 225 (54) [359]	471 ± 192 (41) [442]
CL/F (mL/h)	38.0 ± 28.6 (75) [32.9]	47.3 ± 35.0 (74) [39.0]	33.5 ± 11.1 (33) [31.7]
Vss/F (L)	11.2 ± 1.96 (17) [11.1]	11.9 ± 2.50 (21) [11.7]	10.9 ± 0.746 (7.0) [10.8]
fu (%)	0.28 ± 0.05 (18) [0.28]	0.26 ± 0.04 (14) [0.26]	0.27 ± 0.03 (9.9) [0.27]
$C_{max,u}$ (µg/mL)	0.00458 ± 0.000590 (13) [0.00455]	0.00414 ± 0.000770 (19) [0.00408]	0.00454 ± 0.000766 (17) [0.00448]
AUC_u (µg.h/mL)	1.26 ± 0.371 (29) [1.19]	1.06 ± 0.488 (46) [0.939]	1.29 ± 0.520 (40) [1.20]
$t_{1/2eff}$ (h)	248 ± 85.8 (35) [228]	256 ± 155 (61) [220]	269 ± 121 (45) [247]
$R_{ac,pred}$	15.4 ± 5.15 (33) [14.3]	15.9 ± 9.33 (59) [13.8]	16.7 ± 7.30 (44) [15.4]

	Mild HI/healthy (N = 8)		Moderate HI/healthy (N = 8)		Moderate HI/mild HI (N = 8)	
Parameter	Estimate	90%CI	Estimate	90%CI	Estimate	90%CI
C_{max}	0.99	(0.88-1.12)	0.95	(0.84-1.07)	0.96	(0.85-1.08)
AUC_{last}	0.97	(0.65-1.44)	0.82	(0.55-1.22)	0.85	(0.57-1.25)
AUC	0.97	(0.64-1.46)	0.82	(0.55-1.23)	0.85	(0.56-1.27)
$C_{max,u}$	1.01	(0.89-1.14)	0.90	(0.80-1.03)	0.90	(0.79-1.02)
AUC_u	0.99	(0.69-1.42)	0.78	(0.55-1.12)	0.79	(0.55-1.14)
$t_{1/2z}$	1.00	(0.74-1.36)	0.90	(0.66-1.22)	0.90	(0.66-1.22)
$t_{1/2eff}$	0.92	(0.62-1.35)	0.90	(0.61-1.32)	0.98	(0.66-1.44)

Safety	Treatment emergent adverse event were reported in 7 of 9 subjects with mild HI (headache in 4 subjects, ALT increased, dry mouth, pharyngitis, periondontitis, and radiculitis in 1 subject each), in 3 of 8 subjects with moderate HI (nasopharyngitis in 1 subject and headache in 2 subjects),

	and in 2 of 8 healthy subjects (headache in 2 subjects)
Conclusion	Pharmacokinetics of HMR1726 (total and unbound) in the subjects with mild and moderate HI were not appreciably different from that observed in healthy subjects.
Dosage Adjustment	None for mild and moderate. Use in severe hepatic impaired is not recommended.

Appears This Way On Original

7 pages of the Duplicate Clinical Pharmacology and Biopharmaceutics Filing Checklist dated 9/28/11 have been Withheld in Full immediately following this page, and can be found in this review

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VENEETA TANDON
06/27/2012

JOO YEON LEE
06/27/2012

JEFFREY B KRAFT
07/01/2012

YANING WANG
07/02/2012

MICHAEL A PACANOWSKI
07/02/2012

YUXIN MEN
07/02/2012

MEHUL U MEHTA
07/03/2012

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	202-992/Original N-000
Submission Date:	08/12/11, 03/23/12, and 04/06/12
Brand Name:	Te be determined
Generic Name:	Teriflunomide Tablets
Formulation:	Immediate release (IR) film-coated oral tablets
Strength:	14 mg
Applicant:	Sanofi-Aventis
Type of submission:	NME (new molecular entity)
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Teriflunomide is the active, predominant metabolite of leflunomide (Arava®), which was approved in the US under NDA 20-905 on 09/10/98 for oral treatment of rheumatoid arthritis (RA).

Teriflunomide is an NME reported as a novel immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for de novo pyrimidine synthesis. The proposed indication for teriflunomide is as a monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (relapsing MS (b) (4) .

Current Submission

On 08/12/11, Sanofi-Aventis submitted NDA 202-992/N-000 for teriflunomide IR 14 mg tablets. Two dosage strengths of final formulation, 7 and 14 mg, were developed and tested in the pivotal clinical trials. They have the same qualitative composition with exception of the shapes and colorant. (b) (4) The commercial drug products for both dosage strengths, 7 and 14 mg film-coated tablets are submitted. However, only a single strength, 14 mg, is proposed for marketing. On 03/23/12, the Applicant responded to the Agency's information request dated 03/16/12.

Biopharmaceutics Review

The Biopharmaceutics review is focused on the evaluation and approvability of the dissolution development report and proposed dissolution method and acceptance criterion.

Based on the review of the overall dissolution information/data for both, the 7 and 14 mg of teriflunomide IR tablets the proposed dissolution method is adequate and acceptable. However, the dissolution profile data clearly showed that (b) (4) of teriflunomide is dissolved in 20 min, thus the proposed acceptance criterion of Q= (b) (4) at 30 min is not appropriate.

On 03/16/12, an information request was conveyed to the Applicant asking for the revision of the dissolution acceptance criterion to Q= (b) (4) at 20 min. In their response they proposed keeping their original Q= (b) (4) at 30 min proposal. However, the Agency

Reference ID: 3115241

did not accept this proposal and recommended that the dissolution acceptance criterion for teriflunomide 14 mg IR tablets be revised from Q= (b) (4) at 30 min to Q= (b) (4) at 30 min. The following comments were conveyed to the Applicant on 03/30/12.

> *The proposed dissolution acceptance criterion of "Q = (b) (4) in 30 minutes" for teriflunomide tablets is not supported by the provided dissolution data. The provided data from the clinical, stability, and commercial batches clearly indicate that a mean amount dissolved of at least (b) (4) is achieved in 20 minutes. However, we acknowledge that several batches may require Stage 2 or Stage 3 testing at the 20 minutes timepoint; therefore, we are willing to accept a criterion of Q = (b) (4) at 30 minutes for your product. Nevertheless, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing.*
>
> *Accordingly, please revise the dissolution acceptance criterion for Teriflunomide IR 14 mg tablets to ' (b) (4) in 30 minutes" and provide the revised specification table for your teriflunomide film-coated 14 mg tablet drug product.*

On 04/06/12, the Applicant accepted the revision of the dissolution acceptance criterion for teriflunomide 14 mg tablets to "Q = (b) (4) in 30 minutes" for release and stability testing. Please note that in their response the Applicant mentioned that the dissolution acceptance criterion for teriflunomide film-coated tablets 7 mg will also be revised to "Q = (b) (4) in 30 minutes" for consistency.

RECOMMENDATION

ONDQA-Biopharmaceutics has evaluated the overall dissolution information/data and considers that the following dissolution method and acceptance criterion are acceptable.

Dissolution Method and Acceptance Criterion for Teriflunomide IR Tablets					
USP Apparatus	**Spindle Rotation**	**Medium Volume**	**Temperature**	**Medium**	**Acceptance Criterion**
Type 2 (Paddle)	50 rpm	1000 mL	37°C ± 0.5°C	Phosphate Buffer pH 6.8	Q = (b) (4) at 30 minutes

From the Biopharmaceutics perspective, Original NDA 202-992 for teriflunomide IR Tablets is recommended for approval.

Tien-Mien Chen, Ph.D.
ONDQA Biopharmaceutics Reviewer

04/06/12
Date

Angelica Dorantes, Ph.D.
ONDQA Biopharmaceutics Supervisory Lead (acting)

04/06/12
Date

CC: DARRTS/NDA202-992/Original N-000

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Teriflunomide (an NME) is the active, predominant metabolite of leflunomide (Arava®), which was approved in the US under NDA 20-905 on 09/10/98 for oral treatment of rheumatoid arthritis (RA).

Teriflunomide is reportedly a novel immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for de novo pyrimidine synthesis. Teriflunomide does not affect pyrimidine synthesis that occurs via salvage pathway that is used predominantly by resting or slowly dividing cells.

The proposed indication for teriflunomide is as a monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (relapsing MS (b) (4) The proposed recommended dose is 14 mg administered orally once daily, with or without food.

CURRENT SUBMISSION

On 08/12/11, Sanofi-Aventis submitted NDA 202-992/N-000 for teriflunomide IR 14 mg tablets. Two dosage strengths of the final formulation, 7 and 14 mg, were developed and were all investigated in pivotal clinical trials. Later, the clinical phase-3 formulations (No. 5) were modified to commercial formulation with development image (No. 6; different shapes) for stability testing. The formulation No. 6 is further modified to the commercial formulation with final image (No. 7; with different shape, curvature, and logo engravings).

The Applicant reported that 1). The qualitative composition of both dosage strengths is the same, with exception of the shape and colorant and 2). The manufacturing process is the same for both strengths. A single strength, 14 mg, is proposed for marketing, however, the commercial drug products for both dosage strengths, 7 and 14 mg film-coated tablets, are described in the dossier for review. On 03/23/12, the Applicant responded to the Agency's information request dated 03/16/12.

BIOPHARMACEUTICS REVIEW

The ONDQA/Biopharmaceutics review is focused on the evaluation and acceptability of the information/data supporting the dissolution development report, proposed dissolution method and the acceptance criterion.

FORMULATION COMPARISONS

The clinical Phase-3 and the commercial formulations are the same except some minor differences in shape, coating agent, and colorant. The composition/formulation of the 7 and 14 mg teriflunomide IR tablets is shown below.

Reference ID: 3115241

Table 1. Composition of Clinical and Commercial 7 mg Teriflunomide Film-Coated Tablets

Components [a]	Composition per film-coated tablet				Function	Reference to standards [b]
	Current clinical formulation		Commercial formulation			
	[%]	[mg]	[%]	[mg]		
Tablet core						
Teriflunomide	(b) (4)	7.00	(b) (4)	7.00	Drug substance	In-house
Lactose monohydrate	(b) (4)					Ph. Eur. [c], NF [c]
Maize starch						Ph. Eur.,
[Corn starch]						NF
Hydroxypropyl cellulose						Ph. Eur., NF
Microcrystalline cellulose						Ph. Eur., NF
Sodium starch glycolate (b) (4)						Ph. Eur.,
[Sodium starch glycolate]						NF
Magnesium stearate						Ph. Eur., NF
(b) (4)						
Film-coating						In-house [d]
Hypromellose [e]	(b) (4)					Ph. Eur., USP [c]
Titanium dioxide (b) (4)						Ph. Eur., USP
(b) (4)						
Talc [e]						Ph. Eur., USP
Macrogol [e]						Ph. Eur.,
[Polyethylene glycol]						NF
Indigo carmine aluminum lake (b) (4)						(b) (4)
[FD&C Blue #2], (b) (4)						
Ferric oxide [e]						
[Iron oxide yellow (b) (4)						
(b) (4)						
Mass of film-coated tablet	100	155.00	100	155.00		
Process aid						
(b) (4)						

a Components are listed according to their pharmacopoeial names. If more than one monograph exists, other names are given in brackets, along with the compendial reference.

b Reference is made to the current edition of the Pharmacopoeia.

c Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia; NF = National Formulary

d (b) (4)

e

f EC = European Commission

g CFR = Code for Federal Regulations (of the United States)

Table 2. Composition of Clinical and Commercial 14 mg Teriflunomide Film-Coated Tablets

Components [a]	Composition per film-coated tablet				Function	Reference to standards [b]
	Current clinical formulation		Commercial formulation			
	[%]	[mg]	[%]	[mg]		
Tablet core						
Teriflunomide	(b) (4)	14.00	(b) (4)	14.00	Drug substance	In-house
Lactose monohydrate	(b) (4)					Ph. Eur. [c], NF [c]
Maize starch [Corn starch]						Ph. Eur., NF
Hydroxypropyl cellulose						Ph. Eur., NF
Microcrystalline cellulose						Ph. Eur., NF
Sodium starch glycolate (b) (4) [Sodium starch glycolate]						Ph. Eur., NF
Magnesium stearate						Ph. Eur., NF
Mass of tablet core						
Film-coating						In-house [d]
Hypromellose [e]	(b) (4)					Ph. Eur., USP [c]
Titanium dioxide (b) (4) (b) (4)						Ph. Eur., USP
Talc [e]						Ph. Eur., USP
Macrogol [e] [Polyethylene glycol]						Ph. Eur., NF
Indigo carmine aluminum lake (b) (4) [FD&C Blue #2], (b) (4) [e]						(b) (4)
(b) (4)						
Mass of film-coated tablet	100	155.00	100	155.00		
Process aid						
(b) (4)						

a Components are listed according to their pharmacopoeial names. If more than one monograph exists, other names are given in brackets, along with the compendial reference.

b Reference is made to the current edition of the Pharmacopoeia.

c Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia; NF = National Formulary

d (b) (4)

e

f EC = European Commission

g CFR = Code for Federal Regulations (of the United States)

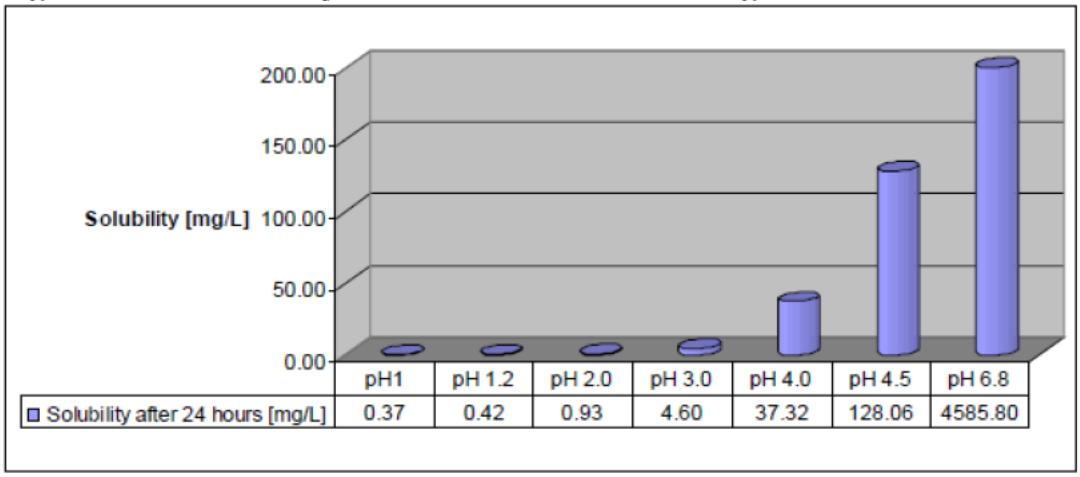
DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

The Applicant reported that

- According to the biopharmaceutical classification system (BCS), teriflunomide is considered as BCS class II compound; thus, comprising good permeability, but poor solubility.
- Teriflunomide is a weak acid with a pKa of 3.1 not displaying any polymorphic forms.

The solubility of teriflunomide drug substance in various pHs is shown below.

Figure 1. The Solubility Profile of Teriflunomide Drug Substance



The dissolution development report, which included comparative dissolution testing in (b) (4) were reviewed and found acceptable.

The Applicant's selected dissolution method and the proposed acceptance criterion are shown below.

USP Apparatus: **2 (Paddle) with 50 rpm**
Medium: **pH 6.8 Phosphate Buffer, 1000 mL at 37°C**
Acceptance Criterion: (b) (4) **at 30 min**

The following batches were employed in the comparative dissolution testing. A full production batch size is (b) (4)

Table 3. Clinical Batches (Formulation No. 5) used in the Comparative Dissolution Testing

Dosage strength	Drug product batch no.	Formulation number	Manufacturing		Batch size	Scale	Drug substance batch no.
			date	site			
7 mg	6J68	HMR1726/FT/00007/03/05	04-Oct-2006	(b) (4)		Production	W002 (0500024551)
14 mg	6J69	HMR1726/FT/00014/03/05	05-Oct-2006			Production	W002 (0500024551)

Best Available Copy

Best Available Copy

Table 4. Commercial Batches with Development Image (Formulation No. 6) used in the Comparative Dissolution Testing

Dosage strength	Drug product batch no.	Formulation number	Manufacturing		Batch size	Scale	Drug substance batch no.
			date	site			
7 mg	HMR1726_09_32	HMR1726/FT/00007/ 1766P01/06	09-Jan-2009	[redacted]	(b) (4)	Pilot	W003
14 mg	HMR1726_09_33	HMR1726/FT/00014/ 1766P01/06	12-Jan-2009			Pilot	W003

Table 5. Commercial Batches with Final Image (Formulation No. 7) used in the Comparative Dissolution Testing

Dosage strength	Drug product batch no.	Formulation number	Manufacturing		Batch size	Scale	Drug substance batch no.
			date	site			
7 mg	C1013560 (1A53)	HMR1726/FT/00007/ 1776P01/07	09-Feb-2011	[redacted]	(b) (4)	Production	0900082245
14 mg	C1013566 (1A56)	HMR1726/FT/00014/ 1776P01/07	15-Feb-2011			Production	0900082245

The comparative dissolution data/profiles are provided below which link the clinical Phase-3 formulation (No. 5) to the commercial formulation (No. 6) with development image (for stability studies), and to the commercial formulation with the final image (No. 7).

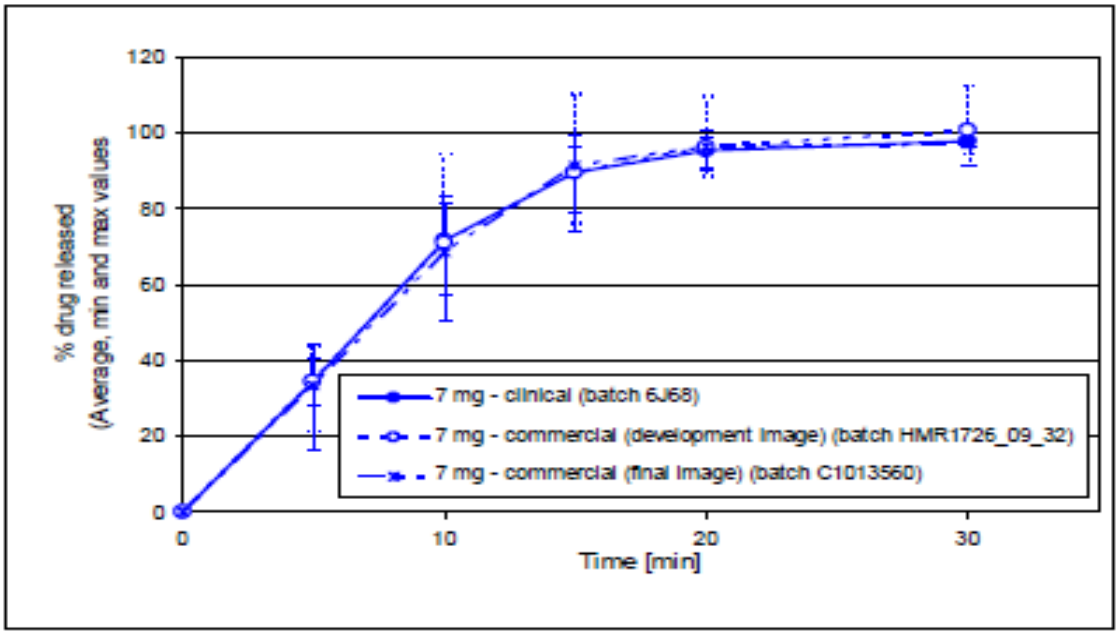
I. For Teriflunomide 7 mg IR Tablets

Table 6. Mean Dissolution Data of Teriflunomide IR 7 mg Tablets (n=12)

	7 mg tablet, clinical % drug released (n = 12)				7 mg tablet, commercial (development image) % drug released (n = 12)				7 mg tablet, commercial (final image) % drug released (n = 12)			
Sampling time [min]	Average	RSD	Min	Max	Average	RSD	Min	Max	Average	RSD	Min	Max
0	0	0.0	0	0	0	0.0	0	0	0	0.0	0	0
5	34	19.2	16	45	34	21.8	21	44	33	11.6	28	41
10	72	12.1	51	81	71	18.3	50	94	68	10.7	62	83
15	89	7.2	74	96	90	10.9	76	110	91	5.8	87	99
20	95	2.6	90	99	97	6.7	88	109	96	2.9	91	100
30	98	1.4	96	101	101	5.8	94	112	97	2.8	91	101

For teriflunomide 7 mg IR tablets, the values of similarity factor (f2) are calculated to be 94.5 (No. 6 vs. No. 5) and 77.4 (No. 7 vs. No. 5) indicating the formulation Nos. 6 and 7 are similar to formulation No. 5.

Figure 2. Mean Comparative Dissolution Profiles of Teriflunomide Film-Coated IR Tablets 7 mg Clinical and Commercial Formulations using the Proposed Dissolution Method



II. For Teriflunomide 14 mg IR Tablets:

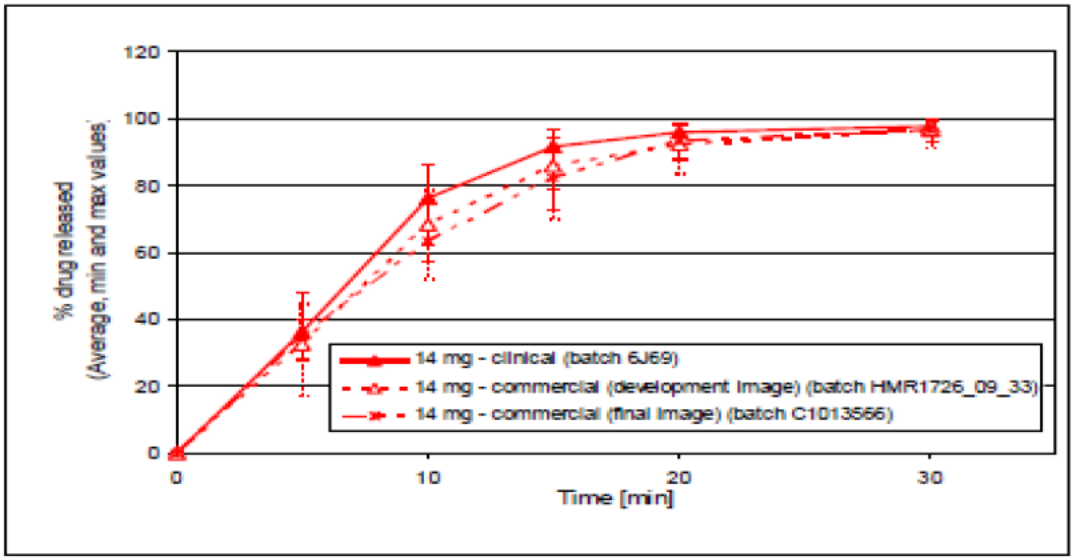
Table 7. Mean Dissolution Data of Teriflunomide IR 14 mg Tablets (n=12)

	14 mg tablet, clinical % drug released (n = 12)				14 mg tablet, commercial (development image) % drug released (n = 12)				14 mg tablet, commercial (final image) % drug released (n = 12)			
Sampling time [min]	Average	RSD	Min	Max	Average	RSD	Min	Max	Average	RSD	Min	Max
0	0	0.0	0	0	0	0.0	0	0	0	0.0	0	0
5	36	14.8	28	48	33	25.9	17	45	35	10.6	27	40
10	76	8.6	62	86	68	11.6	52	79	63	8.4	57	74
15	92	5.1	79	97	86	7.9	70	97	82	6.9	72	94
20	96	3.1	88	99	92	4.5	83	99	94	3.6	87	98
30	98	1.3	95	99	97	3.0	91	102	97	2.6	93	100

For teriflunomide 14 mg IR tablets, the values of similarity factor (f2) are calculated to be 60.7 (No. 6 vs. No. 5) and 52.7 (No. 7 vs. No. 5) indicating the formulation Nos. 6 and 7 are similar to formulation No. 5.

Reference ID: 3115241

Figure 3. Mean Comparative Dissolution Profiles of Teriflunomide Film-Coated IR Tablets 14 mg Clinical and Commercial Formulations using the Proposed Dissolution Method



Reviewer's Comments:

1. The above dissolution profile data support the approvability of the proposed dissolution method. However, these data clearly show that when using the proposed method, teriflunomide IR 7 and 14 mg tablets all dissolved (b) (4) in 20 min. Therefore, the proposed acceptance criterion, Q= (b) (4) at 30 min is not acceptable.

2. On 03/16/12, an information request was conveyed to the Applicant, asking for the revision of the dissolution acceptance criterion to Q= (b) (4) at 20 min. In their response they proposed keeping their original Q= (b) (4) at 30 min proposal; however, the Agency did not accept this proposal and recommended that the dissolution acceptance criterion for teriflunomide 14 mg IR tablets be revised from (b) (4) at 30 min to Q= (b) (4) at 30 min.

3. On 04/064/12, the Applicant accepted the revision of the dissolution acceptance criterion for teriflunomide 14 mg tablets to "Q = (b) (4) in 30 minutes" for release and stability testing.

4. Based on the evaluation of the overall dissolution information/data the following dissolution method and acceptance criterion are acceptable.

Dissolution Method and Acceptance Criterion for Teriflunomide IR Tablets					
USP Apparatus	**Spindle Rotation**	**Medium Volume**	**Temperature**	**Medium**	**Acceptance Criterion**
Type 2 (Paddle)	50 rpm	1000 mL	37°C ± 0.5°C	Phosphate Buffer pH 6.8	Q = (b) (4) at 30 minutes

5. From the Biopharmaceutics perspective, Original NDA 202-992 for teriflunomide IR Tablets is recommended for approval.

Reference ID: 3115241

NDA 202-992 for Teriflunomide IR Tablets 14 mg

Appendix 1

3 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Summary of Dissolution Development Report

Reference ID: 3115241

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANGELICA DORANTES
04/11/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202992**	**Brand Name**	**AUBAGIO or** [redacted] (b) (4)
OCP Division (I, II, III, IV, V)	**DCP-1**	**Generic Name**	**Teriflunomide**
Medical Division	**HFD-120**	**Drug Class**	**Anti-inflammatory agent**
OCP Reviewer	**Veneeta Tandon, Ph.D.**	**Indication(s)**	**For treatment of patients with relapsing forms of multiple sclerosis (monotherapy)**
OCP Team Leader	**Angela Yuxin Men, M.D., Ph.D.**	**Dosage Form**	**7 and 14 mg film-coated tablets (immediate release)**
Pharmacometrics Reviewer **Pharmacogenomics Reviewer** **Safety Reviewer**	**Joo-Yeon** **Hobart Rogers** **Pavel Zhichkin**	**Dosing Regimen**	**14 mg orally once daily, with or without food**
Date of Submission	**8/12/2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**3/12/2012**	**Sponsor**	**Sanofi Aventis**
Medical Division Due Date	**4/12/2012**	**Priority Classification**	**S**
PDUFA Due Date	**6/12/2012**		

Clin. Pharm. and Biopharm. Information

Summary:

Teriflunomide is the active metabolite of leflunomide (Arava®), which has been approved worldwide since 1998 for oral treatment of rheumatoid arthritis. Teriflunomide is an orally delivered immunomodulator with both anti-proliferative and anti-inflammatory activity. These activities is based on a selective and reversible inhibition of the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH) (IC_{50}=1.25 µM). The result is a blockade of the de novo pyrimidine synthesis and a cytostatic effect on proliferating T-and B-lymphocytes in the periphery and a subsequent reduction of the number of activated lymphocytes available to enter the central nervous system.

The targeted indication is the monotherapy treatment of patients with relapsing forms of MS (b) (4) [redacted]

Safety and Efficacy Clinical Trials in the submission

File name: Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

Study	Phase	Main objective of the study	Comparator	Treatment duration	Number of patients randomized	Status
Monotherapy						
Core studies						
2001	2	Assess the effect on MRI activity, clinical efficacy, and safety of teriflunomide 7 and 14 mg	Placebo-controlled	36 weeks	179	Complete
EFC6049/TEMSO	3	Evaluate the efficacy and safety of teriflunomide 7 and 14 mg in reducing the frequency of relapses in patients with relapsing MS	Placebo-controlled	108 weeks	1088	Complete
EFC10531/TOWER	3	Evaluate the efficacy and safety of teriflunomide 7 and 14 mg in reducing the frequency of relapses in patients with relapsing MS	Placebo-controlled	Fixed end for all patients, 48 weeks for last patient randomized	1096[a]	Ongoing Interim analysis[b]
Extension studies						
LTS6048 (extension of 2001)	2	Assess the long-term safety and efficacy of teriflunomide in patients who had completed Study 2001	Uncontrolled	Open-ended	147	Ongoing Interim analysis
LTS6050 (extension of EFC6049)	3	Assess the long-term safety and efficacy of teriflunomide in patients who had completed Study EFC6049	Uncontrolled	Open-ended	742	Ongoing Interim analysis

Clinical pharmacology studies

The PK and PD of teriflunomide were assessed in 18 clinical pharmacology studies. Two hundred thirty two (232) healthy subjects were exposed to a single oral dose from 7 to 70 mg. Among them, 6 subjects were exposed to a single 10 mg intravenous (IV) administration. Two hundred twenty three (223) subjects were exposed to repeated doses of teriflunomide following a supratherapeutic regimen (repeated QD) oral doses of 70 mg up to 14 days) or a dosing regimen used to achieve concentrations in the therapeutic range (70 mg once daily for 3 to 4 days followed by 14 mg once daily for 8 to 11 days orally) or 2 consecutive doses of 100 mg/day.

At the end of all clinical studies, either cholestyramine or activated charcoal was administered to the subjects and the patients to accelerate the elimination of teriflunomide.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Biopharmaceutical studies		
Bioequivalence tablet (b) (4) (b) (4)	BDR6639	14 mg single dose
Bioequivalence tablet (test[a] versus reference)	BEQ10169	7 and 14 mg single dose
Food effect (early tablet)	1002	20 mg single dose
Food effect (Phase 3 tablet)	ALI6504	7 and 14 mg single dose
Pharmacokinetics, pharmacodynamics, and initial tolerability in healthy subjects		
Single dose IV	1024	10 mg single dose
Single and multiple ascending dose oral	1001	20 mg SD and 100 mg QD for 2 days
Multiple ascending dose	TDR10892	70 mg QD for 14 days
Excretion balance, pharmacokinetics, metabolism	BEX6038	70 mg single dose
Intrinsic factors		
Mild and moderate impairment	POP6507	14 mg single dose
Severe renal impairment	POP11432	14 mg single dose
Age and gender	POH0290[b]	--
Impact of drug metabolizing enzyme phenotype and genotype on teriflunomide systemic exposure	PHM0086[c], PMH0091[d]	--
Extrinsic factors		
Rifampin	INT6039	70 mg single dose
Effect of teriflunomide on other drugs		
Warfarin (CYP2C9 probe)	INT6040	70 mg QD for 3 days then 14 mg QD for 8 days
Midazolam (CYP3A probe)	INT10563	70 mg QD for 3 days then 14 mg QD for 11 days
Cocktail (CYP1A2, 2C19, and 2D6)	INT11720	70 mg QD for 3 days then 14 mg QD for 9 days
Repaglinide (CYP2C8) [g]	INT11697	70 mg QD for 4 days then 14 mg QD for 8 days
Bupropion (CYP2B6)	INT11932	70 mg QD for 4 days then 14 mg QD for 10 days
Oral contraceptives	INT10564	70 mg QD for 4 days then 14 mg QD for 10 days

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Pharmacokinetics in efficacy/safety studies		
	2001	14 or 28 mg QD for 7 days and 7 or 14 mg QD thereafter
	LTS6048 (2002)	7 and 14 mg QD
Monotherapy	EFC6049/TEMSO (3001)	7 and 14 mg QD
	LTS6050	7 and 14 mg QD
	EFC10531/TOWER	7 and 14 mg QD
Adjunct with IFN-β	PDY6045	7 and 14 mg QD
	LTS6047	7 and 14 mg QD
Adjunct with glatiramer acetate	PDY6046	7 and 14 mg QD
	LTS6047	7 and 14 mg QD
Population pharmacokinetics in clinical pharmacology and efficacy/safety studies		
Population pharmacokinetics	POH0290[b]	--
	SIM0041[k]	--
Pharmacokinetics/pharmacodynamics in efficacy/safety studies		
PK/PD	POH0295[l]	--

In vitro studies	
Intestinal permeability	AIV0202, AIV0213
Protein binding	HMR8477, HMR10274, HMR15182, HMR14543
Metabolism	DMPK/USA/2005-0050, HMR14997, HMR017949, MIH0794
CYP inhibition	DMPK/USA/2005-0097, MIH0376, MIH0542, MIH0793, MIH0882
CYP induction	MIH0318
Transporters	TRE0029, TRE0034, DIV1516

All isoenzymes have been evaluated in these in vitro and in vivo studies

Formulation BE

The in vitro bridging strategy to compare clinical and commercial formulations was agreed by the Agency (19 May 2010 letter to the Sponsor). Accordingly, no in vivo bioequivalence study was performed comparing the TBM and Phase 3 drug products.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			

File name: Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		
Isozyme characterization:	**-**			
Blood/plasma ratio:	**-**			
Plasma protein binding:	**X**	**1**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**2**		
multiple dose:	**X**	**2**		
Patients-				
single dose:				
multiple dose:	**X**			
Dose proportionality -	**X**			
fasting / non-fasting single dose:	**X**			
fasting / non-fasting multiple dose:	**X**			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**6**		
In-vivo effects of primary drug:	**X**			
In-vitro:	**X**			All isoenzymes conducted
Subpopulation studies -				
ethnicity:	**X**			
gender:	**X**			
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**		
hepatic impairment:	**X**	**1**		
PD -				
Phase 2:	**X**			
Phase 3:	**X**			
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**2**		
Phase 3 clinical trial:	**X**			
Population Analyses -				
Data rich:	**X**			Rich sampling from Phase 1 studies
Data sparse:	**X**	**2**		Sparse sampling from Phase 2/3 study
II. Biopharmaceutics				
Absolute bioavailability	**X**			cross studies comparison
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:		**2**		
Bioequivalence studies -				
traditional design; single / multi dose:	**X**			
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**		
Bio-waiver request based on BCS				
BCS class	**X**			II
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**			
Chronopharmacokinetics				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Pediatric development plan				Sponsor requesting a deferral and a partial waiver in pediatric patients 10-17 years and less than 10 years of age, respectively
Literature References				
Total Number of Studies		18 PK 2 PopPK 1 PK-PD 6 in vitro studies (19 reports) 6 assay validation reports (assays and metabolite ID)		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	Yes			
2	Has the applicant provided metabolism and drug-drug interaction information?	Yes			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	Yes			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	Yes			
5	Has a rationale for dose selection been submitted?	Yes			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	Yes			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	Yes			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	Yes			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	Yes			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	Yes			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	Yes			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	Yes			Two doses were tested in phase 2 and 3 studies. PK/PD and PopPK was conducted.
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	Yes			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	Yes			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	NA			Sponsor requesting a deferral and a partial waiver in pediatric patients 10-17 years and less than 10 years of age, respectively
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	NA			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Yes			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	NA			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.
Inspection: none

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

File name: Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VENEETA TANDON
09/28/2011

YUXIN MEN
09/28/2011