

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202992Orig1s000

MEDICAL REVIEW(S)

MEMORANDUM

DATE: August 25, 2012

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 202,992

SUBJECT: Recommendation for Action on NDA 202,992, for the use of teriflunomide in the treatment of patients with relapsing forms of Multiple Sclerosis (MS)

NDA 202,992, for the use of teriflunomide in the treatment of patients with relapsing forms of Multiple Sclerosis (MS), was submitted by Sanofi Aventis on 8/12/11. Teriflunomide is a selective and reversible inhibitor of mitochondrial dihydroorotate dehydrogenase (DHO-DH), which is necessary for pyrimidine synthesis. Presumably by inhibiting the enzyme, teriflunomide inhibits pyrimidine synthesis, which results in a cytostatic effect on peripheral T- and B-lymphocytes. This presumably decreases the number of activated lymphocytes that enter the Central Nervous System (CNS), thereby decreasing the inflammatory response known to be present in the CNS in patients with MS. Teriflunomide is the active metabolite of leflunomide, marketed as ARAVA for the treatment of rheumatoid arthritis (RA), since 1998. Indeed, leflunomide is essentially entirely metabolized to teriflunomide, and the plasma levels of teriflunomide that circulate at the sponsor's proposed dose of teriflunomide of 14 mg/day are comparable to the circulating levels of teriflunomide when leflunomide is given at the recommended dose of 20 mg/day.

The sponsor has submitted the results of a single adequate and well-controlled study, TEMSO, as the primary basis for the approval of the application. They have also submitted the results of a smaller controlled trial, 2001, and interim results of an on-going controlled trial (TOWER), of similar size to TEMSO, as supportive evidence of effectiveness. In addition, they have submitted reports of two additional placebo-controlled, relatively short-term, add-on trials, in which teriflunomide was added to interferon (Study 6045) or glatiramer acetate (Study 6046) as additional support.

The NDA has been reviewed by Drs. Prafull Shiromani and Sarah Miksinski, Office of New Drug Quality and Assessment (ONDQA, CMC); Dr. Tien-Mien Chen, ONDQA, Biopharmaceutics; Dr. Richard Houghtling, pharmacology/toxicology reviewer; Dr. Lois Freed, pharmacology supervisor; Dr. Matthew Jackson, statistician (carcinogenicity); Drs. Vaneeta Tandon, Joo-Yeon Lee, and Jeffrey Kraft, Office of Clinical Pharmacology; Dr. Katherine Bonson, Controlled Substance Staff; Upasana Bhatnagar, Pediatric and Maternal Health Staff; Jung Lee, Division of Medication Error and Prevention and Analysis

(DMEPA); Robin Duer and Reema Jain, Division of Risk Management (DRISK); Dr. Antoine El-Hage, Office of Scientific Investigations; the Interdisciplinary Review Team for QT Studies; Drs. Lourdes Villalba and Evelyn Mentari, safety reviewer; Dr. John Senior, Office of Pharmacovigilance and Epidemiology (OPE); Dr. Sally Yasuda, safety team leader; Dr. Sharon Yan, Office of Biostatistics; Dr. Jody Green, medical reviewer, and Dr. Billy Dunn, neurology team leader and Cross-Discipline Team Leader (CDTL). The review team recommends that the application be approved.

I will briefly describe the relevant effectiveness and safety data, and offer the division's recommendation for action on the NDA.

Effectiveness

TEM SO

This was a multi-national study in which patients with relapsing forms of MS (Relapsing-Remitting, Secondary Progressive, and Progressive Relapsing) were randomized to receive either placebo, teriflunomide 7 mg, or teriflunomide 14 mg/day. The study was 108 weeks in duration. The outcomes assessed were:

Primary outcome

Reduction of confirmed relapses/year (annualized relapse rate, or ARR), defined as a documented 1 point increase in at least 2 FS functions (see below) or a 2 point increase in one FS function from the previous examination, or an increase of at least 0.5 points on the EDSS score (see below), or a 1 point increase if the EDSS=0, compared to the previous score.

Key secondary outcome

Time to confirmed disability progression as defined by change in Expanded Disability System Score-this standard measure of disability in patients with MS consists of assessment in 7 functional systems (FS); each FS is rated from 0-6. The scale is rated from 0 (Normal) to 10 (death due to MS). A score above 5.5 indicates that the patient is non-ambulatory. For this outcome, an increase of 1 point sustained over 12 weeks indicated progression of disability for patients with a baseline EDSS of 5.5 or less, and an increase of 0.5 points for patients with a baseline EDSS of 6 or above.

Other clinical secondary outcomes

Proportion of patients free of disability progression at 6, 12, and 24 months

Fatigue Impact Scale (FIS)-a patient reported outcome measure

Multiple Sclerosis Functional Composite (MSFC)-consisting of Timed 25 Foot Walk; 9 Hole Peg Test; and Paced Auditory Serial Addition Test (PASAT-3), each component assessing a different function

Medical Outcome Study SF-36-a self-administered quality of life scaleEuroQoL EQ-5D-another patient-rated quality of life scale

Other secondary imaging measures

MRI variables:

Burden of Disease (BOD), defined as the total volume of abnormal brain tissue, further defined as the sum of the T2 lesion load and the T1 hypointense lesion component.

Volume of post-gadolinium T 1 hypointense black holes

Total number of gadolinium enhanced T1 lesions

Total volume of enhanced T1 lesions/scan

Volume of T2 component

Average number of unique active lesions/scan

Atrophy

Volume of white matter

Volume of gray matter

Analyses were to be performed on the 14 mg dose-placebo contrast for the ARR first, then for the 7 mg-placebo contrast for ARR, then for the 14 mg-placebo contrast for disability progression, then for the 7 mg-placebo contrast for disability progression. The protocol also stated that the following endpoints would be tested in the following order, each at alpha 0.025, only if the proceeding contrast was significant at 0.025 (presumably independent of dose):

- 1) Change from baseline in total FIS at week 108
- 2) Total number of gadolinium enhancing T1 lesions/scan over the treatment period
- 3) Change from baseline in MRI BOD at Week 108

Results

The trial was conducted at 126 sites in 21 countries. For some analyses, countries were grouped into regions; Americas (23%), Eastern Europe (31%), and Western Europe (46%). The greatest percentage of study subjects from one country was Canada, which supplied about 17% of the study sample. There were only 8 patients from the US.

A total of 1088 patients were randomized; 1086 were included in the intent-to-treat population. The following chart displays the progression of patients through the study:

	Placebo	Ter 7	Ter 14
Randomized	363	366	359
Completed 108 weeks	259 (71%)	274 (75%)	263 (73%)
Reason for Discontinuation			
Adverse event	29	37	38
Lack of efficacy	24	14	17
Progressive disease	11	4	2
Patient request	33	32	26
Protocol violation	3	2	5
Lost to follow-up	4	0	2
Other	0	2	5

Important baseline characteristics were acceptably well distributed (see, for example, Dr. Yan's Tables 3, 4, pages 10 and 11 of her review).

The following charts display the results of the primary (ARR) and key secondary (time to disability progression) outcomes:

	Placebo	Ter 7	Ter 14
Adjusted ARR	0.54	0.37	0.37
Relative Risk		0.69	0.69
P-value		0.0002	0.0005
Relapse Free	49%	58%	61%

Although there were numerical trends in favor of both doses of teriflunomide in the Americas and Eastern Europe, statistical significance was achieved only in Western Europe, as displayed below:

	ARR		
	Placebo	Ter 7	Ter 14
Americas	0.31 (N=82)	0.21 (N=83)	0.27 (N=80)
Eastern Europe	0.52 (N=114)	0.42 (N=116)	0.42 (N=108)
Western Europe	0.71 (N=167)	0.45 (N=166)	0.4 (N=170)
P-value		0.001	<0.0001

Time to Disability Progression

	Placebo	Ter 7	Ter 14
Number of patients With progression	86 (24%)	68 (19%)	62 (17%)
Hazard ratio		0.76	0.70
P-value		0.08	0.03

The estimate of the percentage of patients with disability progression at Week 108 was 27%, 22%, and 20% for the placebo, 7 mg, and 14 mg groups, respectively.

For this outcome, statistical significance was seen only in Eastern Europe, with numerical superiority of the 7 mg group compared to the 14 mg group.

Secondary outcomes

Fatigue Impact Scale

There were no significant differences between either treatment group and placebo (P=0.4 and 0.09 for the 7 and 14 mg groups, respectively).

MSFC

There were no statistically significant differences between either group and placebo, except on the PASAT-3 component (p=0.04 for each dose contrast).

MRI Outcomes

The following chart displays the results of the key MRI outcomes:

Outcome	Pla	Ter 7	Ter 14
BOD			
Mean Change from baseline Cubic volume	0.13	0.08	0.04
P-value		0.03	0.0003
Cumulative			
Gd-enhancing lesions/scan	1.3	0.57	0.26
P-value		<0.0001	<0.0001
Mean Change			
Volume of T1 hypointense Lesions	0.1	0.08	0.07
P-value		0.2	0.02
Mean Change			
Volume of T2 lesions	0.12	0.065	0.03
P-value		0.04	0.0004

TOWER

As described above, the sponsor has submitted the results of an interim analysis of the TOWER study. This trial has several key similarities to TEMSO, including comparing the same treatments (placebo and teriflunomide 7 and 14 mg/day) and the same primary outcomes (ARR and time to disability progression). A key difference was that each patient did not have a fixed duration in study.

Specifically, the study was to be terminated when the last patient enrolled completed 48 weeks of treatment. There was no plan to terminate the study based on the results of the interim analysis.

Other outcomes assessed were the FIS, the Medical Outcome Study SF-36, the Hospital Anxiety and Depression Scale (HADS), a self-assessment scale, and the Suicidality Tracking Scale (STS), an assessment of suicidal behavior.

Results

The study was performed at 190 sites in 26 countries in the Americas (22%), Eastern (31%) and Western (32%) Europe, and Asia/Australia (15%). About 19% of the patients were enrolled in the US, which was the largest single enrolling country.

The planned total enrollment was for 1110 patients to be randomized. At the time of the interim analysis, a total of 1096 patients were randomized and 1092 received treatment. That is, enrollment was essentially complete when the interim analysis was performed. All patients randomized in the study as of 11/30/10 were included in the analysis. Patient data are included through 2/28/11; all patients had at least 3 months of treatment at the time of the analysis. At the time of the analysis, 861 patients were still being treated. About 44% of patients in all groups completed at least 48 weeks.

The following chart displays patient disposition:

	Pla	Ter 7	Ter 14
Randomized	366	379	351
Treatment on-going	293	293	275
Median duration (days) in study	313	302	318
Discontinued	72	85	74
Adverse event	16	40	40
Lack of efficacy	24	17	7
Poor compliance	12	2	3
Other	20	26	22
Lost to follow-up	0	0	2

The only results presented are for the ARR, and are presented below:

	Placebo	Ter 7	Ter 14
Adjusted ARR	0.53	0.37	0.32
Relative Risk		0.7	0.6
P-value		0.0072	0.0002

Study 2001

This was a double blind, randomized trial in which patients were also randomized to receive either placebo, teriflunomide 7 mg, or teriflunomide 14 mg/day. Treatment was to be continued for 36 weeks. The primary outcome of the trial was based on MRI: the number of unique active lesions/scan. Other MRI variables were also assessed, as well as several clinical outcomes:

- 1) EDSS
- 2) MSFC
- 3) Relapse rate
- 4) FIS
- 5) Multiple Sclerosis Quality of Life Questionnaire (MSQOL-54)-a 54 item patient self-assessment questionnaire

Results

The study was performed in 10 sites in Canada and 6 sites in France. A total of 179 patients were randomized. The following chart displays patient disposition:

	Pla	Ter 7	Ter 14
Randomized	61	61	57
Completed	57	58	45
Discontinued			
Adverse event	4	3	8
Lack of efficacy	0	0	2
Patient preference	0	0	2

The following chart displays the results for the primary outcome:

Average number of unique lesions/scan

	Placebo	Ter 7	Ter 14
Mean lesions/scan	2.62	1.04	0.98
P-value		0.03	0.01

The following chart displays the results of the analyses of other MRI endpoints:

Outcome	Pla	Ter 7	Ter 14
T1			
Newly enhancing	1.8	0.7	0.7
P-value		0.04	0.01
Persistently enhancing	0.44	0.16	0.1
P-value		0.14	0.02
Total	2.3	0.9	0.8
P-value		0.03	0.01
T2			
New	1.07	0.3	0.4
P-value		0.003	0.008
Newly enlarging	0.37	0.1	0.2
P-value		0.008	0.09
Persistently enlarging	0.07	0.02	0.04
P-value		0.35	0.55
Combined	1.5	0.44	0.7
P-value		0.003	0.02
Unique newly active (T1 and T2)	2.16	0.9	0.84
P-value		0.03	0.005
Unique persistently active (T1 and T2)	0.53	0.2	0.16
P-value		0.04	0.07

Clinical outcomes

The relapses in this study were not qualified, as they had been in both TEMSO and TOWER. Nonetheless, the following chart displays the results of the ARR analysis:

Placebo	Ter 7	Ter 14
0.8	0.58	0.55

The following chart displays the proportion of patients who met the definition of sustained disability:

Placebo	Ter 7	Ter 14
21%	29%	7%

The sponsor has performed two additional small controlled trials, in which teriflunomide was given as adjunctive therapy, added on to interferon-beta or glatirimer acetate. They are briefly described below.

Study 6045

In this study, patients were randomized to receive placebo, teriflunomide 7 mg or teriflunomide 14 mg/day added to interferon-beta. The study was of 24 weeks duration. There was no single primary outcome; multiple MRI measures were assessed, as was ARR.

Results

A total of 116 patients were randomized (41 placebo, 36 teriflunomide 7 mg/day, and 39 teriflunomide 14 mg/day). According to the sponsor, there was a dose related reduction in the number and volume of T1 Gd-enhancing lesions. Patients on teriflunomide 7 mg/day had a 55% reduction and patients on 14 mg/day had an 80% reduction in lesions compared to placebo added to interferon ($p < 0.001$ for both comparisons). Further, 5/41, 5/36, and 2/39 patients had relapses on placebo, teriflunomide 7 mg, and teriflunomide 14 mg/day.

Study 6046

This study was of similar design to Study 6045 described immediately above, except in this trial, teriflunomide (or placebo) was added to glatiramer acetate. A total of 41, 42, and 40 patients were randomized to placebo, teriflunomide 7 mg,

and teriflunomide 14 mg/day, respectively. There were presumably no clear drug-related beneficial effects in this trial.

Safety

As noted above, teriflunomide is the primary circulating moiety when ARAVA (leflunomide) is administered; ARAVA has been approved since 1998, for the treatment of patients with RA. The recommended dose of ARAVA is 20 mg/day, which results in circulating levels of teriflunomide that are comparable to the levels of teriflunomide when it is given at the sponsor's proposed recommended dose of 14 mg/day. Therefore, we would expect that the adverse event profile of teriflunomide would mirror that of ARAVA, assuming no major differences in response between the RA and MS populations.

The ARAVA package insert includes language related to the following important adverse reactions:

Boxed Warning:

- 1) Teratogenesis (Pregnancy Category X)
- 2) Liver toxicity-including liver failure and fatalities

Warnings (in addition to above):

- 1) Immunosuppression/Bone Marrow Suppression
- 2) Serious skin reactions-including Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
- 3) Malignancy
- 4) Peripheral Neuropathy

Precautions:

- 1) Interstitial Lung Disease
- 2) Blood Pressure Monitoring

Adverse Reactions

- 1) Diarrhea
- 2) Increased Liver Function Tests (LFTs)
- 3) Alopecia
- 4) Rash

Exposure

Safety data on a total of 2289 patients with known assigned treatment (total of teriflunomide 7 mg/day and 14 mg/day) was submitted by the sponsor. This represents a total of 5667.1 patient years of exposure. However, 776 of these patients were in on-going studies.

Safety data from 1513 patients in completed Phase 2/3 studies (representing both mono-and adjunctive therapy in MS), with a total of 4514.3 patient-years of exposure, were submitted. The following chart displays exposure by daily dose and duration of exposure:

Dose	>3 months	>6 months	>12 months	>24 months
7 mg/day	735	691	585	381
14 mg/day	737	692	643	361
Total	1427	1334	1120	742

In her safety review, Dr. Villalba primarily focuses on 2 data pools:

- 1) Pool 1-Consisting of the data in the 2 controlled monotherapy studies: Study 2001, and TEMSO (including placebo)
- 2) Pool 2-Consisting of teriflunomide exposure in the 2 monotherapy controlled trials above and their open-label extensions (no placebo)

The following chart displays exposure by dose and duration for Pools 1 and 2:

Dose	Duration	Pool 1	Pool 2
Total			
7 mg	Any	429	587
14 mg	Any	415	548
7 mg	>48 weeks	305	484
14 mg	>108 weeks	129	155

Deaths

There were a total of 9 deaths reported during development (8 on drug, 1 on placebo). A total of 4 occurred in the extensions to the monotherapy studies, and 5 occurred in on-going studies (4 drug, 1 placebo). A brief description of the 8 deaths that occurred on drug is supplied below:

- 1) A 54 year old woman treated for 3022 days (about 9 years) with 7 mg/day died of a myocardial infarction. She had been started on treatment for hypertension after about 2 years on drug. About 4 years prior to death, she had been diagnosed with coronary artery disease.
- 2) A 57 year old woman treated for 1750 days with 7 mg/day died of cardiac disorder/respiratory failure with a complicated, incomplete description of her final episode.
- 3) A 41 year old woman treated for 302 days with 7 mg/day was found dead.
- 4) A 41 year old man treated for 558 days with 14 mg/day was found dead.
- 5) A 19 year old woman treated for 71 days with 14 mg/day committed suicide. She had a history of depression.
- 6) A 47 year old man treated for 477 days with 7 mg/day was killed in a motor vehicle accident.
- 7) A 24 year old woman treated for 633 days with 14 mg died of gram negative sepsis.
- 8) A 51 year old man treated for about 4 years with 7 mg died in his sleep. Hypertension was documented after about 16 months on drug (he had slight hypertension at baseline).

Serious Adverse Reactions (SAR)

The following chart displays the incidence of selective SARs in which the incidence appears greater on drug than on placebo in Pool 1:

Primary system	Placebo N=421 %	Ter 7 mg N=429 %	Ter 14 mg N=415 %
Gastrointestinal Disorders	0.2	1.9	1.9
Hepatobiliary Disorders	0.5	2.1	0.5
Blood Disorder	0.2	0.5	0.7
Injury, Procedural Complications	1.0	1.2	2.2

The increased incidence of GI disorders included in the chart above is mostly driven by Inguinal Hernia in the 14 mg group (4 cases, none in either of the other groups), and single cases each of (non-exhaustive list): diarrhea, duodenal ulcer, colitis, colitis ulcerative, Crohn's Disease, intestinal functional disorder. Most of these cases resolved with continued treatment, except for the case of Crohn's Disease, in which there appeared to be a positive dechallenge and rechallenge.

The cases of Hepatobiliary Disorder were primarily driven by cholelithiasis (N=6 in the 7 mg group, N=1 in placebo).

There was no meaningful difference in the incidence of patients with abnormal LFTs between the three treatment groups. However, one patient, a 35 year old

woman, became symptomatic (fever, vomiting, dark urine) on Day 135 of treatment with 14 mg/day. Ultimately, she became jaundiced, and was noted to have an ALT 32 X ULN, AST 20 X ULN, GGT 4.7 X ULN, total bilirubin 1.7 X ULN (direct bili 2.5 X ULN), and Alk Phos 3.1 X ULN. She had a washout procedure (drug was discontinued) and her condition resolved on Day 319 (3 days after her last washout). Viral serology was negative.

Another patient, a 38 year old woman, had a documented increase in LFTs (ALT 10 X ULN, AST 6.4 X ULN, Bili 1.2 X ULN) on Day 141 of treatment with 7 mg/day. Drug was discontinued on Day 143, and she underwent a washout procedure with cholestyramine from Day 147-157. Her LFTs increased to ALT 23 X ULN, AST 12.3 X ULN, and GGT 5.5 x ULN on Day 160. She was also reportedly icteric. She recovered on Day 189; viral serologies were negative.

The increased incidence of Blood disorders was primarily related to mild neutropenia (with or without lymphopenia and/or thrombocytopenia) that either resolved after discontinuation and did not recur with re-initiation of treatment or resolved on continued treatment. Another case of significant “pancytopenia” occurred in a 50 year old man treated for 11 months, but all values were normal about one month later with continued treatment.

Two patients, a 25 year old woman, and a 57 year old woman, experienced elevations of lipase (one with a maximum increase of 5 X ULN, resulting in discontinuation, one with a maximum elevation of 3.5 X ULN, who continued treatment with resolution).

The following chart displays the incidence of selected SARs in Pool 2:

System Class	Ter 7	Ter 14
	N=587	N=548
	%	%
Infections	3.6	4
Investigations	4.5	4.7
GI disorders	2.2	2.6
Injury, Procedural complications	2.7	2.4
Nervous System disorder	2.4	1.6
Hepatobiliary disorder	2.7	0.5

The cases of GI disorders included inguinal hernia (4 cases in the 14m g group), diarrhea, duodenal ulcer (N=2 each), and single cases each of (non-exhaustive

list): upper GI bleed, gastric ulcer bleed, colitis, colitis ulcerative, Crohn's Disease, gastroduodenal bleed, intestinal functional disorder.

Regarding Hepatobiliary disorders, two patients are of interest.

A 43 year old man treated for 335 days with 14 mg/day, developed ALT 3 X ULN, AST 2.5 X ULN, and GGT 1.6 X ULN. On Day 362, his ALT was 18.2 X ULN, with direct bilirubin 1.3 X ULN. The patient's lab abnormalities resolved 3 weeks after cholestyramine washout.

A 37 year old man reported dark urine, pale stools, and itching on Day 283 of treatment with 7 m g/day. His ALT was 6.3 X ULN with total bilirubin of 2.1 X ULN. Apparently, a "tiny" gall stone was noted in the "extreme" lower common bile duct. Drug was discontinued on Day 296, at which point is bilirubin was 2.1 X ULN. He had a cholecystectomy on Day 444, about 130 days after a washout period.

Other serious cases represented LFT elevations without elevations in bilirubin.

The increased incidence of Infections was primarily driven by Urinary tract infection (UTI) and pyelonephritis (7 cases of the former N=3, 7 mg; N=4, 14 mg; 3 cases of the latter in the 14 mg group, one in the 7 mg group). There were also 5 cases of appendicitis, all in the 7 mg group.

Numerous events were included in the Nervous System Disorders group (e.g., few cases of MS, convulsions, other isolated events), as well as 4 cases of loss of consciousness (N=1, 7 mg; N=3, 14 mg) and one case of syncope (14 mg). These occurred after extended exposure, and did not appear to be related to treatment.

Of interest, there were 2 cases of pulmonary tuberculosis (one in Hungary, 14 mg; one in Ukraine, 7 mg) and one case of ileal tuberculosis (in Turkey, 14 mg), and one case each of osteomyelitis, caused by prevotella species (14 mg), and enterococcal endocarditis (7 mg). None of these cases could be unambiguously attributed to treatment with teriflunomide.

Discontinuations due to adverse reactions

The following chart displays the incidence of discontinuations due to adverse reactions in Pools 1 and 2:

Pool 1	Placebo	Ter 7	Ter 14
	N=421	429	415
	%	%	%
	8	9	11
Pool 2	Ter 7	Ter 14	
	N=587	N=548	
	%	%	
	16	15	

The following chart displays the incidence (%) of selected important adverse reactions leading to discontinuation in Pool 1:

System	Placebo	Ter 7	Ter 14
GI Disorders	0.2	1.4	1.2
Skin	0	0.9	3.1

In the GI disorders, few events were reported more than once (diarrhea, N=2, one each dose; and upper abdominal pain, N=2, 7 mg).

The increased incidence of events in the Skin organ class is primarily driven by alopecia, which occurred in 6 patients in the 14 mg group, and 2 patients in the 7 mg group (0 placebo patients). The mean time to onset was 77 days, and all cases resolved, though the time to recovery varied from 2-6 months.

Of interest, in Pool 1, there were 2 cases coded as polyneuropathy (one in each active dose group). One patient recovered, one did not. Both cases were confirmed by electrical studies.

In Pool 2, the most common reasons for discontinuations related to adverse reactions are displayed below:

System	Ter 7	Ter 14
Investigations	6.6%	5.8%
Skin	1.2%	2.4%
GI disorders	1.5%	1.6%
Nervous System Disorders	1.7%	0.4%

Almost all of the discontinuations in the Investigations class were related to LFT elevations (no dose relationship). There were also 4 cases of neutropenia (all in the 7 mg group).

Of interest, there were 3 cases coded as polyneuropathy that led to discontinuation in Pool 2 (N=2, 7 mg; N=1, 14 mg).

Common Adverse Events

The following chart displays the most common adverse events seen in Pool 1, for which the incidence is greater on drug than placebo:

Event	Placebo N=421 %	Ter 7 N=429 %	Ter 14 N=415 %
Diarrhea	8	14	17
Alopecia	4	11	15
Nausea	7	9	14
ALT increased	7	13	14
Influenza	9	10	12
Paraesthesia	8	10	11
Rash	4	5	6

Laboratory findings

The following chart displays the mean changes in important laboratory analytes in Pool 1:

Mean change from baseline

Analyte	Placebo	Ter 7	Ter 14
Uric acid (range 125-428 umol/L)	-3.8	-58.3	-77.8
CK (0-190 U/L) (measured only in 2001)	-2.89	-2.62	+10.77
LDH (range 0-479 U/L) (measured only in 2001)	-0.43	+17.89	+15.98
ALT (range 6-34 U/L)	0.009	0.112	0.095
WBC (range 3.8-10.7 GIGA/L)	0.01	-0.67	-0.85
Neutrophils (range 1.96-7.23 GIGA/L)	0.00	-0.47	-0.59
Lymphocytes (range 0.91-4.28 GIGA/L)	0.00	-0.22	-0.28
Hemoglobin (range 116-164 G/L)	-1.3	-1.9	-2.4
Platelets (range 140-400 GIGA/L)	8.2	-14.1	-14.7

In general, these changes tend to occur early (within the first 6-12 weeks) and then remain stable.

Outliers

The following chart displays the percent of patients who met criteria for potentially clinically important changes for the various laboratory analytes:

Analyte	Placebo	Ter 7	Ter 14
Phosphorus			
>0.6 and <LLN	9%	18%	22%
>0.3 and <0.6	1%	5%	6%
Potassium			
>7 mmol/L	0.2%	1%	1%
Creatinine			
>150 umol/L	0%	1%	1%
> 2 X baseline	0%	1%	1%
> 3 x Baseline	0%	1%	1%
Uric acid			
< 120 umol/L	4%	18%	29%
ALT			
< 3 X ULN	30%	48%	50%
AST			
< 3 X ULN	17%	32%	34%
> 3 - < 5 X ULN	0.5%	2%	2%
GGT			
> 2.5 - < 5 X ULN	2.4%	4%	3%
WBC			
< 2-3 Giga/L	1%	6%	10%
<1-1.5 Giga/L - >0.5	5%	10%	4.5%
Lymphocytes			
<0.8 - > 0.5 Giga/L	5%	7%	10%
Eosinophils			
> 0.5 Giga/L	8%	8%	12%
Hemoglobin			
> 100 g/L- LLN	11%	13%	16%
< 80 g/L	0%	0.2%	1%

	Placebo	Ter 7	Ter 14
Platelets < 100 Giga/L	0%	1%	1%

Vital signs

The following chart displays mean changes from baseline in systolic and diastolic blood pressure in patients in Pool 1:

Measure	Placebo	Ter 7	Ter 14
Systolic (mm Hg)	-1.3	+2.2	+2.6
Diastolic (mm Hg)	-0.9	+1.1	+1.4

In general, these changes begin within the first several weeks, and can be persistent.

The following chart displays the incidence of patients who met criteria for potentially significant changes in systolic or diastolic blood pressure;

Measure	Placebo	Ter 7	Ter 14
Systolic			
> 160 mm Hg plus increase of 20 mm Hg	2%	4%	6%
Diastolic			
> 110 mm Hg plus increase of 10 mm Hg	0.5%	2%	1.4%

Weight

The following chart displays the incidence of weight loss reported as an adverse event in Pool 1:

Weight loss

Placebo	Ter 7	Ter 14
1%	3%	2%

The following chart displays the incidence of patients who experienced a potentially significant change in weight in Pool 1:

Weight	Placebo	Ter 7	Ter 14
> 5% decrease	27%	39%	44%

Adverse Events of Special Interest

As noted above, teriflunomide is known to be associated with several significant adverse events. Dr. Villalba has provided a comprehensive review of these events, a list of which follows:

- 1) Nausea
- 2) Diarrhea
- 3) Interstitial lung disease
- 4) Peripheral neuropathy
- 5) Malignancy
- 6) Hypertension
- 7) Hematopoietic cytopenias
- 8) Infections
- 9) Anaphylactic reactions
- 10) Pancreatic disorders
- 11) Cardiac arrhythmias
- 12) Convulsions
- 13) Hemorrhages
- 14) Embolic and thrombotic events
- 15) Alopecia

Although there was an increased incidence of most of these events on drug compared to placebo in Pool 1 (though not for cardiac arrhythmias, malignancy, interstitial lung disease, pancreatic disorders, and embolic events), only Nausea, Diarrhea, Hepatic Disorders, Peripheral Neuropathy, Alopecia, and Hemorrhages were dose related. For the most part, previous sections of the review describe these events. Here, I will discuss only those that have not been discussed elsewhere.

Interstitial Lung Disease (ILD)

Although there were no cases of ILD in Pool 1, there were several cases of apparent ILD in the open-label experience:

- 1) a 50 year old woman treated with teriflunomide 14 mg/day for 397 days was diagnosed with pulmonary fibrosis by CT. She had no symptoms referable to these changes. She had a history of cardiomyopathy and

- autoimmune thyroiditis. Drug was not discontinued, and there was no additional imaging.
- 2) A 53 year old woman was diagnosed with respiratory failure on Day 533 of treatment with 7 mg/day. PFTs showed “mixed ventilatory deficiency”. Chest X-ray showed bilateral increased markings at the base. She had a dry cough, which improved with discontinuation of the treatment, and which recurred with resumption of treatment.
 - 3) A 38 year old woman was diagnosed with ILD on Day 71 of treatment with 7 mg/day; she presented with difficulty breathing. She was a heavy smoker. X-ray showed reticular-nodular changes at the bases of both lungs. She recovered off drug, but had residual dyspnea.

Peripheral Neuropathy

The following chart displays the incidence of terms possibly related to peripheral neuropathy that occurred at a greater incidence on drug compared to placebo:

Event	Placebo	Ter 7	Ter 14
Neuralgia	0	1%	1%
Polyneuropathy	0	0.2%	1%
Carpal Tunnel Syndrome	1%	1%	3%
Hyperaesthesia	1%	0	2%
Paraesthesia	10%	11%	13%

A total of 1% (N=3), 4% (N=12), and 3% (N=9) of placebo, teriflunomide 7 mg, and teriflunomide 14 mg patients, respectively, were suspected of having peripheral neuropathy. Of these, 0, 4, and 6 patients, respectively, had a neuropathy confirmed by electrical studies. Several of these were related to entrapment (ulnar neuropathy; carpal tunnel syndrome), diabetes, though at least several appeared to have no other obvious cause. Several cases were also reported in the open-label extension studies (2 reported as polyneuropathy, 9 as peripheral neuropathy, 5 as neuralgia).

Hypersensitivity

There were no life-threatening events that could reasonably be considered related to hypersensitivity. However, the following adverse reactions were reported more frequently on drug than on placebo in Pool 1:

Event	Placebo	Ter 7	Ter 14
Rash	4%	5%	6%
Pruritis	2%	4%	3%
Erythema	0.5%	2%	1%
Urticaria	0.5%	1%	1%

Two cases of erythema nodosum and one case of erythema multiforme were reported in patients on teriflunomide (both doses) but these resolved with continued treatment.

Several cases of eosinophilia were reported in Pool 1 (N=3, 14 mg; N=5, 7 mg; N=2, placebo), but these generally resolved with continued treatment.

Acute renal failure

As noted earlier, 10 patients were documented to have had at least a doubling of their baseline creatinine values (in one patient, the doubled value was still within normal limits). Dr. Mentari has examined the data for these 10 patients, and determined that 7 of them had creatinine clearances below 30 cc/min. Nine (9) of these patients had decreases in serum uric acid (with values ranging from 5-57% below baseline). Three (3) of these patients had potassium levels greater than 6.0, and 4 patients did not have potassium levels documented at the time of the abnormal creatinine. Most important, however, is the fact that, in all cases, the creatinine became normalized with continued treatment at the next assessment with, which varied from 6 to 48 days after the abnormal value was noted (of the 9 patients with abnormal creatinines, 5 returned to normal in less than 10 days).

Pregnancy

Teriflunomide is embryo-lethal and highly teratogenic, causing major malformations in rat and rabbit. As noted earlier, ARAVA is labeled as Pregnancy Category X, and this effect is described in the boxed warning.

As of June 2011, the results of 53 pregnancies (in 56 women) have been reported. A total of 41 of these pregnancies occurred in women taking teriflunomide; 12 occurred in women whose partners were taking teriflunomide.

In the 41 pregnancies in which the women took the drug, there were 8 live births, 8 spontaneous abortions, 20 elective abortions, and in 5 the pregnancy was still on-going.

In the 12 pregnancies in which the women's partners took the drug, there were 8 live births and one spontaneous abortion.

None of the 16 babies born had malformations detected at birth.

Of the 8 women who took the drug and gave birth, all had the rapid elimination procedure.

QT

An adequate thorough QT study, examining the effects of 14 mg/day, did not show any meaningful prolongation of the QT interval.

Pharmacokinetics

Teriflunomide is essentially 100% bioavailable, and only a single metabolite, 4-TFMA, was detectable in plasma, and only in very small amounts, and only after multiple dosing. On a molar basis, the levels of 4-TFMA were about 12,000-17,000 times lower than teriflunomide levels. Numerous metabolites are found in the urine (8 total urinary metabolites accounted for about 20% of a radioactive dose). Teriflunomide is about 99.5-99.7% bound to plasma proteins (primarily albumin) and it is not metabolized by CYP enzymes. The median terminal half-life is about 20 days. Steady state is achieved in about 3 months.

Rapid Elimination Procedure

Teriflunomide can be rapidly eliminated from the circulation by utilizing a washout procedure. A regimen of cholestyramine, 8 gms TID for 7 days, reduces the half-life from about 20 days to about 2-3 days. Activated charcoal can also be used.

Comments

The sponsor has submitted the results of a single, large, adequate and well controlled clinical trial, as well as the results of another, smaller, shorter randomized controlled trial and interim results of a second large controlled trial that, taken together, purport to demonstrate that teriflunomide is effective in the treatment of patients with relapsing forms of MS. In addition, they have submitted sufficient safety data to assess the safety of the drug.

The results of the TEMSO study are highly significant for ARR for both the 7 and 14 mg/day dose groups; indeed, the results for both of these doses are

essentially identical. In addition, Study 2001 showed nominal statistical significance for this outcome for both doses (nominal because this was not the primary outcome of this study, and “prior” outcomes did not all show statistical significance).

However, for the key secondary outcome of accumulation of disability, although the estimates of the treatment effect for both the 7 and 14 mg/day dose groups are quite similar in TEMSO, the effect for the 14 mg/day group reached statistical significance, but did not for the 7 mg/day group ($p=0.08$ for the latter).

The only other study that examined accumulation of disability was Study 2001, in which the effect was slightly numerically worse for the 7 mg group compared to placebo, and the effect of the 14 mg group was clearly numerically superior to placebo (and to, of course, the 7 mg group). However, this study was small, and of relatively short duration.

Although the secondary outcomes in TEMSO (including MRI outcomes) cannot, strictly speaking, be formally evaluated (because prior outcomes failed to reach statistical significance), examination of the typical MRI outcomes (BOD, Gd-enhancing lesions, etc.) revealed clear treatment effects for both dose groups, with numerical superiority (often small) of the 14 mg group compared to the 7 mg group. In Study 2001, despite the small number of patients, and relatively short duration, the “primary” outcome, average number of unique lesions/scan, reached statistical significance for both doses, with slight numerical superiority of the 14 mg dose compared to the 7 mg dose. Other MRI outcomes also mostly showed nominally significant differences for both doses compared to placebo; for those outcomes that did show this difference, the 14 mg dose was slightly numerically superior to the 7 mg dose.

Taken together, the data clearly support the conclusion that both doses are effective in reducing the ARR. Multiple MRI outcomes also support an effect of both dose groups (with numerical superiority for the 14 mg group for most outcomes). However, the only direct data on accumulation of disability demonstrated a significant effect for the 14 mg group, but not the 7 mg group. This panoply of results supports the conclusion that both doses are effective in the treatment of patients with relapsing forms of MS, but that only the 14 mg group has been shown to decrease the accumulation of disability. In our view, substantial evidence of effectiveness for both doses has been documented.

For these reasons (safety to be discussed below), I believe that both doses should be approved. We also recommend that the indication to be approved should be somewhat different from that of currently approved treatments for relapsing forms of MS. We are proposing that the indication be, essentially, for “the treatment of relapsing forms of MS”. Current indications state that the drugs are approved for the treatment of relapsing forms of MS to decrease relapses

and slow the accumulation of disability; that is, the specific effects seen in the trials are described in the indications section.

Our current view is that these drugs are prescribed to treat patients with MS (in a global sense), and not for the specific clinical outcomes assessed in the trials. There is considerable precedent for this type of “global” indication in this division; that is, we have approved indications that specify the disease to be treated, but not the specific symptoms assessed in the clinical trials supporting approval.

Such an indication would easily support the description in the label of the 7 mg dose as an effective dose. Specifically, the currently approved indications might preclude the use of the 7 mg dose (because it has not been shown to have an effect on the accumulation of disability). With the more “global” indication, this is no longer a problem (the results of the disability outcome for both doses will be described in the Clinical Trials section of the product label, giving prescribers the information about effectiveness that they would need to choose a dose for a particular patient).

Regarding safety, as noted, teriflunomide is the active metabolite of leflunomide, marketed as ARAVA. As such, teriflunomide is expected to have the same panoply of adverse reactions. Indeed, we have seen that this is the case. Almost all of the events noted in the Boxed Warning, Warnings, and Precautions sections of the ARAVA label have been seen in the teriflunomide development program. Although one cannot say with certainty, for example, that all of these events were, in fact, caused by teriflunomide, the events seen are consistent with the ARAVA label. Little new, from the point of view of adverse events, was seen here, with the possible exception of the cases of acute renal failure.

With regard to these cases, they were all acute events, with rapid resolution. As has been pointed out, drugs known to lower serum uric acid and that are uricosuric (as teriflunomide is) can be associated with acute renal failure that is typically reversible. Dr. Mentari also points out that acute exercise in patients with hereditary hyperuricosuria can result in this picture, as it can in healthy controls. At least one report suggests that patients with hereditary hyperuricosuria and exercise-induced acute renal failure do not recover as quickly as healthy controls post-exercise. As far as I know, none of the patients in the studies who developed acute renal failure were known to have this hereditary condition.

In several of these cases, though, serum potassium reached dangerously high levels. Dr. Villalba also notes that there were several cardiovascular deaths, and several deaths with no identifiable cause, which could have been due to acute cardiac events.

Although I do not agree with Dr. Villalba that the sponsor must perform a Phase 4 study to further evaluate the cardiac effects of teriflunomide (there were few

events that were clearly identifiably cardiac in origin) I do believe that the sponsor has demonstrated that treatment with teriflunomide can be associated with an increase in cardiac risk factors, especially hypertension and elevated potassium. I believe, however, that these risks can be described in labeling, which should be adequate to inform prescribers about how to manage patients.

There were few adverse events of concern in this development program, save, perhaps, for one or two “Hy’s Law” cases, neither of which was unambiguously due to treatment.

Some adverse events were dose related, namely nausea, diarrhea, and alopecia, though the differences between doses in the incidences of these events were small. There was no real dose dependency of serious adverse events, or for discontinuations due to adverse reactions, save for alopecia.

There was dose dependency for changes in several laboratory values, though the vast majority of these changes were not clinically important.

Teriflunomide is clearly embryo-lethal and teratogenic in two animal species, and these findings are the basis for ARAVA’s classification as Pregnancy Category X. Although there have been 16 live births (only 8 in women who had been taking leflunomide; the other 8 were in women whose partners had been taking leflunomide), all 8 of the women who had taken teriflunomide had had a washout procedure as soon as they had become aware that they were pregnant. For these reasons, the human data do not, and cannot, be understood to mean that teriflunomide is not teratogenic in people. Therefore, it must still be considered a presumptive significant human teratogen, and should be classified as Pregnancy Category X.

The review team has recommended that the sponsor perform several studies as Post Marketing Requirements (PMRS):

- 1) Pregnancy Registry
- 2) A drug interaction study with rosuvastatin, because it is a substrate for the transporters BCRP and OAT3, both of which are inhibited by teriflunomide.
- 3) A Pediatric study [REDACTED] ^{(b) (4)} required by PREA.

I agree that these studies should be requested.

For the reasons given above, we recommend that the NDA be approved.

Russell Katz, M.D.

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/s/

RUSSELL G KATZ
09/05/2012

CLINICAL REVIEW

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(Proposed) Trade Name Aubagio
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Applicant Sanofi-Aventis U.S. Inc.

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Dosing Regimen Orally, once/day
Indication(s) Relapsing Multiple Sclerosis
Intended Population(s) Ages 18-65

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1 Recommendations/Risk Benefit Assessment

This review supports the recommendation that the application which seeks the approval of teriflunomide 14 mg as a new oral medication for relapsing multiple sclerosis be approved.

1.1 Recommendation on Regulatory Action

Review of the clinical efficacy data in this submission demonstrates that a daily oral dose of teriflunomide 14 mg reduces the frequency of relapses and delays the accumulation of physical disability in patients with relapsing multiple sclerosis (RMS). The basis for approval of teriflunomide was a single pivotal trial, TEMSO, as well as several supportive trials. TEMSO was a superiority trial of two doses of teriflunomide 7 mg and 14 mg compared with placebo over 108 weeks. In this trial with 1088 RMS patients both doses of teriflunomide had robust results ($p < 0.0002$) for reducing the primary endpoint, the annualized relapse rate (ARR), over placebo. Sensitivity analyses performed included the ARR in the per protocol population (on treatment without major protocol violations), those with all relapses (not just confirmed relapses), and those who continued to have relapses after treatment ended; all had robust findings with $p < 0.0012$. The risk of relapse was reduced by 31.5% for both doses of the drug studied lending support to the consistent effectiveness of this product at reducing relapse. The treatment effect on relapse appeared to be greatest among those more at risk for relapse, namely those less likely to have progressive disease (those who began with an EDSS score ≤ 3.5 at baseline), and in those with known relapsing remitting disease. The risk reduction from this agent appears to be in line with that seen with other immunomodulators but is not expected to be superior to those products. Discontinuations in the trial were high overall (27.6%) but were well balanced. The interim analysis of the as yet incomplete pivotal trial, TOWER, appears to be consistent with the reduction in the ARR as well.

(b) (4)

This was explored with the key secondary endpoint in the pivotal trial, a reduction in the time to three month confirmed disability progression using the Expanded Disability Status Scale (EDSS). Statistically significant findings ($p=0.0279$) were present for the teriflunomide 14 mg dose for the secondary endpoint in the ITT population with a hazard ratio of 0.702 (CI 0.506, 0.973) on the 14 mg dose compared with the placebo. This was further supported by the results for the per protocol population. The risk for disability reduction trended positive but was not significantly reduced, at the end of the trial for the 7 mg dose. At 108 weeks, only 20.2% of those on teriflunomide 14 mg had progressed whereas 27.3% of those on placebo had progressed and risk of progression was reduced by 25.1% ($p = 0.1259$).

There were numerous MRI endpoints that were evaluated in the pivotal trial that confirmed the benefit of the drug. They included the burden of disease (BOD), the volume of gadolinium-enhanced T1 lesions, the volume of T2 lesions, and the volume of T1 hypointense lesions. All had statistically significant results (between $P = 0.0161$ to 0.0001) for the 14 mg dose of teriflunomide including the volume change of the T1-hypointense lesions, the volume of the T2 lesions, and the volume of the T1 gadolinium-enhanced lesions. At every time point measured in the 108 week study the BOD was greater on placebo than on 14 mg of teriflunomide. This finding was further supported by the primary endpoint in the phase 2 trial, 1726/2001, which was the number of unique active lesions/MRI scan seen for the double-blind portion of the trial with a statistically significant effect ($p=0.0052$) in those treated with teriflunomide 14 mg. The average number of lesions was 2.69 on placebo and 0.98 on 14 mg of teriflunomide.

The sponsor proposed an indication that would include treatment for RMS. The vast majority of patients in the TEMSO trial had relapsing remitting multiple sclerosis (RRMS) (91.3%). Those with secondary progressive multiple sclerosis (SPMS) and progressive relapsing multiple sclerosis (PRMS) entered the TEMSO trial, (4.8%, 3.9% respectively), but a treatment effect or trend on reduction of relapse rate was only seen in the 14 mg dose for the group as a whole and in those with RRMS but not for the SPMS or PRMS subgroups. Past approvals for drugs for relapsing MS have not required more than what was demonstrated in this trial, namely that the effective dose reduces relapses in those with RRMS including those most at risk for progressive disease, namely those with greater physical disability (higher EDSS scores). Although subjects in the pivotal trial were almost entirely foreign, it is felt that this was unlikely to have had a significant effect on the reliability of the outcome measures for the US population.. Overall the demographics of the population studied in terms of age, race, sex, type of MS appears consistent with what would be seen in a clinical trial conducted in the US. It is known that safety reporting from foreign sites may be more likely to be different from that of US sites as foreign subjects typically report less side effects and foreign narratives are often less comprehensive than those from US sites. The effects of having primarily foreign data will be commented on more fully by the safety reviewer. The interim results of the TOWER trial which confirm the TEMSO trial and which contained 18.6% US subjects suggests that lack of US subjects in the present application does not pose a problem that would preclude an approval at this time.

It was noted that the discontinuation rate was high (28.5% or 305 subjects) in the TEMSO trial and this is a concern as a high discontinuation rate can adversely affect study validity by compromising randomization. The unblinding in this trial was also high (3.6% or 40 subjects), but primarily included those who dropped out for reasons that

appeared reasonable and not arbitrary. Since the discontinuations and the unblindings appear to have been well balanced among treatment arms, neither was felt to have significantly biased the outcome of the study. The three most common causes of discontinuation were lack of efficacy, significant side effects and pregnancy related issues.

1.2 Risk Benefit Assessment

In this submission there is evidence that teriflunomide has demonstrated benefit at the 14 mg dose for both reducing the frequency of clinical exacerbations as well as delaying the accumulation of physical disability as measured by the EDSS in those with relapsing MS. Efficacy has been further substantiated by various MRI endpoints. This drug has the added benefit that it is easy to use because it is an oral agent rather than parenteral as most of the drugs in its class. Although teriflunomide has side effects that involve multiple organ systems, most notably liver, bone marrow suppression with the potential for opportunistic infections and malignancies, pulmonary toxicity, peripheral neuropathy, weight loss, and hypertension, these have already been reasonably well characterized because the drug is the major metabolite of leflunomide which has more than two million patient years of use. Although risk of serious and at times fatal liver disease is largely idiosyncratic, risk factors have already been identified that can help mitigate risk such as not treating subjects that have signs of acute and chronic liver disease. With adequate safety monitoring as recommended in the label it is anticipated that the benefit will be greater than the risk.

Although most safety signals seen with teriflunomide had already been noted with leflunomide, some that have been seen in this application were not previously identified and further evaluation might be part of a postmarketing requirement. The side effects and postmarketing requirements and commitments will be described in further detail in the review by Dr. Lourdes Villalba and Dr. Evelyn Mentari, the safety reviewers.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Please see recommendations of the Safety and OSE Reviewers.

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend a postmarket requirement to evaluate treatment with teriflunomide in the population ages 10 to 17. As recommended by the Pediatric Review Committee (PeRC) the protocol should be submitted by December 28, 2012 and completed by November 3, 2016. The final study report should be submitted to the FDA by June 17, 2017. Please see further recommendations of the Safety and OSE Reviewers.

2. Introduction and Regulatory Background

Multiple Sclerosis (MS) is a chronic, inflammatory, demyelinating disorder of the central nervous system (CNS) which in some individuals can lead to progressive neurological disability. It is one of the most common causes of disability in young adults and typically presents between the ages of 20-40. The disease is more common in women than in men. Symptoms can range from visual loss, weakness, dysesthesias, spasticity, coordination problems, incontinence, cognitive decline as well as other symptoms. Typically the disease presents with recurrent attacks or “relapses” characterized by focal neurological symptoms with variable recovery between attacks. As described by Lublin and Reingold, MS is characterized by four distinct clinical categories which include: relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), primary-progressive MS (PPMS), and progressive-relapsing MS (PRMS). RRMS accounts for at least 85% of all initially presenting MS cases and 15% present with a progressive form of MS. Ultimately of those with active cases of MS about 58% have RRMS, 27% have SPMS, 6% have PRMS and 9% have PPMS. The average life expectancy of an MS sufferer is probably 5-7 years less than that of an age matched control and their life may be characterized by multiple medical problems warranting treatment. Often the ability to live independently is compromised and specifically 50% of MS sufferers have a severe enough gait disorder that use of a cane or wheelchair is necessary after having the disease for 15 years or more.

Treatment goals for this disorder is to shorten the duration and severity of symptoms associated with relapses, prevent the incidence of relapses, and delay the accumulation of disability. Numerous disease modifying drugs have become available to the public since 1993, but most are parenteral and not oral and their predominant effect is on relapses and not the accumulation of disability. It is thought that about 50% of MS patients switch treatment or discontinue treatment within 18 months of starting therapy due to dissatisfaction with their current treatment. This leaves much room for alternative therapies.

2.1 Product Information

The product, Teriflunomide, is a film-coated immediate-release (IR) oral 14 mg tablet. It is an orally delivered immunomodulator product which is both anti-proliferative and anti-inflammatory, although the exact mechanism of action is not fully understood. It blocks de novo pyrimidine synthesis and has a cytostatic effect on proliferating T-cells and B-cells in the periphery, but does not affect resting or slowly dividing cells that occur via the salvage pathway. This blockage causes less activated lymphocytes to enter the central nervous system, but slowly dividing cells are spared. 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 product was shown to have anti-inflammatory effects in a rat model of experimental autoimmune encephalomyelitis (EAE) where prophylactic treatment with teriflunomide delayed the development of disease onset and reduced symptoms compared with rats receiving placebo. It was found to reduce inflammation, demyelination, and axonal loss in rats.

2.1.1 Pharmacologic Class

Teriflunomide is 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.

2.1.2 Chemical Name

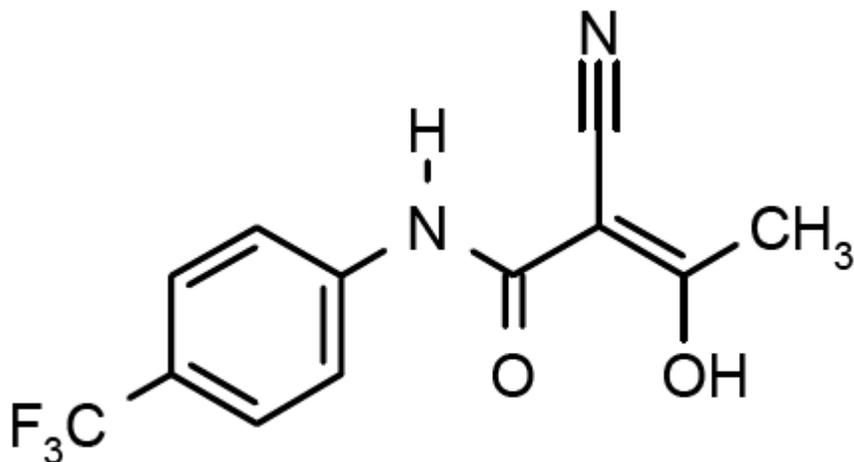
[Z]-2-cyano-3-hydroxy-but-2-enoic acid-[4'-trifluoromethyl-phenyl]- amide

2.1.3 Trade Name Aubagio

2.1.4 Chemical structure

The molecular weight of teriflunomide is 270.21. The molecular structure is found in Figure 1.

Figure 1 Molecular Structure of Teriflunomide



2.1.5 Applicant's proposed dosing regimen and age group recommendation

The sponsor recommends a dose of 14 mg administered orally once daily, with or without food.

2.2 Table of Currently Available Treatments for Proposed Indication

Table 1 Treatment for Proposed Indications (as of January, 2012)

Medication	Indication	Maintenance Dose/Route of delivery	Efficacy	Safety concern 1 st or 2 nd line
Avonex (IFNβ-1a) BLA 103628	↓ Exacerbations & slows physical disability in relapsing forms	30 mg q week IM	32% reduction RR 37% reduction disability	Decreases blood count, hepatic injury, flu-like symptoms 1 st line
Rebif (IFNβ-1a) BLA 103780	↓ Exacerbations & slows physical disability in relapsing forms	22 mcg tiw SQ	29% reduction in RR	Hepatic injury, flu-like symptoms, injection site reaction 1 st line
		44 mg tiw SQ	32% reduction in RR	
Betaseron (IFNβ-1b) BLA 103471	↓ Exacerbations & delay physical disability in relapsing forms	0.25 mg every other day SQ	30% reduction in RR	Injection site necrosis, flu-like symptoms 1 st line

Copaxone (glatiramer acetate) NDA 020622	↓ Exacerbations In RRMS and Includes patients with CIS	20 mg/1 ml qday 20 mg/0.5 ml qday SQ (filed, not approved)	29-75% reduction in RR	Transient chest pain, post-injection reaction, skin necrosis 1 st line
Tysabri (natalizumab) BLA 125104	↓ Exacerbations and delays physical disability in relapsing forms of MS	300 mg q4 weeks IV	61% reduction in RR, 33% reduction in disability progression	PML, immunosuppression, malignant melanoma, hepatic toxicity
Novantrone (mitoxantrone) NDA 021120	↓ Exacerbations & neurological disability in SPMS or worsening RRMS	12 mg/m ³ q3 months IV	60% reduction in RR, 64% reduction in disability progression	Cumulative cardiotoxicity, AML 2 nd line
Gilenya (fingolimod) NDA 022527	↓ Exacerbations & delays physical disability in relapsing forms of MS	0.5 mg PO qday	55-58% reduction in RR, 29-30% reduction disability	AV conduction delay, decrease in HR with first dose, infections, macular edema, decreased pulmonary functions, increase in liver enzymes 1 st line

Based on most currently available drug labels

2.3 Availability of Proposed Active Ingredient in the United States

Teriflunomide is not marketed in the US and is an investigational product for the treatment of multiple sclerosis.

2.4 Important Safety Issues with Consideration to Related Drugs

Disease modifying therapies for MS have been available since 1993. All disease modifying therapies for MS can be characterized by effect on relapse rate and some also prevent or delay the accumulation of disability, as measured by effect on the EDSS. Most products are approved for all of the relapsing forms of MS as summarized below and in Table 1.

Treatments approved for decreasing the number of relapses in MS include immunomodulatory and immunosuppressive agents. First line agents are those which are associated with less risk and include the various recombinant interferon β , Gilenya, and Copaxone (GA). Other agents are recommended for those who have had an inadequate response to alternate MS therapies such as Tysabri or second-line agents such as Mitoxantrone because they are associated with greater toxicity.

The interferon β safety profile in adult patients with a diagnosis of relapsing MS has been established and is summarized here. There are four products that are approved in the US, IFN β -1b (Betaseron and Extavia) and IFN β -1a (Avonex and Rebif). All are

injectable. The interferon drugs are made from recombinant technology and are intended to mimic the action of interferon molecules made in the body. As such, all can elicit an immune response and cause hypersensitivity reactions, rare anaphylaxis and immunogenicity. It has been reported that as much as one third of treated patients can develop abnormal liver function tests. Localized injection site reactions (ISRs) such as redness, swelling, pain, edema and even infrequently, necrosis can occur. In addition, some have been associated with a flu-like symptom complex (fever, chills, muscle aches, fatigue), and headache which can be moderated by taking nonsteroidals before injection. Severe adverse reactions are rare, and most are mild. Leukopenia, lymphopenia, thrombocytopenia and even pancytopenia have been associated with some of their use, but are not only rare, but generally reversible with drug cessation. Thyroid dysfunction and depression have also been associated with many of the products as well as other autoimmune disturbances. In general these agents lower relapse rate by approximately 30% compared with placebo and delay the accumulation of disability

Copaxone (GA) is an immunomodulator whose mechanism of action is not fully understood. It is a random polypeptide which resembles myelin basic protein which can affect T cell activation and differentiation. Because GA can modify immune function, concern exists about its potential to alter naturally occurring immune responses. According to the label, results of a limited battery of tests designed to evaluate this risk produced no finding of concern, nevertheless, this possibility cannot be excluded. GA-reactive antibodies are formed in most patients with chronic use which are almost exclusively IgG. No IgE type antibodies have been detected; nonetheless the possibility of anaphylaxis can not be excluded. Special warnings and precautions for GA include immediate post-injection reaction, chest pain, usually transient, lipoatrophy and skin necrosis. Common adverse reactions found in $\geq 10\%$ include injection-site reactions, vasodilatation, rash, dyspnea, and chest pain. GA is approved for RRMS and those with clinically isolated syndrome (CIS) but does not have an indication for delaying the accumulation of disability. In terms of preventing relapses, GA has been shown in clinical trials to be comparable in effectiveness to the interferons.

Tysabri is a humanized antibody to α integrin and it is an immunomodulatory medication. It is recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy. In addition to demonstrating evidence for being one of the most effective medications for reducing relapse rate (approximately reduces relapse rate by 60%), it also is known to reduce the progression of disability by about 33%. Tysabri is not typically first line treatment because of the side effect of Progressive Multifocal Leukoencephalopathy (PML) which ranges between < 1 to 11% of users depending upon currently identified risk stratification factors which include duration of use, prior use of immunosuppressants and presence of antiJCV antibody. Tysabri binds to the $\alpha 4$ -subunit of $\alpha 4\beta 1$ or $\alpha 4\beta 7$ integrins which are expressed on the surface of all leukocytes other than neutrophils. Other potential risks

include liver dysfunction, infusion reactions and increased risk of other opportunistic infections including herpes infections of the central nervous system.

Mitoxantrone, a chemotherapeutic agent, is a second line agent which is indicated for reducing relapses and disability in both SPMS as well as RRMS. It is highly effective with approximately a 60% reduction in both relapses and disability progression. Due to the cardiotoxicity associated with this product, it cannot be used beyond two years. Melanoma has been observed with this product. Mitoxantrone affects replication of DNA especially in rapidly dividing cells such as lymphocytes and can affect the immune system by altering production of cytokines, interfering with antigen production, and altering leukocyte trafficking.

Gilenya is the most recently approved agent with an MS indication. It is a sphingosine 1-phosphate receptor modulator which was approved as a first line agent and it is the first oral agent to treat RMS. It is thought to reduce relapse rate by about 55% and disability rate by about 30%. Significant safety signals that have been identified in clinical trials include the potential to decrease the heart rate and cause atrioventricular conduction delays after the first dose, macular edema which can occur with or without visual symptoms, decrease in pulmonary function, increased risk of infections related to the reduction in peripheral lymphocyte count, and increase in liver transaminases. Since approval there have been at least 10 deaths due to Gilenya, but none to date can be directly attributed to the product.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Investigational New Drug application (IND) for teriflunomide was initiated in the United States on August 27, 2004 for the treatment of multiple sclerosis. At the time that the IND was initiated the product was already at the end of Phase 2 development of monotherapy and the sponsor was preparing to embark on a Phase 3 study to support the registration of teriflunomide. Over the course of the last eight years there have been four regulatory meetings and numerous teleconferences and correspondences culminating in this NDA submission. This review of the regulatory history will primarily be confined to details of the clinically relevant information as modules 3 and 4 will primarily be reviewed by their respective disciplines. Requests concerning the datasets structure and the presentation of electronic submissions will also be omitted.

2.5.1 May 28, 2004 Clinical Hold of IND

The IND was submitted on March 30, 2004, but before the thirty day meeting commenced, the IND was placed on inactive status on April 14, 2004. At the sponsor's request the IND was reactivated on April 29, 2004. The sponsor then followed up asking for an EoP2 meeting on April 30, 2004. This time the 30 day review was completed and a Clinical hold letter was issued on May 28, 2004 and cited the following deficiencies:

- The Clinical Investigator's Brochure needed to be revised as it was felt to be misleading, erroneous and materially incomplete.
- The Informed Consent needed to be revised to include notifying subjects that teriflunomide might have genotoxicity and carcinogenicity.
- If subjects drop out of the study the protocol should include a teriflunomide elimination program with cholestyramine until the drug concentration drops to 0.02 ug/mL or below. It was stated that without cholestyramine it might take as much as two years to clear the body of teriflunomide.

The Agency received an adequate complete response to the clinical hold on the IND on July 28, 2004 and on August 30, 2004 the clinical hold was lifted.

2.5.2 November 12, 2004 End of Phase 2 meeting (EoP2)

An EoP2 meeting was held on November 12, 2004 to discuss phase 3 development of teriflunomide for monotherapy. The items cited below were discussed.

Several clinical pharmacology studies were requested including a mass balance study, characterization of the metabolic pathways, conduct of drug-drug interaction studies and a PK study in patients with hepatic impairment. At this meeting it was also concluded that studying renally impaired subjects might become necessary.

It was agreed that the TEMSO trial could potentially serve as a pivotal trial with a primary endpoint of ARR but a second trial would be necessary to meet the usual standard of two independent trials for substantiation of efficacy. It was agreed that the previously performed phase 2 trials could help support the safety database of the product but that the previously performed trial 1726/2001 had an inadequate design to be relied on for proving efficacy. It was possible that the combination trials with either Copaxone or interferon-beta might lend support to registration.

The sponsor was advised that even if the drug made its primary endpoint of reducing the ARR, labeling typically would not include that the drug showed an effect on the underlying disease itself.

Policy regarding secondary endpoints was discussed and the following points were made.

- They must be prospectively designated
- They must be replicated
- They must be in a domain separate from the primary outcome
- The statistical analysis plan must include a priori method for dealing with multiplicity if multiple outcomes were to be analyzed

Specific endpoints were discussed. It was agreed that EDSS and MRI endpoints would be likely acceptable secondary outcomes depending on the specific proposal. The Fatigue Impact Scale (FIS) was discussed as an instrument and the agency agreed that it could probably be used as a secondary outcome if so desired.

The criteria for diagnosing MS were discussed and all agreed that use of the McDonald criteria were acceptable for the pivotal trial.

The sponsor was given advice about statistical analyses. The sponsor would need to justify the use of the Poisson analysis. They would need to clearly describe in their statistical analysis plan (SAP) the statistical order of testing the various doses to be studied and how dropout would be handled.

The sponsor was informed that there was an inadequate safety database to support initiating a phase 3 trial (TEMSO) because of concerns regarding bone marrow toxicity seen in a 3-month dog study. The sponsor responded by saying that they were going to officially withdraw three protocols from the IND (EFC6049/TEMSO, PDY6045 and PDY6046) in order to avoid being placed on Clinical Hold again.

There was some disagreement about the need for studying combination toxicity of teriflunomide as an adjunctive treatment in animals and the agency felt that such studies were necessary.

The agency asked for greater stringency on contraception with requirement for double contraception in clinical trials.

The agency's requirement for HIV testing was discussed at length. As the sponsor thought that HIV testing was unnecessary, they were asked to prepare an argument justifying their position.

Pertaining to adjunctive treatment with teriflunomide, the sponsor was advised that the effects of concomitant teriflunomide and the INF-beta and GA should be evaluated to address concerns for the potential PK and or PD interactions.

2.5.3 August 2, 2005 Teleconference

A teleconference was held to discuss multiple issues of concern between the agency and the sponsor which included answering submitted questions as well as issues raised during the teleconference. The following items were discussed.

Leflunomide and teriflunomide were compared and it was concluded that there were differences noted between the two drugs that warranted further investigation. The potential genotoxicity of [REDACTED] (b) (4) impurity/ of teriflunomide not found in leflunomide, needed to be further explored. Discrepancies between leflunomide and

teriflunomide with respect to bone marrow and pancreatic toxicity in animals needed to be more fully investigated.

The agency described its concerns regarding the 14 mg dose of teriflunomide. They were concerned that the 14 mg dose would not lead to a potential plasma exposure within the range of what had been achieved with the marketed leflunomide and requested further elucidation of dosing before starting phase 3 trials. There was additional concern that smoking status could affect the PK parameters.

The agency was concerned about how the sponsor described adverse events in previously performed trials and advised the sponsor to reanalyze past studies by combining various treatment emergent events to better understand side effects such as peripheral neuropathy, alopecia, seizures.

The sponsor was advised that HIV testing was mandatory for patients in trials with teriflunomide and that collecting history or performing a CD4 count was not an adequate substitute.

Post-marketing reports for leflunomide were reviewed and concerns about peripheral neuropathy, bone marrow toxicity, pancreatic toxicity, seizures, arteritis/vasculitis, and hypertensive crisis were discussed and the sponsor was advised that safety monitoring would need to be substantially upgraded to protect patients in phase 3 trials.

In addition, concerns from preclinical studies suggesting various signals suggested a need for better characterization of neurotoxicity, arteritis, and panarteritis associated with teriflunomide use.

The agency's concern about the need for preclinical adjunctive treatment studies was alleviated by data that the sponsor submitted and it was deemed that they would not be required.

2.5.4 June 27, 2006 Full Clinical Hold of IND

The sponsor issued a Special Protocol Agreement (SPA) for the TOPIC trial on May 16, 2006. This protocol was an international, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of 7 mg and 14 mg of teriflunomide vs. placebo in patients with a first clinical episode suggestive of MS. The issues of concern lead to a clinical hold which involved the following items:

The agency remained concerned about genotoxicity associated with (b) (4) and asked for more information.

The agency expressed reservations about the adequacy of clinical safety monitoring particularly how bone marrow toxicity, hepatotoxicity, pancreatic, neuropathic, and

pulmonary toxicity should be monitored during the study and how they should be described in the Informed Consent and Investigator's Brochure. The sponsor was advised that at a minimum they needed to follow the ARAVA labeling recommendations for clinical laboratory monitoring regarding bone marrow toxicity and hepatotoxicity. To guard against interstitial lung disease they were advised to have patients get pulmonary function tests at baseline and then every 6 months during treatment. They were advised to monitor for pancreatic toxicity and for peripheral neuropathy. Safety algorithms were recommended so that investigators would know when to stop the drug if signs of toxicity should occur.

In the Clinical Hold letter several sponsor related questions regarding the TOPIC trial were addressed as well as issues regarding eventual drug registration for monotherapy. The sponsor wanted to know if the TOPIC and TEMSO trials could serve as pivotal trials that would support the registration of teriflunomide for the indication "treatment of patients with the relapsing forms of M (b) (4)". The sponsor was advised that since TEMSO was withdrawn from the IND and had not been carefully reviewed there was no clear understanding of the experimental design. Regarding the TOPIC trial, there was concern about the use of the composite primary endpoint which could potentially be problematic. (b) (4)

(b) (4) The sponsor was advised that the exact wording of the indication statement would depend both on the specific endpoint chosen and the results of the study. If the drug was deemed efficacious, acceptable wording of indication could be similar to Avonex which states that the drug is indicated for "patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with MS".

Non-Hold issues were also discussed. The sponsor was warned not to have too many exclusion criteria, such as those with past history of tuberculosis or those who use Saint John's Wort. If numerous exclusion criteria were provided then they needed to be justified and they could lead to major restrictions in labeling. The rationale for dosing, such as why higher and lower doses were not explored, should be clarified. For registration at least one monotherapy study providing evidence of safety and efficacy of two years duration should be provided. In the PK/PD analysis under fed conditions the timing of dosing in relationship to food intake should be documented as a covariate for the final analysis. Various co-medications that could have an impact on the metabolism of teriflunomide also should be included as potential covariates. Pulmonary function testing should follow the American Thoracic Society/European Respiratory Society guidelines.

The sponsor responded to the Clinical Hold with a satisfactory Complete Response dated December 20, 2006 and the hold was lifted on January 18, 2007.

2.5.5 June 5, 2007 Response to sponsor's questions in lieu of meeting

The sponsor sent in written questions a written response was issued. Many previously discussed issues were reiterated including the following items.

Two independent positive trials would be needed for registration. The phase 2 trial, 1726/2001, was not considered adequate to prove clinical benefit. It might be possible for one of the adjuvant treatment trials to serve as a supportive trial but the design should be a superiority trial. The method of assessing relapses as a primary endpoint was discussed and the agency expressed a preference for looking at group relapses rates over other measures such as percentage relapse free. The requirements for secondary outcome measurements for labeling were reiterated as previously discussed at the EoP2 meeting. The agency added that EDSS would likely be seen as an acceptable secondary outcome measure if relapse rate was the primary outcome measure. The agency recommended limiting secondary outcome measures to one or two that should not overlap with the primary outcome measure. An MRI outcome was suggested as a secondary outcome measure. The need for justifying the Statistical Analysis Plan (SAP) was again made including a plan for dealing with drop-outs. The McDonald criteria were acceptable as an inclusion criterion for the TEMSO trial and FIS could also be a secondary outcome in the trial if desired.

In addition, comments regarding trial design for the TOPIC trial were reiterated as previously discussed at the time of the Full Clinical Hold of June 27, 2006. The sponsor was referred back to the comments made at the EoP2 meeting.

2.5.6 September 28, 2007 Correspondence regarding HIV issue

The agency sent the sponsor a letter regarding a misunderstanding that had arisen over the inclusion of HIV patients in the clinical trials. The agency made it clear that they did not want HIV positive patients to be solicited for the clinical trials. They recommended that all subjects be screened for HIV before entering clinical trials with teriflunomide. The sponsor was cautioned that if they choose not to screen patients for HIV prior to treatment, then the data from the clinical trials will be deemed unacceptable at NDA filing because of the unethical way the trial was conducted.

2.5.7 September 1, 2010 Letter regarding Fast Track designation

The sponsor submitted a Fast Track designation on September 1, 2010 based on treating a serious condition and the unmet need for effective, convenient, well-tolerated treatments, but this was denied by the agency on October 27, 2010 since there already was an orally approved agent for this condition in addition to numerous parenteral treatments.

2.5.8 September 14, 2010 EoP2 meeting Teriflunomide as adjunctive therapy

At the end of the EoP2 meeting for teriflunomide as an adjunctive therapy to beta-interferon, the issue of the development program for monotherapy with teriflunomide was raised as it appeared that the recently completed TEMSO trial had very robust findings. The sponsor was encouraged to present a more complete overview of their program to determine if a preNDA meeting should be scheduled.

The sponsor responded to the agency's request for further information about the status of their trials with a briefing document dated October 8, 2010. In this document the sponsor proposed that efficacy for teriflunomide would be based on the TEMSO trial, the 1726/2001 proof of concept study, the two adjunctive treatment trials PDY6045 and PDY6046 as well as the extension trials LTS6048 and LTS6050. They provided evidence of a robust treatment effect for the primary end point for both the 7 mg and 14 mg dose of teriflunomide in the TEMSO trial. Multiple sensitivity analyses also supported efficacy as did analyses of the time to first relapse and the proportion of relapse free patients. The drug also showed efficacy of the 14 mg dose for lengthening the time to disability progression sustained for 12 weeks. The 14 mg dose was superior with many of the MRI endpoints including lowering the burden of disease (BOD), reducing the T2 hypointense lesion volume, lowering the number of gadolinium-enhanced lesions/scan, lowering the number of unique active lesions/scan as well as other measures.

The sponsor provided safety data from multiple trials to confirm the size of their safety database to support an approval with evidence that the drug was well tolerated. The sponsor expressed a willingness to do an interim analysis of their second pivotal trial, TOWER, in order to confirm the benefit/risk profile of their product. As the evidence for efficacy seemed quite strong based on the information in the briefing document, the sponsor was encouraged to proceed with their plans to submit an NDA as stated in a letter dated December 20, 2010 by the agency.

2.5.9 January 11, 2011 PPSR

On January 11, 2011 the sponsor submitted their first Proposed Pediatric Study Request (PPSR). This was discussed on a preliminary basis at the preNDA meeting on March 28, 2011. Before responding to the PPSR the FDA requested that the sponsor submit the 60 day comments of the Pediatric Committee (PDCO) of the European Medicines Agency (EMA), Response to Request from PDCO/EMA for Pediatric Investigation Plan (PIP) Modifications, and Revised PIP. In summary, PDCO asked for the following changes to the proposed study:

- Change to a randomized study
- Change in the primary endpoint to brain MRI measure of the number of new or enlarged T1 lesions/MRI scan

- Addition of various secondary endpoints
- PK run-in phase with 7 mg adult equivalent dose
- Change in the duration of the proposed study as well as a possible extension study

After reviewing the PPSR and the European comments, the agency responded by issuing an inadequate study request on July 21, 2011. The agency recommended that the sponsor submit a partial waiver for those under age 10 because of insufficient number of patients in that age range making completion of such studies impossible or impractical.

The agency also recommended a deferral of pediatric studies for those ages 10 to under 17. In response to agency feedback the sponsor complied. The agency suggested the deferral so that they would have the time to do a preliminary review of the safety and efficacy data first and to determine if the pediatric development plan was appropriate and if the nonclinical data was adequate to support the clinical studies. This would also give time to complete necessary preclinical studies in juvenile rats. It was suggested that pediatric clinical studies may need to be staggered to include those ages 10 to under 11 first so that the lengthier adolescent rodent studies could be completed before conducting a trial including those ages 12-17. The agency stated that a Written Request could be issued prior to approval, but sometime after the submission of the NDA that would meet the requirements of the Pediatric Research Equity Act (PREA) and the best Pharmaceuticals for Children Act (BPCA).

The planned nonrandomized efficacy trial was felt to be inadequate and likely to render uninterpretable results. If an MRI endpoint was to be utilized, then a compelling argument needed to be made that it was appropriate to bridge product efficacy from the adult to the child with MRI and that 6 month MRI data would be predictive of clinical endpoints at a later time point.

The toxicology program that was proposed was reviewed by Pharm Tox who had the following comments:

- The juvenile animal study should include an expanded neurohistopathological evaluation of the brain and a neurobehavioral assessment.
- The neurohistopathological evaluation should include examination of all the major brain regions and cellular elements, particularly those that might indicate developmental insult.
- The neurobehavioral tests should assess sensory function, motor function, learning and memory.
- The T cell dependent antigen response (TDAR) should be assessed in addition to other immunotoxicology parameters in recovery animals.

2.5.10 March 28, 2011 preNDA meeting

The sponsor agreed to consider data from the TEMSO trial with support from Trial 1726/2001 for registration of the NDA. The agency agreed that the TOWER trial should be presented as an interim descriptive analysis. A plan to preserve the integrity of the study by using an independent group to prepare the report was also agreed upon. Analyses for the TEMSO trial needed to include both supportive analyses of the primary endpoint as well as secondary analyses. Specifically analyses for the ARR should include a sensitivity analysis of the Per Protocol (PP) population as well as those with confirmed relapses, all relapses, relapses including those that occurred after treatment discontinuation and an analysis of first relapse. The sponsor also made clear that for Trial 1726/2001 an analysis of ARR could not be done for those with confirmed relapses, as relapse confirmation was not performed.

The safety analysis was discussed and was to include an analysis of the worldwide knowledge of the product including data from PDY6045, PDY6046, LTS6050 and LTS6047. Adjunct therapy would not be pooled with monotherapy and would be under its own separate heading of "Adjunct Phase 2 Studies".

The pooling strategy for the safety analysis was discussed including a placebo-controlled pool and a non-comparative active treatment pool. The analysis of the placebo-controlled pool (TEMSO + Trial 1726/2001) would be in the Summary of Clinical Safety/Integrated Summary of Safety (SCS/ISS). The agency requested detailed TEMSO safety study results to include deaths, discontinuations, serious adverse events and common adverse events as part of the ISS as well as in the clinical study report. Narratives were to be included for all deaths, discontinuations, and serious adverse events. Unblinded safety data from the TOWER study would be filed as a separate submission in a nonintegrated interim analysis.

Blinded safety data presented in this NDA would include the extension trials LTS6048 (2001 extension), LTS6050 (TEMSO extension) as well as the blinded EFC10981/TENERE (nonIND active comparator study) and the EFC6260/Topic (treatment for Clinically Isolated Syndrome). The Agency also requested that safety data from EFC6058/TERACLES studying adjunctive therapy which begins recruitment in February, 2011 should be included in the NDA. For all ongoing studies, individual summaries for any deaths or SAE that occur up to June 11, 2011 would be included.

Since quite a number of the studies involving safety were ongoing including the two extension trials, the dates for data cut-off and interim "lock" were agreed upon for each ongoing study.

Other safety requests included the following for planned analyses of Phase 1 studies:

- Summary of the protocols for collecting ECG data in Phase 1 studies. For both the single dose and repeated dose study pools, it was requested that the

sponsor report on the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

- Analyses and narratives for deaths, all discontinuations, and SAEs.
- Table of treatment-emergent adverse events and a table of treatment emergent SAEs reported in $\geq 1\%$ of all teriflunomide-treated subjects in phase 1 studies sorted by SOC and then MEDRA Preferred Term. These should include separate columns for teriflunomide and for placebo.
- Vital signs analyses for the phase 1 pools should include a table of the incidence of treatment-emergent abnormal vital signs at any visit during the phase 1 studies.
- Outlier analyses of phase 1 vital sign data which include the number and percentage of subjects with at least one post-treatment vital sign measurement meeting these criteria: Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mm Hg, Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg, Pulse Rate: <60 bpm, >100 bpm, Body Weight: decrease of $\geq 7\%$ from baseline and increase of $\geq 7\%$ from baseline, Temperature: >38.0 °C or <36.0 °C.

The sponsor plans to present the safety data as requested with the exclusion of study TES10952 (thorough ECG study) which will be provided separately. The sponsor also defined clinically significant ECG QTc abnormalities a bit differently than the agency and planned to use the following definitions:

	<i>Males</i>	<i>Females</i>
Borderline	431-450 ms	451-470 ms
Prolonged	> 450 ms	> 470 ms
QTc	≥ 500 ms	≥ 500 ms

The agency requested that planned integrated vital sign analyses for phase 1 studies needed to be done for both single and repeated dose studies. It was deemed sufficient for the sponsor to provide summaries by the pooled teriflunomide dose groups for phase 1 studies.

Tentatively the agency agreed that the size of the safety database appeared adequate for determining the risk/benefit of teriflunomide.

Regarding the phase 2 and 3 studies, the agency requested that the sponsor provide an analysis and narrative for all deaths, discontinuations and SAEs. A table of treatment-emergent adverse events and SAEs report in $\geq 1\%$ of all teriflunomide-treated subjects should be sorted by SOC and then MEDRA Preferred Term. There should be a column for each dose of teriflunomide and placebo. ECG data should be report on the frequency of post treatment QTc > 450 ms, >480 ms, and > 500 ms. Treatment – emergent abnormal vital signs should be reported in a tabular fashion similar to phase 1 results. Patients should be counted only once even if they cross the threshold multiple times. Outlier analyses should be performed as for the phase 1 subjects.

The list of adverse events of special interest were agreed upon as well as how they should be presented included nausea, diarrhea, hepatic disorders, pulmonary disorders/ interstitial lung disease, peripheral neuropathy, blood pressure increase/ hypertension, bone marrow disorders, hypersensitivity/anaphylactic reaction, pancreatic disorders, infections, alopecia, pregnancy, cardiac arrhythmias, convulsions, hemorrhage, embolic and thrombotic events, and malignancy. Common treatment emergent adverse events (TEAEs) $\geq 2\%$ in either teriflunomide group compared to placebo would be provided for pool 1 in addition to other planned and requested summaries.

The agency agreed that no further drug abuse liability assessments (DALA) needed to be performed based on the available nonclinical and clinical data and that the NDA should include all related primary data in the DALA document.

The format of narratives was agreed upon to include at a minimum a line listing for each event even if one narrative contains several events. Narratives should include patient age and gender, signs and symptoms related to the AE, exposure duration, pertinent medical history, physical examination findings, test results, concomitant medications, discussion of the diagnosis and or differential diagnosis, treatment provided, re-challenge results if performed, outcome and follow-up information.

Treatment discontinuations not due to adverse events were to be presented in a tabular format and not with written narratives. Since it was anticipated that the total number of narratives in the NDA would be more than 1000, it was agreed that some could be provided at the time of the 120-safety update report.

Datasets were agreed upon for the efficacy analysis, clinical pharmacology analysis and safety analysis. Datasets for phase 2 and 3 trials should contain verbatim and MedDRA coding and each SAS transport file should have a unique patient identifier.

The nonclinical program appeared adequate for supporting an NDA but would be a matter of review.

The sponsor planned to submit the final study reports to the TOWER study and the TENERE study (non-IND active comparator study) as an efficacy supplement upon completion of the NDA.

The pediatric development plan was discussed. Final decisions about partial waivers for those under age 10 and deferrals for those between ages 10 to up to 17 with a pediatric plan would be a matter of review. The sponsor was given clearance to begin the preclinical juvenile toxicology program and when the clinical pediatric trials begin they should stagger enrollment and start with those for whom there is adequate preclinical support.

Labeling was briefly discussed and it was agreed that labeling content would be determined after review.

2.6 Other Relevant Background Information

At this time, in addition to the United States, clinical trial applications are open in Europe and Canada, as well as Africa, Asia and Latin America. Teriflunomide has not yet been the subject of any marketing authorization worldwide.

Teriflunomide is the active metabolite of Leflunomide which was approved September 10, 1998 [REDACTED] ^{(b) (4)} as ARAVA by Hoechst for the treatment of rheumatoid arthritis. Nearly 2 million patient years of exposure data has been collected since the drug was approved. The patent for ARAVA expired on September 13, 2005 and leflunomide has been marketed as a generic drug since then by several companies.

At the time of approval for leflunomide a number of safety signals were observed. The drug can be associated with bone marrow suppression, persistent peripheral neuropathy, pulmonary reactions, and increased risk of malignancy including lymphoproliferative disorders and toxic epidermal necrolysis or Stevens - Johnson syndrome. Although it was known that liver toxicity was associated with the drug it was only in the post-marketing period that 18 cases of fatal liver failure were observed. This led to an Advisory Committee meeting in 2003 to discuss the safe use of this product and it was determined that when Avara was used in combination with methotrexate the risk for liver failure was greatest. A boldface warning was added to label as a result in 2003. The black box warning was added in 2010 and contains contraindications to the use of Arava in those with preexisting acute or chronic liver disease, those with serum alanine aminotransferase greater than 2xULN and those who are pregnant.

Although not included in the label, it is noted that in the post-marketing setting two cases of Progressive Multifocal Leukoencephalopathy (PML) have been identified, one in a lupus patient and one in a rheumatoid arthritis patient. Both cases were confounded by the use of other immunosuppressant medications specifically methotrexate in the lupus patient and azathioprine in the rheumatoid arthritis patient.

The last ARAVA label was approved 7/8/2011 and can be found at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.LabelApprovalHistory#apphist>

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA data integrity was good but the NDA quality had room for improvement. There were some deficiencies in content that made it difficult to review. These included not providing the financial disclosures in a reasonable format, not providing a copy of the final drafts of the relevant trials, not providing baseline disease characteristics of the subgroups or baseline MRIs. Often times in the submission the sponsor offered their opinion rather than presenting the facts. There were also some slight problems with datasets not consistently being in CDISC format. In particular data in some of the ADAM datasets regarding discontinuation could not be further analyzed using Jreview because of formatting issues. Review of several CRFs and the appropriate dataset content appeared consistent for the primary endpoint and main secondary endpoint.

Typically reporting financial disclosures is relatively straightforward and all that needs to be presented is evidence that the sponsor has done due diligence in collecting financial disclosure information. Presenting the financial disclosures in a laundry list format of 1071 pages without a summary made it nearly impossible to determine if the sponsor had done due diligence in collecting disclosures. After approximately three requests the sponsor did provide the information requested in a more succinct fashion.

The NDA is supposed to be submitted as a completely intact document. Initially the NDA only included a copy of the initial protocols for the studies used to substantiate efficacy and safety as well as the Amendments, but not a copy of the final drafts of the protocols. When the protocols were finally submitted they were submitted as new submissions and not entered into the NDA with a descriptive leaf title and this made it difficult to navigate the submission and find the final protocols with ease.

The regulatory history had some gaps particularly in the period of time before the EoP2 meeting in November, 2004 and during the fall of 2010 when the sponsor was negotiating to submit their NDA with only a single pivotal trial including the briefing document of October 8, 2010, but fortunately the later could be found in the electronic portion of the IND.

The submission was often difficult to navigate. For example Trial 2001 was presented as a Legacy Clinical Study report that was 10892 pages long without adequate bookmarks. This made it initially difficult to locate protocols, datasets, and statistical analyses plans as these were not linked or indexed in the Table of Contents. It was also difficult to locate some of the supportive analyses of the primary endpoint for TEMSO as they were not located in the Efficacy section of the Clinical Trial Report but were in the Integrated Summary of Clinical Efficacy (ISE).

3.2 Compliance with Good Clinical Practices

The sponsor states that their clinical data was collected in compliance with Good Clinical Practice as required by the International Conference on Harmonization (ICH) E6 “Guideline for Good Clinical Practice and according to applicable local and legal requirements and standard operating procedures. The studies also met with the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the sponsor, applicable national laws and regulations and the ethical principles of the Directive 2001/20/EC. Preliminary review of the reports issued by the Division of Scientific Investigations (DSI) suggested that the efficacy trials were conducted using good clinical practices. In addition the trials conducted contained a sufficient number of patients to allow for adequate efficacy and safety review.

Issues identified by the Division of Scientific Investigations (DSI) Audit and Inspection

The Division of Scientific Investigations (DSI) at the FDA was asked to inspect three sites that participated in the pivotal trial. Large representative sites from each region were chosen as preliminary analysis revealed no specific concerns. The Americas was represented by a Canadian site, #1241209, Eastern Europe was represented by a site in the Czech Republic, #2034101, and Western Europe was represented by a site in France, #2502407. No sites were chosen from the US due to the small number of subjects recruited locally. At the time of this review the finalized DSI review was not yet complete and one should refer to the complete review of Dr. Antoine el-Hage when it becomes available. Comments were available about the Canadian and Czech sites. According to Susan Leibenhaut, MD of DSI, there were no concerns raised by the inspection of the Czech site. Out of 32 subjects screened, 28 were randomized into the study and 17 completed the study. The medical records were found to be well organized and the data were verified and appeared reliable. Comments about the Canadian site were made by Tejashri Purohit-Seth, MD of DSI who felt that the Canadian site had no significant findings that would impact the reliability of their results or patient safety. Out of the 55 subjects screened at this site 49 were randomized and 42 completed the study. Fourteen records were audited and were found to be in good order with minimal deficiency.

3.3 Financial Disclosures

Of the 5306 investigators, sub-investigators and additional personnel from whom financial disclosure was sought a total of 297 or 5.6% did not provide disclosure. The reason that there were a substantial number of investigators who did not disclose is that it was not until 2010 that the sponsor attempted to harmonize the data, long after some of the trials had been completed. This is when the sponsor became aware that disclosures were lacking. As a result of the harmonization effort the sponsor sought to

include radiologists who read the study MRIs and nurses who performed the MSFC as sub-investigators needing documentation. The whereabouts of many of these investigators were no longer known. The sponsor does confirm that they made a reasonable effort to get this information by sending at least two requests for information to each investigator.

According to the sponsor there was no evidence that those who did not disclose had received any financial remuneration. Of the 297 who did not disclose, 162 were from nurses who administered the MSFC, and since this was not a primary or secondary endpoint, any impropriety in this assay would not be likely to affect the outcome of the approval decision. In addition, the pivotal trial was done in a double-blind, placebo-controlled fashion and any potential prejudice of an investigator should have been immaterial because of blinding.

For the other investigators the sponsor certified that none had a proprietary interest in the tested product such as a patent, trademark, copyright or licensing agreement with the except of those cited below. A total of 13 investigators did disclose financial interests including equity interests in the sponsor and significant payments. Only six of those who disclosed financial interests participated in the pivotal trial TEMSO providing the key evidence for efficacy. Since the study was double-blinded it is unlikely that this would have introduced bias.

1. (b) (6) was a PI who received 18,569 Euros (\$23,954) for speaker's fees and participation in congresses. At (b) (6) center four patients in the pivotal trial were enrolled.
2. (b) (6) was a PI who received 24,998 Euros (\$32,247) as research grant, speaker's fees and participation in a variety of congresses. At (b) (6) center three patients were included in the pivotal trial.
3. (b) (6) was a principal investigator who received 126,841 CAD (\$124,304) honoraria for payments related to research and development study professional fees. At (b) (6) site there were 49 subjects in the pivotal trial. This site was audited by the agency and no significant impropriety was detected.
4. (b) (6) was a sub-investigator who received 39,470 Euros (\$50,916) as honoraria for consulting and participation in congresses and workshops. At (b) (6) site five patients were enrolled in the pivotal trial.
5. (b) (6) was a subinvestigator who received 33,084 Euros (\$41,678) as honoraria for consulting, participation in

congresses and workshops. At (b) (6) site nine subjects were enrolled in the pivotal trial.

6. (b) (6) was a radiologist who read MRI who received honoraria as significant payment of other sorts. At Dr. (b) (6) site nine patients were enrolled in the pivotal trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Teriflunomide is a new molecular entity (NME) which is synthesized from a 3-step chemical synthesis made from commercially available products. The medicine is prepared in an immediate release film-coated tablet for oral use once/day.

Please see the review of the agency CMC reviewer, Dr. Prafull Shiromani for further details.

4.2 Clinical Microbiology

The microbiological quality of the teriflunomide including the drug substance and its excipients was prepared in accordance with European Pharmacopoeia and the United States Pharmacopoeia.

4.3 Preclinical Pharmacology/Toxicology

Please see the Pharmacology/Toxicology review by the Agency Pharmacologist, Dr. Richard Houghtling for more complete information. The following is a summary of information provided by the sponsor. There is preclinical evidence that teriflunomide consistently delays relapses in chronic-relapsing experimental autoimmune encephalomyelitis (EAE) as well as delays the onset of disease, decreases clinical symptomatology including mortality and reduces inflammation, demyelination and axonal loss. Several potential signals were identified in toxicology studies that were done in the mouse, rat and dog. The primary target organs that were found to be injured by the drug included the bone marrow (evidence of decreased erythropoiesis and granulopoiesis) atrophy of the lymphoid tissue, epithelial degenerative changes in the oral cavity and gastrointestinal tract, tubular degenerative changes in the testes and ovaries, anemia, leukopenia, lymphopenia, thrombocytopenia and secondary infections. Additionally in the long term 12-month dog study the pancreas was identified as an organ of toxicity and due to an absence of a safety margin, safety monitoring for

pancreatic disease was instituted as part of the clinical trial. No carcinogenicity was observed in the 1-year oral carcinogenicity studies in mice and rats at the highest dose administered but anti-proliferative changes were seen in the thymus, skin, and gastrointestinal tract leading to higher mortality. Only at the highest doses were there lesions noted in the liver, mesenteric lymph nodes, and bone marrow and these changes were considered secondary to ulcers and inflammation. The inflammation also led to the development of generalized amyloidosis and an increase in chronic progressive nephropathy.

4.4 Clinical Pharmacology

The recommended dose of teriflunomide is 14 mg orally once a day, with or without food. The following section is a summary of information provided by the sponsor. Please see the review of the agency Clinical Pharmacologist, Dr. Veneeta Tandon, for further details.

4.4.1 Mechanism of Action

Teriflunomide is the active metabolite of leflunomide used for rheumatoid arthritis. It is an inhibitor of the de novo synthesis of pyrimidine. Teriflunomide works on rapidly dividing cells in the periphery including activated T cells and it is a selective non-competitive and reversible inhibitor of dihydroorotate dehydrogenase (DHO-DH) which is the enzyme that blocks pyrimidine synthesis.

4.4.2 Pharmacodynamics

Bone Marrow

Teriflunomide does lead to a modest mean reduction in white blood cell count, mainly neutrophils and lymphocytes which is dose related. The reduction predominantly is in the first 6 weeks, followed by stabilization over time on treatment. Typically the decrease is no more than 15% over the baseline; the decrease in platelets is <10% and red blood cells < 2% from baseline.

Uric Acid levels

Teriflunomide is known to decrease plasma level of uric acid by causing an increase in urinary clearance. This effect is thought to be due to the inhibition of renal transport of urate through the apical urate/anion exchanger.

Cardiac Effects

According to the sponsor, the QT study in healthy subjects showed no potential for prolonging the QTcF interval compared with placebo. In vitro in an animal model of isolated rabbit Purkinje fibers, teriflunomide induced a slight and statistically significant shortening in the action potential duration and may have enhanced the rate of cardiac repolarization, possibly leading to a shortened QT interval.

4.4.3 Pharmacokinetics

Absorption

Following the oral administration of teriflunomide, peak blood levels are between one to four hours. When bioequivalent doses of intravenous and oral doses of teriflunomide were administered, the bioavailability of both was the same suggesting that teriflunomide is highly bioavailability when administered orally. This is further confirmed with a radioactive labeled study where <2% of the oral dose was unabsorbed by checking the cumulative dose in the excreted feces over 48 hours. It is noted that teriflunomide has low solubility when the pH is < 4.0 and increases with higher pH. At physiologic pH of 4.5 to 8 there is no solubility limit of the 14 mg dose. The effect of food is thought to have minimal effect.

Distribution

In vitro, teriflunomide is highly protein bound in humans. Binding was found to be 99.5% bound and 0.49% unbound when the concentration of teriflunomide ranged between 0.750 to 570 ug/mLs. The protein binding was primarily to albumin.

Metabolism

Teriflunomide is moderately metabolized in vivo either with hydrolysis or oxidation. The major pathway is hydrolysis and the secondary pathway is oxidation, followed by N-acetylation and sulfate conjugation. In plasma no major metabolites were noted in the systemic circulation only unchanged teriflunomide. Only after repeated dosing was a very small amount of 4-TFMA detected. In the feces 35.7% +/- 12.7% of the dose was unchanged teriflunomide and <2% were three metabolites. In the urine ≤ 1.3% of the dose was teriflunomide+methylhydroxyl teriflunomide out of which 0.147% was unchanged teriflunomide. Another 18.1% +/- 3.3% of the dose was the metabolite 4-TFMA oxanillic acid.

Excretion

After a single oral dose of various doses of teriflunomide (7 mg to 70 mg), the half life was noted to be 10-12 days. After a single IV infusion of 10 mg of teriflunomide the mean teriflunomide total body clearance was 30.5 mL/hr. Repeated dose assessments were not done but based on post-hoc PopPK modeling in healthy volunteers and MS patients the median terminal half-life was noted to be 19.4 days for the 14 mg doses. The excretion in the gastrointestinal tract is mainly through the bile as unchanged drug. If it is necessary to accelerate teriflunomide removal from the body then use of oral cholestyramine or activated charcoal can interrupt the reabsorption process in the intestines and can aide in removing > 98% of teriflunomide plasma concentration over 11 days.

5 Sources of Clinical Data

All documents and datasets used by this reviewer for this NDA clinical review were in electronic format. This information may be found in DARRTS at the following link:
: <\\Cdsesub1\evsprod\nda202992\0000>

5.1 Tables of Studies/Clinical Trials

Table 2 is a listing of clinical studies which contributed to efficacy and safety used for this review. The pivotal trial is study EFC 6049/TEMPO a randomized, double-blind, placebo-controlled phase 3 study. An interim analysis of a second ongoing randomized, double-blind, placebo-controlled phase 3 trial, EFC 10531/TOWER, was provided with descriptive results. Another trial which provided supportive evidence was study 1726/2001 which is a completed, randomized, double-blind, placebo-controlled, proof of concept trial evaluating the use of teriflunomide over 36 weeks.

In addition, further safety data was provided by open-label extension trials LTS6048 and LTS 6050 (the long-term extension trials of Study 2001 and Study EFC6049), study PDY6046 (study where two doses of teriflunomide or placebo are adjunctive treatment to IFN- β) and study PDY 6045 (study where two doses of teriflunomide or placebo are adjunctive treatment to GA) and LTS 6047 (the extension trial of PDY 6046 and PDY 6045).

The sponsor does have several ongoing studies that contributed to the blinded safety pool but which are not included in the efficacy analysis. These include study EFC10891/TENERE (has recently been completed although the clinical study report is not yet available) which evaluated teriflunomide 7 mg/day and 14 mg/day against an active-control IFN- β 1. This study was conducted outside the US. Study EFC 6260/TOPIIC is an ongoing placebo controlled study evaluating patients with clinically isolated syndrome. Study EFC6058/TERACLES is an ongoing placebo controlled adjunctive study of teriflunomide 7 mg/day and 14 mg/day or placebo in patients on a stable dose of IFN- β .

Table 2 Studies used to provide evidence of efficacy and safety of teriflunomide

Study	Phase	Main objective of the study	Comparator	Treatment duration	Number of patients randomized	Status
<i>Monotherapy</i>						
Core studies						
2001 (5.3.5.1 [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/TEMPO (5.3.5.1 [EFC6049])	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-controlled	Fixed end for all patients, 48 weeks for last patient randomized	1096 ^a	Ongoing, Interim analysis ^b
Extension studies						
LTS6048 (extension of 2001) (5.3.5.2 [LTS6048])	2	Assess the long-term safety and efficacy of teriflunomide in patients who had completed Study 2001	Uncontrolled	Open-ended	147	Ongoing, Interim analysis

Study	Phase	Main objective of the study	Comparator	Treatment duration	Number of patients randomized	Status
LTS6050 (extension of EFC6049) (5.3.5.2 [LTS6050])	3	Assess the long-term safety and efficacy of teriflunomide in patients who had completed Study EFC6049	Uncontrolled	Open-ended	742	Ongoing, Interim analysis
Adjunctive therapy						
Core studies						
PDY6045 (5.3.5.4 [PDY6045])	2	Adjunctive safety and efficacy study of teriflunomide 7 and 14 mg and a stable dose of IFN- β compared to placebo and IFN- β	Placebo-controlled	24 weeks	118	Completed
PDY6046 (5.3.5.4 [PDY6046])	2	Adjunctive safety and efficacy study of teriflunomide 7 and 14 mg and a stable dose of glatiramer acetate compared to placebo and glatiramer acetate	Placebo-controlled	24 weeks	123	Completed
Extension study						
LTS6047 (extension of PDY6045 and PDY6046) (5.3.5.4 [LTS6047])	2	Double-blind long-term safety extension study enrolling patients who had completed Studies PDY6045 and PDY6046	Placebo-controlled	24 additional weeks	182	Completed

MRI = magnetic resonance imaging

a Number of patients randomized by the end of November 2010. Study randomization completed 17 February 2010 with a total of 1169 patients.

b Will be provided as an amendment to the current registration dossier

NDA 202992 Clinical Overview section 2.5 Table 3, p 24-25

5.2 Review Strategy

The main support of efficacy was the TEMSO trial with supportive data coming from the phase 2 trial, HMR 1726/2001. It is noted that the later trial had an MRI endpoint as its primary outcome measure (unique active lesions). Although a secondary endpoint of relapse rate was obtained in this study, it could not be used to validate the pivotal trial because the relapses were not confirmed. As a second pivotal trial, TOWER, was ongoing at the time of NDA submission, an interim analysis was reviewed so that a trend supporting efficacy could be confirmed. The completion of the TOWER trial is slated for mid 2012.

The review strategy focused on the following issues:

- Is Teriflunomide at either dose superior to placebo for reducing the ARR in patients with relapsing MS? The demonstration of efficacy is based on
 - Primary Efficacy data in the ITT population from the pivotal TEMSO trial with both doses

- Sensitivity analyses from the completed pivotal TEMSO trial are also evaluated for further confirmatory evidence to include an analysis of the per protocol population as well as those with all relapses and those who continued to have relapses after discontinuing treatment
- Analyses of subpopulations in the TEMSO trial
- Primary efficacy data from the Interim analysis of the TOWER trial both confirmed and all treatment relapses in a descriptive fashion
- Is teriflunomide at either dose superior to placebo for delaying the accumulation of physical disability and is there a dose response?
 - Sustained over 12-weeks?
 - Sustained over 24 weeks?
 - As evaluated by the MSFC?
- Do MRI findings support efficacy? Is there a dose response?
- Do patient reported outcome (PRO) data support efficacy?
- Do the long-term open-label extension trial results support efficacy of one or both doses?
- Does the TEMSO trial have sufficient substantial evidence to serve as a single pivotal trial supporting efficacy without replication?
 - Is the trial large and multinational?
 - Is there internal confirmation of the endpoints such as between doses?
 - Are the secondary endpoints also confirmatory of the primary endpoint?
 - Are the results sufficiently robust?
 - Do sensitivity analyses also provide support?
 - Do other tertiary analyses show a treatment effect?
 - Were treatment arms well balanced in demographics, disease characteristics, and treatment withdrawals so that results were deemed reliable?

In addition the sponsor provided further data to support efficacy. Evidence came from extension trials LTS6048 and LTS6050 which are both long-term extension trials. Two phase 2 trials where teriflunomide was used as an adjunctive treatment in patients on stable doses of IFN β or GA, Study PDY6045, and Study LTS6046 were considered as indirect support of the monotherapy program. These trials primarily provided safety data, but did assess the burden of disease (BOD) and ARR.

The safety data is reviewed by Dr. Evelyn Mentari and Dr. Lourdes Villalba in a separate document.

5.3 Clinical Studies

5.3.1 Pivotal trial Protocol EFC 6049 TEMSO

Study title:

A randomized, double-blind, placebo-controlled, parallel-group design study to evaluate the efficacy and safety of teriflunomide in reducing the frequency of relapses and delaying the accumulation of physical disability in subjects with multiple sclerosis with relapses.

Objectives:

Primary and key secondary objectives

- To determine the effect of two different doses of teriflunomide (7 mg and 14 mg) and placebo on reducing the frequency of confirmed relapses per patient year in subjects with the relapsing forms of MS in patients treated for up to 108 weeks
- To evaluate the effect of teriflunomide on delaying the accumulation of disability as assessed by the Kurtzke EDSS confirmed at a three month visit at the end of two years

Other secondary objectives

To evaluate the effect of teriflunomide (7mg and 14 mg) relative to placebo on the following objects

- To evaluate the effect on MRI variables including burden of disease, number of gadolinium-enhanced T1 lesions, volume of gadolinium-enhanced T1 lesions, volume of T2 lesions, volume of T1 hypointense lesions, brain atrophy and a composite score
- Evaluate the effect on subject-reported fatigue as assessed by the Fatigue Impact Scale (FIS)
- Evaluate the safety and tolerability by means of adverse event reports, physical examinations, vital signs, and laboratory evaluations

Tertiary objectives

- Explore the impact of teriflunomide on general health status using the Short Form general health survey (SF-36) subject reported questionnaire
- Explore the economic impact of teriflunomide through an evaluation of resource utilization, work productivity and activities impairment (WPAI), and the EuroQoL (EQ-5D) subject-reported questionnaire
- Explore the impact of teriflunomide on disease progression using the Multiple Sclerosis Functional Composite (MSFC)
- Investigate the relationship between dose, concentration, efficacy, safety and blood levels of teriflunomide
- Assess the association between the main enzyme systems of teriflunomide metabolism and hepatic safety, and other potential associations between gene variations and clinical outcome (optional pharmacogenomic substudy)

Study Design:

This was a double-blind, placebo-controlled, parallel-group 108 week multicenter study in patients with relapsing forms of multiple sclerosis. The subjects were stratified by center and by baseline EDSS ≤ 3.5 and > 3.5 before randomization. During the study there were at least 25 visits. (See Tables 3, 4, 5)

The study had three phases.

- The screening phase was up to 4 weeks prior to the baseline visit.
- The patients were randomized at baseline. After randomization the double-blind treatment was for 108 weeks. There were three study arms with patients treated in a 1:1:1 ratio. They were seen monthly for the first 6 months and thereafter every 6 weeks until the last study drug at week 108. Unscheduled visits were permitted for relapse assessment and close-out visit if drug was withdrawn prematurely.

After dosing ended wash-out began and subjects were offered optional enrollment in the long-term extension study (LTS6050). Washout was administered over 11 days and follow-up visits extended for 16 weeks. The recommended procedure was the administration of 8 grams of cholestyramine Q 8 hours for 11 days. Alternatively activated charcoal powder 50 grams could be administered every 6 hours over 11 days. The study concluded with visits 4 and 6 weeks after drug cessation. The Independent Data Monitoring Committee (IDMC) oversaw the safety and risk/benefit of the study. Depending upon the results of their findings they had the right to ask the sponsor to stop the study.

Assessment Schedule:

Table 3 TEMSO Schedule Screening to week 24

Visit name	Screening	MSFC practice	Study treatment period												
			3	Safety blood visit 4	Safety blood visit 5	Safety blood visit 6	Safety blood visit 7	Safety blood visit 8	Safety blood visit 9						
Visit number	1	2	3	4	5	6	7	8	9						
Week	up to	-5 to	0 Baseline	2	4	6	8	10	12	14	16	18	20	22	24
Time point ¹	-4 weeks	-7 days													
Randomization			x												
Informed consent/Re-consent	x														
HIV Informed consent															
Review inc./excl. criteria	x		x												
Demographics	x														
Medical & surgical history	x														
MS diagnosis ³ /MS History ⁴	x		x												
Chest X-ray	x ⁵														
Prior/concomitant meds.	x	x	x						x						x
Kurtzke EDSS	x		x						x						x
FS score	x		x						x						x
MSFC	x	x	x												x
MRI ⁶			x												x

Visit name	Screening	MSFC practice	Study treatment period												
			3	Safety blood visit 4	Safety blood visit 5	Safety blood visit 6	Safety blood visit 7	Safety blood visit 8	Safety blood visit 9						
Visit number	1	2	3	4	5	6	7	8	9						
Week	up to	-5 to	0 Baseline	2	4	6	8	10	12	14	16	18	20	22	24
Time point ¹	-4 weeks	-7 days													
FIS			x						x						x
EQ-5D			x						x						x
SF-36		x											x		
WPAI			x	x	x	x	x	x	x	x	x	x	x	x	x
Resource utilization ⁷			x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x								x						
Abdominal ultra sound ¹⁵		x													x
Adverse events ¹⁶		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood sampling for safety ⁸	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Serum pregnancy test	x ⁹	x	x						x						x
Urinalysis sample for safety	x	x							x						x
Vital signs ¹⁰	x		x ¹¹						x						x
Pharmacokinetic sample		x	x ¹²						x ¹³						x ¹³
Dispense study medication ¹⁴			x						x						x

Statistical Analysis Plan Trial 6049 pages 65-70

Best Available Copy

Table 4 TEMSO schedule Week 30 to 108 and post wash-out weeks 112 to 124, un-scheduled visits

Visit name	Study treatment period															
	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24 & 25	
Week																
Time point ¹	30	36	42	48	54	60	66	72	78	84	90	96	102	108 ² Close-out	112 & 124 Post wash-out	Un-scheduled relapse
Randomization																
Informed consent/Re-consent																x
Review inc./excl. criteria																
Demographics																
Medical & surgical history																
MS diagnosis ³ /MS History ⁴																
Chest X-ray																
Prior/concomitant meds.		x		x		x		x		x		x		x		x
Kurtzke EDSS		x		x		x		x		x		x		x		x
FS score		x		x		x		x		x		x		x		x
MSFC				x				x				x				
MRI ⁵				x				x						x		
FIS		x		x		x		x		x		x		x		x
EQ-5D		x		x		x		x		x		x		x		x
SF-36			x				x				x			x		
WPAI	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Resource utilization ⁷	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Physical examination		x				x				x				x		
Abdominal ultra sound ¹⁵				x				x						x		
Adverse events ¹⁶	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood sampling for safety ⁸	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Serum pregnancy test		x		x		x		x		x		x		x		
Urinalysis sample for safety		x		x		x		x		x		x		x		
Vital signs ¹⁰		x		x		x		x		x		x		x ¹¹		x
Pharmacokinetic sample		x ¹³		x ¹³		x ¹³		x ¹³		x ¹³		x ¹³		x	x	
Dispense study medication ¹⁴		x		x		x		x		x		x				
Accountability/compliance review		x		x		x		x		x		x		x		

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Table 5 Table of Assessments TEMSO trial

Variable	Visits
Relapse	Unscheduled relapse visits
EDSS and FS	Screening, baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, and 108, and unscheduled relapse visits
FIS and EQ5D	Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, and 108, and unscheduled relapse visits
MRI	Baseline, Weeks 24, 48, 72, and 108
MSFC	Screening, baseline, Weeks 24, 48, 72, and 96
SF-36	Screening, Weeks 20, 42, 66, 90, and 108
WPAI	Baseline, Weeks 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, and 108
Resource utilization	Same as WPAI and unscheduled relapse visits
Hematology and differential panel	Screening, every 2 weeks till Week 24 and every 6 weeks after Week 24
Coagulation group panel	Screening, every 4 weeks till Week 24 and every 6 weeks after Week 24
Pregnancy testing	Screening, baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, and 108, and in case of unexpected delay of menorrhoea
Blood chemistry panel	Screening, every 4 weeks till Week 24 and every 6 weeks after Week 24
Liver function panel	Screening, every 2 weeks till Week 24 and every 6 weeks after Week 24
Pancreatic enzyme panel	Screening, every 2 weeks till Week 24 and every 6 weeks after Week 24
Urinalysis	Screening, Weeks 12, 24, 36, 48, 60, 72, 84, 96, and 108
Vital signs	Screening, baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, and 108, and unscheduled relapse visits
Physical examination	Screening, Weeks 12, 36, 60, 84, and 108
Abdominal ultrasound	Screening, Weeks 24, 48, 72 and 108
Height	Baseline and Week 108
PK	Screening, Weeks 12, 24, 36, 48, 60, 72, 84, 96, and 108, and 4 weeks and 16 weeks after wash out

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Study Centers:

This was a multicenter study that was conducted in 21 countries and 126 sites. Due to the small sample size in many of the countries the centers were pooled into three regions for statistical analysis purposes.

- Eastern Europe: Czech Republic, Estonia, Poland, Russia, and Ukraine
- Western Europe: Austria, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Portugal, Sweden, Switzerland, Turkey, and United Kingdom
- Americas: Canada, Chile, and USA

At each study center there was at a minimum a treating and an evaluating neurologist. The treating neurologist screened subjects, supervised study medication administration, recorded and treated adverse events and assessed relapses, laboratory results and concomitant medications. The evaluating neurologist or his designee conducted the EDSS. A technician or staff nurse performed the MSFC.

Study Population: The study population consisted of patients that had relapsing forms of MS. Patients did not need to be treatment-naïve. Subjects were randomized after being stratified for their baseline EDSS and center.

Population definitions

Intent to treat population

All randomized subjects who have at least one day of study medication exposure. The ITT population was used for the analysis of all efficacy variables.

Per-protocol population

All of the ITT population, excluding subjects with major protocol deviations. The per-protocol population was used for the analysis of the primary efficacy variable and key secondary variables.

Safety population

All subjects who were randomized and received at least one dose of study medication. For analysis of laboratory values, only subjects who took the test in question were included.

Key Inclusion criteria:

1. A diagnosis of MS as defined by the 2005 revised McDonald criteria either RRMS, SPMS, or PRMS with EDSS \leq 5.5
2. Age 18-55
3. Had to have at least 1 relapse over the preceding year or 2 relapses over the preceding 2 years and no relapses in the 60 days prior to randomization
4. No adrenocorticotrophic hormone or systemic steroids within 60 days prior to randomization

Key exclusion criteria:

Subjects presenting with any of the following were not included in the study:

- Subjects with significantly impaired bone marrow function or significant anemia, hematocrit <24 , and/or leukopenia, absolute white blood cell count $<4,000$ cells/mm³, absolute neutrophil $\leq 1,500$ cells/mm³ and/or thrombocytopenia, platelet count $<150,000$ cells/mm³.
- Subjects with a congenital or acquired severe immunodeficiency, a history of cancer (except for basal or squamous cell skin lesions which have been surgically excised, with no evidence of metastasis), lymphoproliferative disease, or any subject who has received lymphoid irradiation.

- Known history of active tuberculosis not adequately treated
- Persistent significant or severe infection
- Pregnancy, breastfeeding or subjects wishing to parent children during the course of the trial
- Liver function impairment or persisting elevations of SGPT/ALT, serum glutamic oxaloacetic transaminase (SGOT/AST), or direct bilirubin greater than 1.5-fold the upper limit of normal (ULN) or known history of active hepatitis
- Persisting elevations of serum amylase or lipase greater than 2-fold ULN or known history of chronic pancreatic disease or pancreatitis
- Hypoproteinemia (e.g., in case of severe liver disease or nephrotic syndrome) with serum albumin <3.0 g/dL
- Moderate to severe impairment of renal function, as shown by serum creatinine >133 $\mu\text{mol/L}$ (or >1.5 mg/do)
- Previous treatment with teriflunomide or leflunomide
- Clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the subject at risk by participating in the study or likelihood of requiring treatment during the study period with drugs not permitted by the clinical protocol
- History of drug or alcohol abuse or significant mental condition
- Human immunodeficiency virus (HIV) positive subject

Treatment administered:

There were 3 treatment arms in a 1:1:1 ratio.

- Teriflunomide 7 mg capsule for oral administration once in morning
- Teriflunomide 14 mg capsule for oral administration once in morning
- Placebo in capsule for oral administration once in morning

Concomitant Therapy:

Medications with a low therapeutic index such as digoxin needed to be monitored carefully. Although steroids could be used, their use also had to be monitored carefully with frequent checks of the blood pressure. Steroids could only be used to treat an acute MS relapse per protocol specifications.

Drugs that are known to be hepatotoxic, hematotoxic, or immunosuppressive that are used along with teriflunomide could cause an increase in side effects and were to be avoided. This included alcohol.

Prohibited medication:

The following medications were not to be used during the study or if used only for a minimum of 4 weeks prior to entry into the study:

- Steroids, except as mention above
- ACTH
- Cholestyramine

- Phenytoin
- Warfarin
- Tolbutamide
- St. John's Wort
- Other investigational drugs

In addition, other preventive MS medications were not to be used in the six months preceding the study as well as during the study. These drugs include glatiramer acetate, intravenous immunoglobulins, natalizumab, cladribine, mitoxantrone, or other immunomodulatory agents such as azathioprine, cyclophosphamide, cyclosporine, methotrexate or mycophenolate, teriflunomide or leflunomide. The prior use of interferons and cytokine therapy in the 4 months preceding the study as well as during the study was not permitted.

Randomization and Controls

The treatment allocation was determined according to the randomization code provided by an interactive voice response system (IVRS). There was a 1:1:1 randomization to placebo, teriflunomide 7 mg and teriflunomide 14 mg. The block size was 6. Subjects were randomized based on stratification by center and EDSS score. Treatment codes were maintained by the IVRS and no code-breaking material was provided on site. The code was to be broken if it was medically imperative or if patient became pregnant and the decision was made to continue with the pregnancy. If the code was broken then treatment was to be stopped and the sponsor would then decide whether or not the subject would be withdrawn from the study.

Premature patient withdrawals and study drug discontinuations:

All subjects who prematurely withdrew or stopped the drug underwent a washout procedure if they did not enter the extension trial due to the long elimination half-life. The date and reason for withdrawal were recorded. If a subject discontinued before month 24 then all assessments scheduled for the terminal visit were done at a close-out visit which was scheduled as soon as possible after drug discontinuation. These patients were considered early permanent treatment discontinuation (EPTD) patients and were encouraged to enter an EPTD follow-up period until the planned end of study. For these patients, the treatment period and EPTD follow-up period should total approximately 108 weeks. Adverse events were to be reported and followed up. After the cholestyramine washout, subjects had a post-washout visit and blood work was drawn for PK. If the plasma concentration of teriflunomide was >0.02 ug/mL the site was notified and the cholestyramine could be repeated.

Amendments to Protocol

Amendment # Date	Major Changes Made
Amendment 1 10/6/2004	<p>Addition of patient safety measures as requested by the FDA (regarding washout procedures for those who wish to bear children and exclusion of concomitant therapy with St. John's Wort)</p> <p>Change in measurement times for clinical chemistry and hematology to every 2 weeks for the first 6 months</p> <p>Clarification of safety parameters and monitoring (chest X-ray that satisfy local regulations and incidence and risk factors for tuberculosis; blood test repeated within 48 hours for a SGPT/ALT result >3 x ULN; increased frequency of safety blood sampling; MRI not required at unscheduled relapse visit)</p> <p>Clarification of independent DMC access to unblinded data and right to request a futility analysis</p> <p>Increase in number of participating centers from 60 to 120</p> <p>Clarification in pharmacokinetic blood sampling</p> <p>Clarification that resource utilization data on hospitalization was to be required only for MS relapses</p> <p>Change exclusion criteria from 6 months to 4 months for prior use of interferons and cytokines</p>
Amendment 2 7/26/2005	<p>Changes in inclusion/exclusion criteria such as at least 1 relapse in the past 1 year or at least 2 in the past 2 years, no prior use of natalizumab, known history of pancreatic disease, elevated serum amylase or lipase greater than 2-fold over ULN</p> <p>Changes in data collection (documentation of relapses; collection of MS subtype diagnoses at study entry)</p> <p>Changes in safety blood sampling (fasting only necessary for visit 2 and last visit), additional blood sampling added in Amendment 1 to include only liver enzyme tests and bilirubin, pancreatic enzymes, hematology, and differential panel; amylase and lipase to be measured in all blood samples; local laboratory analysis only for emergency treatment; blood sampling window ± 3 days for first 24 weeks then ± 7 days)</p> <p>Changes/clarification in safety procedures (baseline MRI performed within 7 days prior to randomization; chest X-ray if not performed in the past year; abdominal ultrasound at Visit 2, every 24 weeks, and at the end of the study; confirmed serum amylase or lipase >2 x ULN added to alert terms; follow-up details added to alert terms)</p> <p>Clarification that stratification to be based on baseline (Visit 3) EDSS performed prior to randomization</p>

	<p>Clarification of washout procedure (assay sensitivity units, duration between post-washout blood samples, analysis performed by SA)</p>
Amendment 3 5/12/2006	<p>Change in exclusion criteria such as excluding those on mycophenolate</p> <p>Increase in sample size from 870 to 1080 patients due to re-estimate of predicted 2-year placebo response rate</p> <p>Clarification of key secondary objective as effect of teriflunomide on EDSS; analysis plan to evaluate the variable</p> <p>Definition of MRI variables</p> <p>Changes in safety monitoring (extension of washout to 5 days and addition of a post-washout visit; identification of peripheral neuropathy as an adverse event and clarification of assessment and follow-up; addition of elevated amylase and lipase as alert terms and withdrawal criteria; addition of pancreas CT scan with contrast or MRI following an abnormal ultrasound of the pancreas with submission to a central reading center and abnormal pancreatic CT as alert term</p> <p>Description of roles and responsibility of Steering Committee</p> <p>Removal of the Physical Self-Maintenance Scale questionnaire due to difficulty in implementation</p> <p>Clarification of acceptable contraceptive methods</p> <p>Clarification of procedure for re-consent following a confirmed MS relapse</p>
Amendment 4 2/12/2007	<p>Extension of washout to 11 days and revision of washout procedure</p> <p>Revision of investigational product storage conditions</p> <p>Clarification of safety parameters and monitoring (clinical follow-up of patients who discontinued; safety monitoring plan for pulmonary toxicity and alert term for signs and symptoms; alert term for pancreas abnormality detected by ultrasound; intensified follow-up of high amylase or lipase values and study drug discontinuation above 5 x ULN with no pancreatitis signs and symptoms; Finnish patients to be tested for C-reactive protein; double contraception is an acceptable contraception method; wording change in therapy for MS relapse</p> <p>Clarification of list of laboratory parameters and follow-up</p>
Amendment 5 4/3/2007	<p>Changes in inclusion/exclusion criteria</p> <p>Changes to allow HIV positive patients not being treated with anti-retroviral nucleoside and those with adequately treated tuberculosis; St. John's Wort removed from prohibited medications</p> <p>Changes in blood sampling (addition of HIV testing at screening at US sites and CD4 count and viral load testing for HIV-positive patients)</p>
Amendment 6 6/25/2007	<p>Re-addition of St. John's Wort exclusion</p>
Amendment 7 12/12/2007	<p>Changes in inclusion/exclusion criteria to exclude newly enrolled HIV-</p>

	<p>positive patients from the study.</p> <p>Clarification of statistical methodology (primary analysis and premature withdrawal handling; change in key secondary variable to “time to disability progression” and update of secondary analysis; modification of multiplicity control procedures; change of modified intent-to-treat (mITT) primary efficacy population; stratification based on center and EDSS score</p> <p>Implementation of EDSS assessment after treatment discontinuation for at least 24 weeks from first increase onset to document disability progression after discontinuation</p> <p>Updating of contraception requirements to reflect ICH-M3 guidelines</p> <p>Removal of the possibility of Sponsor waivers for inclusion/exclusion criteria</p>
Amendment 8 11/27/2008	<p>Addition of yearly HIV testing for HIV risk assessment; patients instructed to report symptoms suggestive of immunodeficiency</p> <p>Clarifications for harmonization of protocols within the teriflunomide development program (statistical analysis – handling of premature withdrawals and modification of multiplicity control procedure; TEAE period changed to 16 weeks after discontinuation of study medication; detailed instructions for pregnancies; error correction in disability progression based on EDSS scores to 1 point when baseline EDSS score ≤ 5.5; BOD to be principal MRI variable with all others exploratory; examining neurologist qualifications; MS relapse data collected as efficacy variable and not as adverse event</p>
Amendment 9 10/27/2009	<p>Addition of optional pharmacogenomic teriflunomide testing to assess the association between the main enzyme systems of teriflunomide metabolism and hepatic safety and other potential associations between gene variations and clinical outcomes</p>

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Efficacy Outcome Measures

Primary efficacy outcome measure

- Annualized Confirmed Relapse Rate

Key secondary efficacy outcome measure

- Time to disability progression using the EDSS of at least 1 point increase from baseline if baseline score was ≤ 5.5 , or time to at least 0.5 increase if baseline score was > 5.5 . The increase in disability must persist for at least 12 weeks.

Analysis Plan:

The primary and key secondary endpoints were tested in a hierarchical order. Each hypothesis was formally tested for the four comparisons only if the preceding one reached a significance level of 5%.

1. Teriflunomide 14 mg vs. placebo testing treatment difference for ARR (using Poisson regression model with covariates of treatment, baseline EDSS and region)
2. Teriflunomide 7 mg vs. placebo testing treatment difference for ARR (using Poisson regression model with covariates of treatment, baseline EDSS and region)
3. Teriflunomide 14 mg placebo testing treatment difference for time to 12-week disability progression (using log-rank test)
4. Teriflunomide 7 mg vs. placebo testing treatment difference for time to 12-week disability progression (using log-rank test)

Only if the above hypothesis tests were at a significance level of at least 5%, a step down procedure was applied to the following secondary endpoints in the order specified below within each dose at a 2.5% significance level to control for Type-1 error.

1. Change from baseline in total score of fatigue impact scale at week 108
2. Total number of gadolinium enhancing (Gd-enhancing) T1-lesions per MRI scan over the treatment period
3. Change from baseline in MRI burden of disease at week 108

Primary endpoint analysis

The primary analysis for the ARR was performed using a Poisson regression model with robust error variance to accommodate the potential over-dispersed data appropriately. The model included the total number of confirmed relapses with onset between the randomization date and the last dose date as the response variable. Covariates were a 3-level treatment group (placebo, teriflunomide 7 mg, and teriflunomide 14 mg), EDSS strata (baseline EDSS score ≤ 3.5 versus > 3.5) and region (Eastern Europe, Western Europe, and Americas). To account for different treatment durations among patients, the log-transformed standardized treatment duration was included in the model as an “offset” variable for appropriate computation of relapse rate. The robust error variances were estimated by specifying the patient identifier in the repeated statement using SAS PROC GENMOD, which is equivalent to the Generalized Estimating Equation (GEE) model.

Key secondary endpoint analysis

Time to disability progression sustained for at least 12 weeks using the EDSS was the key secondary endpoint for data up to 108 weeks for the ITT population. The log-rank test with time to disability progression was used for this analysis. The two treatment groups were compared to placebo, and hazard ratios were estimated using the Cox regression model with treatment group, region, and baseline EDSS strata as covariates. Kaplan-Meier estimates and curves of cumulative incidence were generated with two-sided 95% confidence intervals for the time to 12-week disability progression at 6 months, 1 year, and 2 years of treatment.

Sample size justification

From available data based on what is known about Betaseron, Copaxone, Avonex and Rebif, it was assumed that the 2-year relapse for placebo was 2.20 and teriflunomide was 1.66. Assuming that the number of relapses followed a Poisson distribution with a common standard deviation (SD) of 1.252, a study with 360 randomized subjects/treatment arm, or 1080 randomized subjects would have a $\geq 95\%$ power to detect a 25% relative risk reduction in the 2-year relapse rate at the 2-tailed significance level of $\alpha = 0.050$. This assumed a 20% dropout rate. This model predicated on a 20% drop-out rate will also provide 80% power to detect a 37% hazard rate reduction in time to disability progression using the log-rank test. This assumed a hazard rate of 0.1783 for placebo and 0.1116 for teriflunomide (that is a 30% probability to disability progression for placebo and a 20% probability for teriflunomide patients at the end of two years).

Handling of dropouts

For the primary outcome measure, if subjects discontinue treatment, standardized study ratio will be calculated as last dose date-randomization date +1/365.25. The total number of relapses occurring during the study before discontinuation will be used as response log transformation. The standard study duration will be used as offset variable.

For the secondary measure of disability progression, subjects who discontinue will be considered to be free of progression until the date of the last measurement during treatment. All visits after Visit 23 will be censored. If the visit after disability is recorded is missing and confirmation cannot take place, then the patient is recorded as not having sustained progression.

Relapse and disability progression definitions

MS relapse

A relapse is defined as the appearance of a new clinical sign/symptom or clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persists for a minimum of 24 hours in the absence of fever.

Confirmed relapse

Each episode of relapse must be confirmed by the treating neurologist, based on the objective assessments by an independent evaluator (the examining neurologist) by documenting either of the following:

- A 1-point increase in at least two FS functions, or a 2-point increase in at least one FS function (excluding bowel/bladder and cerebral) from the previous clinically stable assessment
or
- An increase of at least 0.5 points in the EDSS score (unless EDSS = 0, then an increase of at least 1.0 points is required) from the previous clinically stable assessment

- Symptoms of transient neurological worsening unaccompanied by objective findings will not be considered a confirmed relapse. Each confirmed relapse triggers the subject being re-consented to participate in the study.

Disability progression

- The Kurtzke Disability Status Scale (EDSS) is the primary assay of disability. This is based on a standard neurological examination divided into 7 functional systems (FS). Each FS score is rated from 0 to 6. It is used in conjunction with an assessment of gait and use of assistive devices to determine the EDSS score which falls between 0 to 10, where 10 is equal to death due to MS. The scores are in half point increments and 5.5 is the break-off point where patients can no longer walk.
- Time to (first) disability progression as assessed by the EDSS is defined as a sustained increase of at least 1.0 point from baseline (Visit 3) on the EDSS (0.5 points for subjects with baseline EDSS > 5.5) persisting for at least 12 weeks.
- When patient is observed to have experienced a sustained disability progression they will require a re-consent in order to continue in the study.

Other secondary efficacy analyses

Multiple Sclerosis Functional Composite (MSFC)

This test is a three-part assessment developed by a special Task Force on Clinical Outcomes Assessment appointed by the National Multiple Sclerosis Society's Advisory Committee on Clinical Trials because of their concerns of relying exclusively on the EDSS for disability rating. The goal was for this instrument to fill a void in assessing multiple sclerosis patients by having three components that changed relatively independently and that would be multidimensional with at least one component assessing cognitive function. Three previously validated instruments were combined to produce a composite z score. Unlike the EDSS, the patient is not compared to themselves over time, but is compared to a reference population. Since each subpart has been independently validated and measures different variables, (such as time in the T25RW and 9HP and correct answers in the PASAT-3), each subpart is scored and the scores are transformed into a single standardized z score for each patient at each test session.

It is felt that the timed 25-foot walk (T25FW) captures those with mild impairment and it is the time that it takes to walk 25 feet. The 9-hole peg test (9HP) captures those with more severe impairment and is a test of hand-eye coordination placing 9 pegs into 9 holes. The Paced Auditory Serial Addition Test (PASAT-3) is a cognitive task that captures all levels of impairment, but which is more sensitive to mild to moderate cognitive disability. The PASAT-3 is based on the total number of correct answers out of 60 simple addition computations. Single digits are presented to the individual every three seconds and the patient must add the new digit to the one previously presented. The test is not intended to be a global measure of cognitive function.

Although the MSFC is felt to have good inter-rater and test-retest reliability, it is subject to practice effect and individuals get several trials of training before their score is counted. The MSFC is conducted by a trained examiner who is experienced in this instrument and the test takes approximately 20-30 minutes to conduct. The MSFC was conducted at screening and six other visits during the study.

MRI

MRIs were performed at five time intervals, weeks 0, 24, 48, 72, and 108, respectively. MRIs were performed until a minimum of 14 days after completion of a course of steroids. All subjects needed a qualifying MRI scan to verify that the site they used could acquire data consistent and adequate for the trial. The qualifying scan was acquired using seven image series by certified technicians. All data was electronically archived according to protocol specifications and collected with a scanner that met the standards of an American College of Radiology quality control program. All procedures were standardized and remained the same for the duration of the study. The seven sequences in a series include:

- Series 1 – a set of axial, coronal and sagittal T1-weighted scout scans obtained with a gradient echo sequence used for prescription of all subsequent localized series in the subject's session.
- Series 2 – a set of sagittal FLAIR images.
- Series 3 – a dual fast spin echo axial 3 mm interleaved acquisition.
- Series 4 – a fast FLAIR axial 3 mm interleaved acquisition.
- Series 5 – 3D SPGR volumetric acquisition.
- Series 6 – T1 pre-Gadolinium axial 3 mm interleaved acquisition.
- Series 7 – T1 pre-Gadolinium axial 3 mm interleaved acquisition. Must be delayed a minimum of 5 minutes after injection of contrast; allow about 10 minutes for venous access.

MRI efficacy variables

Key variable

- Burden of Disease (BOD) is defined as the total volume of abnormal brain tissue on MRI defined as the sum of the T2 lesions load and the T1 hypointense lesion component. BOD is thought to provide a measure of past disease activity. Due to the skewed distribution of BOD values, the cubic root of the values was analyzed instead. The cubic root transformation was shown to result in a distribution of the volume data that is closer to the normal distribution. The change from baseline in transformed BOD at week 108 was the key MRI variable.

Other variables

- Volume of post-gadolinium T1 hypo intense lesions (black holes) is thought to indicate axonal loss, gliosis and loss of intracellular matrix. Due to the skew

distribution of values change from baseline in cubic root transformed volume of hypointense post-gadolinium T1 lesions component at week 108 were analyzed.

- Total number of enhanced T1 lesions is correlated with relapses and predicts the short-term course of MS. The cumulative number of Gd-enhancing T1 lesions at each post-baseline visit up to week 108 was calculated for each patient and divided by the number of scans to calculate the total number of Gd-enhancing T1 lesions/scan/visit.
- Total volume of enhanced T1 lesions/MRI scan over the treatment period. Due to the skew distribution of values, change from baseline in cubic root transformed volume of hypointense post-gadolinium T1 lesions at week 108 was analyzed.
- Volume of T2 lesion component. Due to the skew distribution of values, changes from baseline in cubic root transformed volume of T2 lesion component at week 108 were analyzed.

Additional exploratory MRI variables

- Average number of unique active lesions per scan
- Atrophy
- Z4 composite score
- Volume of white matter
- Volume of gray matter

All of these exploratory measures were reported as a change from baseline to week 108 with the exception of unique active lesions which was analyzed as the total number of unique active lesions/scan over the treatment period.

Corticosteroid use and MRI

Any MRI taken within 14 days of taking steroids was excluded from analysis. A sensitivity analysis including excluded MRI values could be done to assess the impact of corticosteroids if necessary.

Subject reported outcomes

- Fatigue Impact Scale (FIS) is a validated patient reported outcome measure (PRO) that evaluates the effect of fatigue on the lives of people with MS. It is thought to differentiate between subjects with MS of different severities. The test consists of 40 statements that measure perceived fatigue impact in three areas: cognitive function, physical function and psychosocial function. The instrument can be self-administered or telephone-administered and consists of a total score and 3 subscales.
- The Medical Outcome Study SF-36 is a self-administered health-reported quality of life outcome measure that is validated for several indications and patient populations. According to the sponsor it is the most widely used measure of health-related quality of life in RRMS and is usually complete in 5-10 minutes. There are 36 questions representing 8 health concepts which include

- physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. There is also a single question assessing health transition. In addition to eight SF-36 domains, two summary scores can be evaluated: the physical health component and the mental health component.
- The EuroQoL EQ-5D is a standardized PRO that measures health outcome which has not undergone PRO validation at the FDA. This is designed for self-completion by subjects, is cognitively simple and takes less than 5 minutes.

Amendments to the Statistical Analysis Plan

December 12, 2007 in Amendment 7

- The primary analysis was changed from Poisson regression model to the Poisson regression model with robust error variance estimate
- Efficacy analysis population was changed from the modified ITT to the ITT population with all randomized and exposed patients

November 28, 2008 in Amendment 8

- Detailed censoring rules were added for the key analysis. Key secondary variable were analyzed using log-rank test and supported by Cox regression model
- Step down approach was used to control the overall type-I error rate for primary and key secondary variables
- End of treatment emergent period was changed from 42 days after the last dose day to 112 after the last dose day

April 20, 2010 in SAP version 2

- SAS codes for the planned key efficacy analyses were added
- Additional sensitivity analysis for the primary efficacy variable were added to include relapses collected during the follow-up period after treatment discontinuation
- Extend the step down procedure for additional secondary variables.

Data Analysis Sets

Using the sponsor's definition, the three analysis sets by treatment category were specified as displayed in Table 6.

Table 6 Data analysis sets TEMSO trial

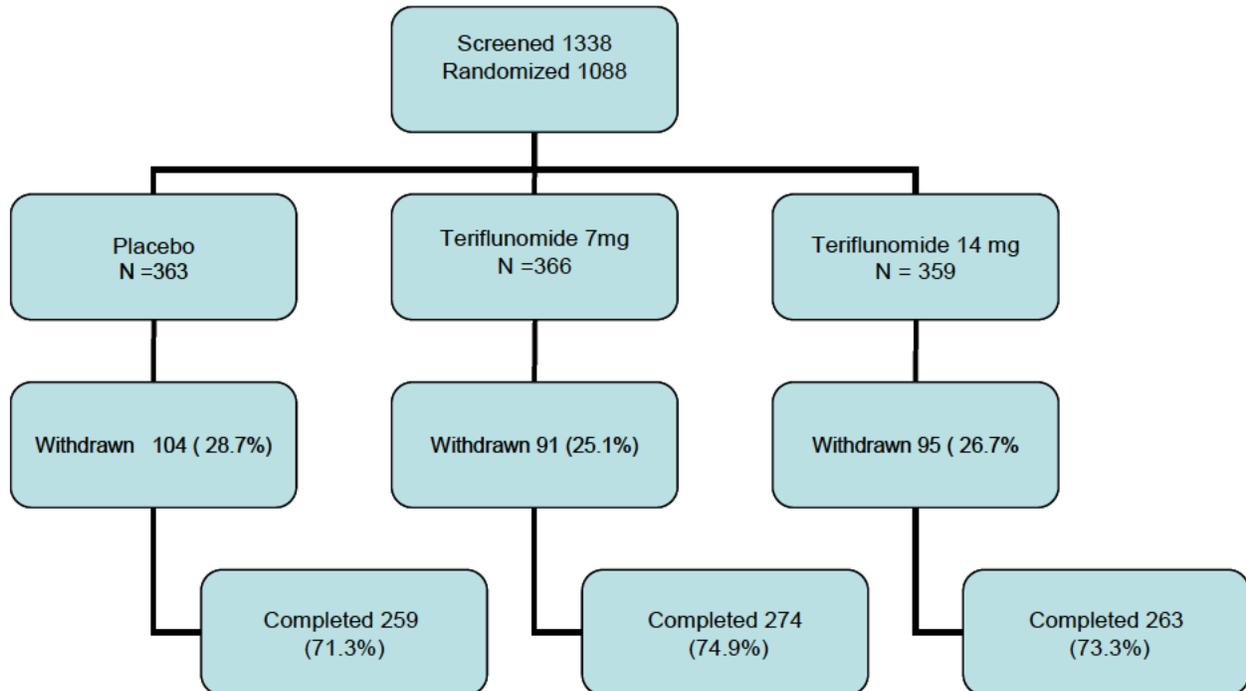
Analysis set	Placebo n (%)	Teri. 7 mg n (%)	Teri. 14 mg n (%)
ITT set	363 (100%)	365 (99.7%)	358 (99.7%)
PP set	353 (97.2%)	356 (97.3%)	350 (97.5%)
Safety set	360	368	358

Trial Population, Enrollment and Patient Disposition

Subject Disposition

A total of 126 sites in 21 countries were included in this study and they screened 1338 patients. Of those screened 250 were screening failures primarily due to not meeting the entrance criteria. Some few did not wish to continue. Of the 1088 randomized patients, in accordance with the 1:1:1 randomization scheme, 363 were randomized to placebo, 366 to teriflunomide 7 mg, and 359 to teriflunomide 14 mg. Of these all but two received treatment with the study medication for a total of 1086 in the Intent to Treat Population (ITT). The two randomized patients that were screening failures and inadvertently randomized were considered protocol violations. Of those treated, a total of 290 did not complete the study for a total withdrawal rate of 26.84%. This was considerably higher than the anticipated 20% anticipated by the sponsor when used to power the trial. Drop out was highest for placebo patients (104 subjects or 28.7%) and a bit lower for those on teriflunomide 14mg (95 subjects or 26.5%), or teriflunomide 7 mg (91 subjects or 24.9%). A total of 796 completed the study and of those 742 entered the extension protocol. (See Figure 2)

Figure 2 Patient disposition TEMSO study randomized population



Discontinuations

Adverse events were the most common cause of drop out (28.7%) particularly on those on drug product (placebo 8%, teriflunomide 7 mg 10.1% and teriflunomide 14 mg 10.6%). Almost as common, subjects who did not wish to continue accounted for 25% of dropouts (placebo 9.1%, teriflunomide 7 mg 8.7%, and teriflunomide 14 mg 7.2%). Withdrawal due to lack of efficacy accounted for 15.1% (placebo, 6.6%, teriflunomide 7 mg, 3.8%, and teriflunomide 14 mg, 4.7%). Of note, those who stopped due to progressive disease accounted for 11 (3%) on placebo, 32 (8.7%) on teriflunomide 7 mg, and 26 (7.2%) on teriflunomide 14 mg. See Table 7 below based on information provided by the sponsor.

Table 7 Major efficacy-related protocol deviations- randomized population

Reasons for Discontinuation	Placebo	teriflunomide 7 mg	teriflunomide 14 mg
Randomized and treated	363	365	358
Completed study treatment period	259 (71.3%)	274 (74.9%)	263 (73.3%)
Total Discontinuation	104 (28.7%)	91 (25.1%)	95 (26.7%)
By patient request	33 (9.1%)	32 (8.7%)	26 (7.2%)
AE	29 (8.0%)	37 (10.1%)	38 (10.6%)
Lack of Efficacy	24 (6.6%)	14 (3.8%)	17 (4.7%)
Poor compliance to protocol	3 (0.8%)	2 (0.5%)	5 (1.4%)
Progressive disease	11 (3.0%)	32 (8.7%)	26 (7.2%)
Lost to follow-up	4 (1.1%)	0	2 (0.6%)
Other	0	2 (0.5%)	5 (1.4%)

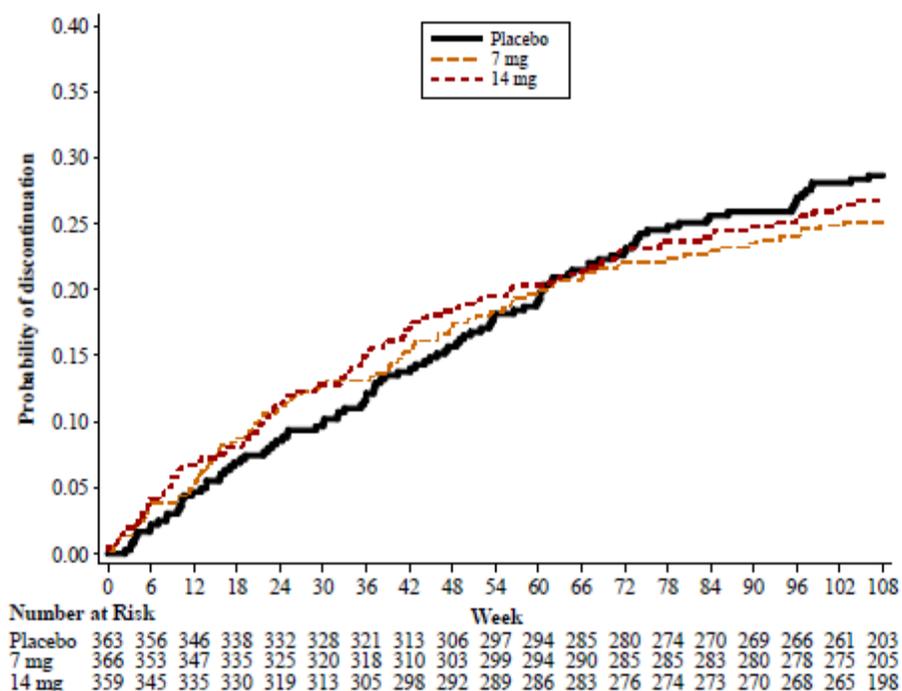
Clinical Study Report EFC6049 pages 70-71

Reviewer's Comments

Discontinuations were higher than the sponsor anticipated when designing the trial and higher than is desirable to preserve randomization. Nevertheless, discontinuations were relatively well balanced. The sponsor split drug discontinuations by separating those who stopped because the drug did not work (had a relapse) from those who stopped because of disease progression. Stopping for either reason is an indication that the drug did not work as desired. The results suggest that patients are more satisfied with the drug's ability to prevent relapse than to prevent disease progression.

The sponsor did analyze the time of treatment discontinuation for subjects as seen in the Kaplan Meier plot of time to treatment discontinuation in the randomized population. From this plot (Figure 3) it appears that those on drug tended to discontinue treatment earlier, presumably due to adverse events and those on placebo tended to discontinue treatment later presumably due to poor efficacy. This would not be expected to be a bias toward treatment effect.

Figure 3 Probability of discontinuation in the TEMSO trial for 3 treatment arms



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Unblinding

The sponsor reported that a total of 40 patients were unblinded in the TEMSO study. Of those who were unblinded, seven went on to complete the study, and the remainder discontinued. Of the 14 placebo patients that were unblinded, 4 did so because of poor efficacy and the others had other side effects or pregnancy related issues. Of the 15 patients on Teriflunomide 7 mg, 4 stopped because of poor efficacy and the remainder due to other side effects or pregnancy. Of the 11 patients on Teriflunomide 14 mg, none stopped due to poor efficacy and the remainder had other side effects or pregnancy issues. (See Table 7)

Table 8 Unblinding of subjects in TEMSO trial

Number unblinded	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Total	14	15	11
Due to poor efficacy	4	4	0
Due to side effects	9	8	8
Due to pregnancy (or planned pregnancy in the case of men)	1	2	3

Treatment Compliance

The compliance rate was well balanced. According to the sponsor the median compliance to the protocol of the 1086 patients in the safety population was 99.5% overall and was similar among all three treatment groups. There were only 6 patients that had an overall compliance rate of less than 80%.

Reviewer's Comments

Treatment compliance was well balanced among treatment groups with few violations resulting in discontinuation. The compliance reported sounds extraordinary. Although a sizeable number of patients were unblinded, the three treatment arms were well balanced for cause of unblinding and premature unblinding appears not to have compromised the study.

Demographics

General Demographics

The TEMSO trial sought to enroll subjects with one of the relapsing forms of multiple sclerosis who were between the ages of 18-55 with a baseline EDSS score of 0-5.5. It is noted that overall 97.5% of the participants were Caucasian, 72.2% were female and the mean age was 37.9 for all subjects in the ITT population. The groups were in general well balanced among all three regions for baseline demographic characteristics according to the sponsor although it was noted that those in the Americas were slightly younger, of greater Hispanic ethnicity and had greater weight and BMI than the general population. Further details can be found in Table 9.

Table 9 Baseline patient characteristics of TEMSO trial- ITT population

Demographic Characteristic	Placebo n=363	Teriflunomide 7 mg n=366	Teriflunomide 14 mg n=359	All n= 1088	Americas Subgroup n = 246
Age (years)					
Number	363	365	358	1088	246
Mean (SD)	38.4 (9.0)	37.5 (9.0)	37.8 (8.2)	37.9 (8.8)	38.5 (8.6)
Median	39.0	39.0	38.0	38.0	40.0
Min Max	18:55	18:55	18:55	18:55	18:55
Sex (n, %)					
Number	363	366	359	1088	246
Male	88 (24.2%)	111 (30.3%)	104 (29.0%)	303 (27.8%)	53 (21.5%)
Female	275 (75.8%)	255 (69.7%)	255 (71.0%)	785 (72.2%)	193 (78.5%)
Race (n, %)					
Number	362	364	357	1085	246
Caucasian	356 (98.3%)	354 (97.3%)	346 (96.9%)	1056 (97.5%)	237 (96.3%)
Black	3 (0.8%)	1 (0.3%)	1 (0.3%)	5 (0.5%)	4 (1.6%)
Asian	1 (0.3%)	6 (1.6%)	8 (2.2%)	15 (1.4%)	4 (1.6%)
Multiracial	1 (0.3%)	2 (0.5%)	2 (0.6%)	5 (0.5%)	1 (0.4%)
Other	1 (0.3%)	1 (0.3%)	0	2 (0.2%)	0
Ethnicity					
Number				1081	246
Hispanic				73 (6.8%)	57 (23.2%)
Nonhispanic				1008 (93.2%)	189 (76.8%)
Weight (kg)					
Number	363	365	358	1086	245
Mean (SD)	69.68 (16.02)	70.66 (14.72)	69.76 (15.15)	70.04 (15.30)	73.76 (17.42)
Median	67.00	69.00	67.50	68.00	71.00
Min Max	39.0 : 139.4	40.7 : 126.2	39.0 :135.0	39.0 :139.4	39.0 :139.4
BMI (kg/m2)					
Number	358	363	352	1073	240
Mean	24.63 (5.01)	24.64 (4.54)	24.55 (4.67)	24.61 (4.74)	26.54 (5.69)
Median	23.63	23.77	23.67	23.68	25.07
Min Max	16.2 : 48.2	15.5 : 44.3	16.8 : 42.6	15.5 : 48.2	17.3 : 48.2

Clinical Study Report EFC 6049 Demographic data Table 14.2.4.1.2 and Submission June 19, 2012 p 6/17

Baseline Disease Characteristics

Subjects were well balanced with disease onset a mean of 5.33 years prior to the entrance to the trial, mean length of 6.35 months from their most recent relapse, and mean number of 1.4 relapses in the preceding year. Details of the three treatments arms can be found in Table 10.

Subjects were stratified by EDSS score for entrance into this study with the bulk having an EDSS \leq 3.5 (77.1%) and those $>$ 3.5 were only 22.9%. The study attempted to recruit patients with all of the types of relapsing forms of MS. The vast majority had RRMS disease (91.4%), and only 4.7% had SPMS and 3.9% had PRMS. The three treatment arms were well balanced for MS subtype.

Table 10 Baseline Disease Characteristics – ITT population

Characteristic	Statistics	Placebo (n=363)	Teriflunomide 7 mg (n= 366)	Teriflunomide 14 mg (n=359)	All N = 1085
Disease Duration in years	N Mean (SD) Median Min; Max	363 5.13 (5.59) 3.25 0.1 : 31.6	364 5.29 (5.36) 3.75 0.1 : 27.6	358 5.59 (5.49) 3.71 0.1 : 30.1	1085 5.33 (5.48) 3.50 0.1 : 31.6
Time since last attack prior to study Day 1 (in months)	N Mean (SD) Median Min; Max	363 6.28 (3.62) 5.00 0.0 : 22.0	365 6.29 (3.29) 5.00 1.0 : 22.0	358 6.50 (3.70) 6.00 2.0 : 22.0	1086 6.35 (3.54) 5.00 0.0 : 22.0
MS subtype (n %)	Number RRMS SPMS PRMS	363 329 (90.6%) 22 (6.1%) 12 (3.3%)	365 332 (91.0%) 17 (4.7%) 16 (4.4%)	358 332 (92.7%) 12 (3.4%) 14 (3.9%)	1086 993 (91.4%) 51 (4.7%) 42 (3.9%)
EDSS baseline	Number Mean (SD) Median Min; Max	363 2.68 (1.34) 2.50 0.0 : 6.0	365 2.69 (1.33) 2.50 0.0 : 6.0	358 2.67 (1.25) 2.50 0.0 : 5.5	1086 2.68 (1.30) 2.50 0.0 : 6.0
EDSS strata baseline		363	365	358	1086
≤ 3.5		281 (77.4%)	280 (76.7%)	276 (77.1%)	837 (77.1%)
> 3.5		82 (22.6%)	85 (23.3%)	82 (22.9%)	249 (22.9%)
Relapse in Prior 12 months (n,%)	Number Mean (SD) Median Min : Max	277 1.4 (0.7) 1.0 0 : 6	283 1.4 (0.7%) 1.0 0 : 6	271 1.3 (0.7) 1.0 0 : 4	831 1.4 (0.7) 1.0 0 : 6
0		10 (3.6%)	9 (3.2%)	18 (6.6%)	37 (4.5%)
1		163 (58.8%)	173 (61.1%)	170 (62.7%)	506 (60.9%)
2		86 (31.0%)	88 (31.1%)	71 (26.2%)	245 (29.5%)
3		16 (5.8%)	10 (3.5%)	10 (3.7%)	36 (4.3%)
≥ 4		2 (0.7%)	3 (1.1%)	2 (0.7%)	7 (0.8%)

Adapted from Table 14.2.4.2.2 Clinical Study Report EFC 6049

Table 11 Baseline MRI by treatment group – ITT population

Characteristic	Statistics	Placebo (n= 363)	Teriflunomide 7 mg (n= 365)	Teriflunomide 14 mg (n= 358)	All (n = 1086)
Number of baseline GD + lesions	N Mean (SD) Median Min; Max	359 1.66 (3.55) 0.00 0.0: 26.0	359 1.51 (3.97) 0.00 0.0 : 38.0	355 1.81 (5.17) 0.00 0.0 : 50.0	1073 1.66 (4.28) 0.00 0.0 : 50.0
Baseline burden of disease	N Mean (SD) Median Min; Max	358 19.34 (18.94) 12.75 0.1 : 83.7	359 20.42 (20.59) 13.98 0.2 : 146.3	355 18.08 (17.49) 12.39 0.3 : 88.8	1072 19.28(19.06) 13.05 0.1 : 146.3
Volume of hypointense lesions on T1-weighted image	N Mean (SD)	363 3.26 (3.64)	366 3.35 (3.96)	359 2.91 (3.25)	
Brain Parenchymal Fraction	N Mean (SD)	363 0.76 (0.02)	366 0.76 (0.02)	359 0.76 (0.02)	

Provided by sponsor as adapted from Table 1 O'Connor P et al NEJM, 2011; 365: 1293-303

According to the sponsor there was no significant difference in baseline MRI findings in the three treatment arms prior to the initiation of medication. (See Table 11)

Prior Disease Modifying Characteristics

The sponsor did not collect information about past use of immunomodulators over the lifetime of the subjects and only reported past use in the previous two years prior to trial entrance. Treatment arms were well balanced for their past use of immunomodulators and for being treatment naive. No one had been on an immunosuppressant in the preceding two years such as mitoxantrone or natalizumab. (see Table 12)

Table 12 Prior two years before randomization of past use of immunomodulators

Disease Modifying Drug in past	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	All
Total Number	363	366	369	1088
Treatment naive	273 (75.2%)	264 (72.1%)	257 (71.6%)	794 (73.0%)
Disease Modifying Drug				
Previously treated	90 (24.8%)	102 (27.9%)	102 (28.4%)	294 (27.0%)
All interferon β -1A	58 (16.0%)	74 (20.2%)	62 (17.3%)	194 (17.8%)
Rebif	39 (10.7%)	52 (14.2%)	37 (10.3%)	128 (11.8%)
Avonex	23 (6.3%)	24 (6.6%)	29 (8.1%)	76 (7.0%)
Betaseron/Extavia	18 (5.0%)	22 (6.0%)	27 (7.5%)	67 (6.2%)
Copaxone	36 (9.9%)	23 (6.3%)	43 (12.0%)	102 (9.4%)
Mitoxantrone	0	0	0	0
Tysabri	0	0	0	0

Clinical Study Report EFC 6049 adapted from table on page 77/18

Applicability of Foreign Data

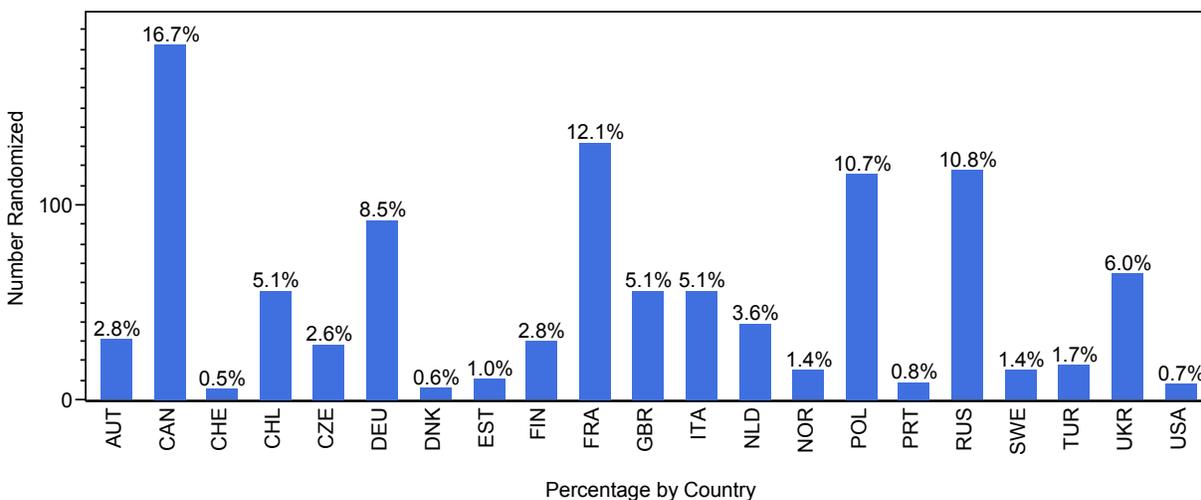
The pivotal trial used to support efficacy contained 0.7% subjects from the US, (8 /1086). Patients were well balanced from three major world regions as seen in Table 13. The greatest numbers of subjects were from Western Europe (46.3%). About 31.1% were from Eastern Europe and 22.6% were from the Americas. Those from the Americas were from either Chile (5.1%) or Canada (16.7%). Figure 4 shows the percentage of subjects from each country.

Table 13 Number of Subjects associated with each region – ITT population

Region [n (%)]	363	365	358	1086
Number				
Americas	82 (22.6%)	83 (22.7%)	80 (22.3%)	245 (22.6%)
Eastern Europe	114 (31.4%)	116 (31.8%)	108 (30.2%)	338 (31.1%)
Western Europe	167 (46.0%)	166 (45.5%)	170 (47.5%)	503 (46.3%)

Clinical Study Report EFC 6049 P 8/116 Demographic data 14.2.4.1.2

Figure 4 Percentage of Subjects from various countries ITT population (n = 1086)



Reviewer's Comment

The sponsor provided no justification for their use of non-US subjects, but presumably this is because the bulk of drug development took place prior to having an approved IND in this country. Subjects on the whole were Caucasian, female, and had RRMS. There were very few Asians and Blacks in the study. Since the demographics of the study are probably similar to what one would expect of US subjects the lack of US subjects was not deemed a problem from the efficacy standpoint. The sponsor did not collect information about their subjects' lifetime use of other immunomodulators but did collect information about their prior use in the past two years. It appeared that approximately 75% of patients who entered the study had no use of other immunomodulators in the past two years. Although this number exceeds what one would expect with a study with more US subjects, as the drug was effective for both those who had and had not used immunomodulators, this demographic was not felt to be of concern.

Analysis of Primary Endpoint

Confirmed Annualized relapse rate (ARR)

The confirmed ARR was the primary outcome measure for the TEMSO trial and is perhaps the most common primary endpoint for studies demonstrating efficacy for the relapsing forms of MS. The relapse was considered confirmed after being evaluated by the treating physician after the independent evaluator, the examining neurologist, had documented either

- A 1-point increase in at least two FS functions, or a 2-point increase in at least one FS function (excluding bowel/bladder and cerebral) from the previous clinically stable assessment
 or
- An increase of at least 0.5 points in the EDSS score (unless EDSS = 0, then an increase of at least 1.0 points is required) from the previous clinically stable assessment

Of the 1086 patients in the ITT population of the TEMSO study the adjusted ARR was 0.539 (95% CI: 0.466 to 0.623) in the placebo group, 0.370 (95% CI: 0.318 to 0.432) in the teriflunomide 7 mg group, and 0.369 (95% CI: 0.308 to 0.441) in the teriflunomide 14 mg group. (Table 14) These results correspond to a risk reduction of 31.2% in the teriflunomide 7mg group and 31.5% in the teriflunomide 14 mg group. An analysis by baseline EDSS strata revealed that those with EDSS ≤ 3.5 at baseline had a lower adjusted ARR (Table 14) than those that started with an EDSS ≥ 3.5.

Table 14 TEMSO primary outcome measure, confirmed ARR in ITT population

	TEMSO ITT population		
Relapses	Placebo N = 363	Teriflunomide	
		7 mg N = 365	14 mg N = 358
Number of relapses	335	233	227
0	179 (49.3%)	211 (57.8%)	217 (60.6%)
1	97 (26.7%)	92 (25.2%)	86 (24.0%)
2	48 (13.2%)	49 (13.4%)	33 (9.2%)
3	22 (6.1%)	10 (2.7%)	16 (4.5%)
4	11 (3.0%)	2 (0.5%)	4 (1.1%)
≥ 5	6 (1%)	1 (0.3%)	2 (0.6%)
Adjusted ARR	0.539	0.370	0.369
95% CI	(0.466, 0.623)	(0.318, 0.432)	(0.308, 0.441)
Relative risk		0.688	0.685
Risk reduction		31.2%	31.5%
P value		0.0002	0.0005
EDSS Score baseline	Placebo	Teri 7 mg	Teri 14 mg
EDSS ≤ 3.5			
n	281	280	276
Adjusted estimate ARR (95% CI)	0.499 (0.425, 0.587)	0.347 (0.292, 0.412)	0.302 (0.246, 0.372)
Relative risk (95% CI)		0.695 (0.552, 0.875)	0.606 (0.470, 0.780)
EDSS ≥ 3.5			

n	82	85	82
Adjusted ARR (95% CI)	0.472 (0.356, 0.625)	0.307 (0.225, 0.419)	0.431 (0.308, 0.604)
Relative risk (95% CI)		0.651 (0.441, 0.960)	0.914 (0.621, 1.345)
P value for interaction		0.8138	0.0656

CSR EFC 6049 Adapted from Table 17 page 80/184 and page 29-30 Appendix 14.2.6

Sensitivity analyses of ARR

As requested the sponsor performed three sensitivity analyses for the primary endpoint

1. ARR in the PP population
2. ARR in those who continued to have relapses after treatment was discontinued including into the follow-up period
3. ARR in those with all relapses, both qualifying relapses and nonqualifying relapses.

In the completed TEMSO trial the Per-protocol population (PP) included the ITT population but excluded subjects with major protocol deviations. Major protocol deviations included those subjects with less than two clinical relapses in the last two years or a relapse in the month preceding randomization, subjects taking prohibited medications which might confound the results, subjects with poor compliance to the study treatment, and subjects with a baseline EDSS > 5.5. The sensitivity analysis confirmed the robust effect of treatment with both doses of teriflunomide and corresponded with a risk reduction of 32.7% for teriflunomide 7 mg and 33.0% for teriflunomide 14 mg. The ARR was 0.545 (95% CI: 0.471 to 0.631) in the placebo group, 0.367 (95% CI: 0.314 to 0.428) in the teriflunomide 7 mg group and 0.366 (95% CI 0.305 to 0.438) in the teriflunomide 14 mg group. (See Table 15)

Table 15 TEMSO trial Clinical efficacy for the primary outcome measure, confirmed ARR in PP population

Relapses	TEMSO PP population		
	Placebo N = 353	Teriflunomide	
		7 mg N = 356	14 mg N = 350
Number of relapses	331	226	223
0	172 (48.7%)	206 (57.9%)	211 (60.3%)
1	95 (26.9%)	90 (25.3%)	86 (24.6%)
2	47 (13.3%)	48 (13.5%)	31 (8.9%)
3	22 (6.2%)	9 (2.5%)	16 (4.6%)
4	11 (3.1%)	2 (0.6%)	4 (1.1%)
≥ 5	6 (1.7%)	1 (0.3%)	2 (0.6%)
Adjusted ARR	0.545	0.367	0.366
95% CI	(0.471,0.631)	(0.314, 0.428)	(0.305, 0.438)
Relative risk		0.673	0.670
Risk reduction		32.7%	33.0%
P value		0.0001	0.0002

CSR EFC 6049 Adapted from Table 18 , p 82/184

Another sensitivity analysis involved looking at the ITT population with additional data coming from patients from the follow-up period in those who had prematurely and permanently discontinued study medicine. This only involved adding seven patients to the analysis, two on placebo, one on 7 mg and four on 14 mg of teriflunomide. The adjusted ARR from this analysis was 0.505 (95% CI: 0.438 to 0.583) in the placebo group, 0.358 (95% CI: 0.308 to 0.416) in the teriflunomide 7 mg group, and 0.358 (95% CI: 0.300 to 0.427) in the teriflunomide 14 mg group which corresponds to a relative risk reduction of 29.1% in both the teriflunomide 7 mg group (p=0.0006) and the teriflunomide 14 mg (p=0.0012) group relative to placebo. (see Table 16)

Finally a sensitivity analysis was done with those with both confirmed and non-confirmed relapses. The ARR was 0.636 (95% CI 0.556, 0.727) in those on placebo, 0.453 (CI 0.394, 0.522) in those on teriflunomide 7 mg, and 0.441 (CI 0.375, 0.518) in those on teriflunomide 14 mg. This meant that the risk reduction was 28.7% for those on teriflunomide 7 mg and 30.7% for those on teriflunomide 14 mg for all relapses, both confirmed and nonconfirmed. (See Table 16)

Table 16 TEMSO trial Further Sensitivity Analyses of ARR

ARR in relapses confirmed and nonconfirmed	Placebo (n = 363)	Teri. 7 mg (n =365)	Teri. 14 mg (n=358)
ARR Estimate (95% CI)	0.636 (90.556, 0.727)	0.453 (0.394, 0.533)	0.441 (0.375, 0.518)
Relative Risk (95% CI)		0.713 (0.594, 0.855)	0.693 (0.571, 0.840)
P value vs. placebo		0.0003	0.0002
ARR with relapse after treatment ended	Placebo (n=363)	Teri. 7mg (n=365)	Teri. 14 mg(n=358)
ARR Estimate (95% CI)	0.505 (0.438, 0.583)	0.358 (0.308, 0.416)	0.358 (0.300, 0.427)
Relative Risk (95% CI)		0.709 (0.583, 0.862)	0.709 (0.575, 0.873)
P value vs. placebo		0.0006	0.0012

Clinical Study Report EFC 6049 Table 19 and Summary of Clinical Efficacy Table 15 Section 2.7.3

Subpopulations

The effect of teriflunomide on ARR in various subpopulations in the TEMSO trial was performed by the sponsor and a treatment effect was noted on many of the subgroups including gender, age group, prior MS immunomodulator treatment, number of relapses in the prior two years, number of baseline Gd-enhancing lesions and baseline BOD. The analysis of the treatment response by region, by type of MS and by prior use of immunomodulator was confirmed by the agency statistician and can be found in Table 17. In general it was noted that those in the Americas has less relapses than those in Eastern and Western Europe. Those that were under age 38 have less relapses than those over age 38. Those that were previously treated with MS medication had more relapses than those that were not. Despite these differences the drug seemed to work in all treatment arms compared with placebo with the exception of those on 14 mg of teriflunomide with progressive cases of MS (SPMS, PRMS).

Table 17 TEMSO trial Adjusted ARR in subgroup population

TEMSO	Placebo N=363	Teriflunomide	
		7 mg N=366	14 mg N=359
Region			
Americas			
N	82	83	80
Adjusted ARR	0.306	0.205	0.274
Relative risk		0.668	0.896
Nominal p-value		0.1144	0.6775

Eastern Europe			
N	114	116	108
Adjusted ARR	0.520	0.416	0.416
Relative risk		0.800	0.800
Nominal p-value		0.2087	0.2443
Western Europe			
N	167	166	170
Adjusted ARR	0.712	0.447	0.398
Relative risk		0.628	0.559
Nominal p-value		0.0010	<.0001
Type of MS			
Relapsing Remitting			
N	329	332	332
Adjusted ARR	0.537	0.371	0.355
Relative risk		0.691	0.661
Nominal p-value		0.0005	0.0002
Prog relapsing or Sec Progressive			
N	34	33	26
Adjusted ARR	0.478	0.305	0.471
Relative risk		0.639	0.985
Nominal p-value		0.2096	0.9708
Previous MS Treatment			
Yes			
N	90	102	102
Adjusted ARR	0.781	0.497	0.470
Relative risk		0.637	0.602
Nominal p-value		0.0069	0.0038
No			
N	273	263	256
Adjusted ARR	0.448	0.307	0.314
Relative risk		0.686	0.702
Nominal p-value		0.0029	0.0091

Reviewer's Comment

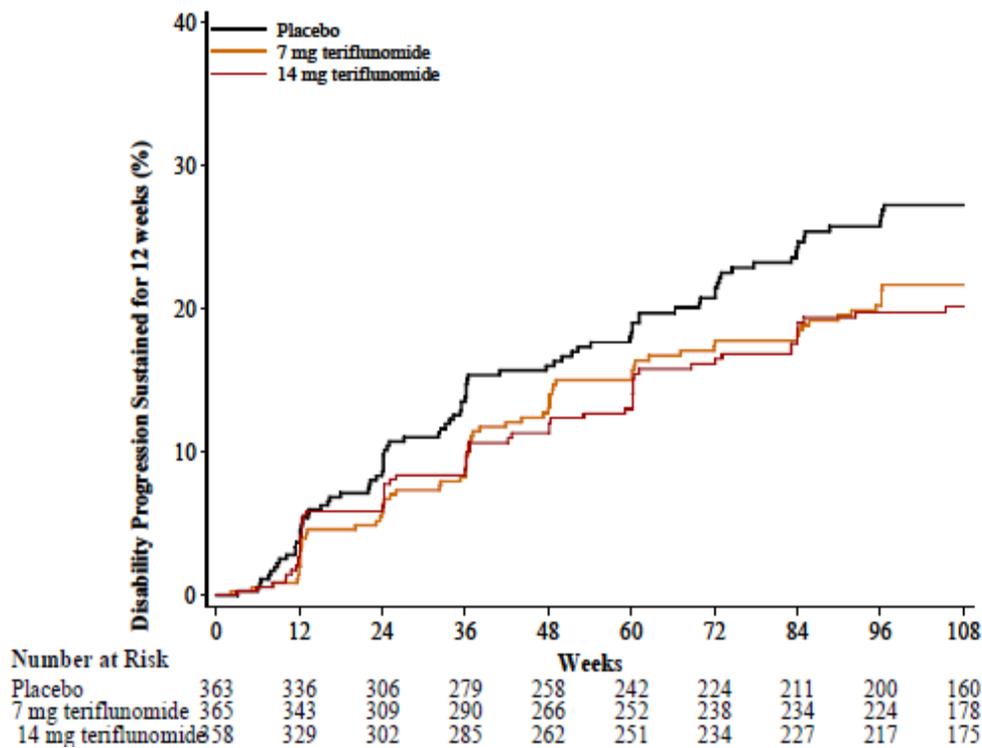
The study was not powered to examine subgroups and subgroups can only be evaluated on a descriptive basis. It is impossible to interpret results of those with progressive MS on 14 mg of teriflunomide that included only 26 subjects out of 1088 randomized. Since regulatory standards do not demand a demonstration of effectiveness specifically in those with SPMS and PRMS in order to get a claim for relapsing MS, the findings in this subgroup was discounted. Past approval for marketed products in the US for the treatment of the relapsing forms of MS have largely been based on trials in RRMS that have demonstrated that the effective dose reduces relapses in those with RRMS including those most at risk for progressive disease, namely those with greater physical disability (higher EDSS scores).

Analysis of Key Secondary Endpoint

Time to sustained disability progression for 12 weeks

The risk of disability progression sustained for 12 weeks was assessed after 108 weeks and it was here that teriflunomide 14 mg appeared to have its most significant effect over the 7 mg dose which only trended positive. Although all groups progressed after 108 weeks, compared with placebo, only the 14 mg dose had a significant benefit. (Table 18) The hazard ratio was 0.702 ($p = 0.0279$) for the 14 mg dose and 0.763 ($p = 0.0835$) for the 7 mg dose. The estimate of those who had 12-week sustained disability at 108 weeks was 27.3% for placebo, 21.7% for the 7 mg dose and 20.2% for the 14 mg dose. (Figure 5)

Figure 5 Kaplan-Meier plot of time to disability progression on EDSS- ITT population



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Table 18 TEMSO Time to disability progression sustained for 12 weeks

	Placebo (N=363)	teriflunomide	
		7 mg (N=365)	14 mg (N=358)
Number of patients with disability progression	86 (23.7%)	68 (18.6%)	62 (17.3%)
Number of patients who were censored	277 (76.3%)	297 (81.4%)	296 (82.7%)
Probability of disability progression (95% CI) at ^a			
24 weeks	0.086 (0.057, 0.116)	0.058 (0.033, 0.083)	0.062 (0.036, 0.088)
48 weeks	0.160 (0.121, 0.200)	0.131 (0.094, 0.167)	0.113 (0.079, 0.148)
108 weeks	0.273 (0.223, 0.323)	0.217 (0.171, 0.263)	0.202 (0.156, 0.247)
Hazard ratio (95% CI) ^b		0.763 (0.555, 1.049)	0.702 (0.506, 0.973)
P-value ^c		0.0835	0.0279

Note: The time-to-event variable is defined as the time (days) from the date of randomization to the date of the first disability progression. For patients who have no disability progression on or before last during treatment EDSS evaluation, it will be censored at the date of last during-treatment EDSS evaluation.

^a Derived from Kaplan-Meier estimates

^b Derived using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

^c Derived from log-rank test with stratification of EDSS strata at baseline and region

Clinical Study Report EFC 6049 page 87 Table 20

A sensitivity analysis was done for the PP population and trended positive for the 7 mg dose [RR by 21.7% (p=0.1144)] but was only statistically significant for the 14 mg dose [RR by 30.1% (p=0.0258)], lending further support to the findings in the ITT population.

Subgroup analyses of time to disability progression

Subgroup analyses were done for all of the usual factors, age, sex, race, baseline EDSS, region, number of relapses within the past two years, type of MS, baseline MRI findings, BOD and was confirmed by the agency statistician. A trend for interaction was found in baseline EDSS as seen in Table 19 with greater effectiveness noted with EDSS \geq 3.5. For those in the Americas no treatment effect was seen with either dose of teriflunomide compared with placebo but treatment effect was seen in both the Eastern and Western European regions.

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Table 19 TEMSO Regional subgroup analysis for ITT population and change in EDSS

Subgroup (N =)	Teriflunomide vs. Placebo	Hazard Ratio	95% CI
Region			
E Europe (n = 338)	7 mg vs. placebo	0.448	(0.230, 0.874)
	14 mg vs. placebo	0.502	(0.258, 0.978)
W Europe (n = 503)	7 mg vs. placebo	0.757	(0.492, 1.164)
	14 mg vs. placebo	0.684	(0.442, 1.060)
Americas (n = 245)	7 mg vs. placebo	1.397	(0.684, 2.851)
	14 mg vs. placebo	1.114	(0.523, 2.371)
EDSS score			
EDSS < 3.5 (n = 837)	7 mg vs. placebo	0.878	(0.614, 1.254)
	14 mg vs. placebo	0.819	(0.569, 1.178)
EDSS ≥ 3.5 (n = 249)	7 mg vs. placebo	0.413	(0.200, 0.854)
	14 mg vs. placebo	0.351	(0.162, 0.765)

In order to further clarify why there may not have been a treatment effect for disability progression in the Americas, the agency statistician performed an analysis to evaluate if those in the Americas may have had a higher or lower EDSS at baseline than those from other regions to account for their difference in treatment responsiveness. The analysis which is found in Table 20 reveals that this was not the case. It also reveals that in the Americas those on either 7 mg of teriflunomide or 14 mg of teriflunomide progressed but those on placebo progressed almost not at all.

Table 20 TEMSO Comparison of baseline EDSS and progression on EDSS between all subjects and those from the Americas

TEMSO	Placebo N=363	Teriflunomide	
		7 mg N=365	14 mg N=358
Overall EDSS mean			
N	363	365	358
Baseline mean (SD)	2.68 (1.34)	2.69 (1.33)	2.67 (1.25)
Mean change from baseline	0.30 (1.02)	0.32 (1.00)	0.22 (0.91)
Americas			
N	82	83	80
Baseline mean (SD)	2.61 (1.25)	2.57 (1.23)	2.68 (1.11)
Mean change from baseline	0.02 (0.98)	0.28 (1.03)	0.20 (0.81)
Number progressed Americas			

N	13	18	14
Baseline mean (SD)	1.85 (1.55)	1.92 (1.44)	2.00 (0.83)
Mean change from baseline	1.31 (0.43)	1.56 (0.82)	1.25 (0.38)
Mean # days to progression	220	254	314

24 week Sustained Disability

An additional analysis was done to estimate the percentage of patients with 24-week sustained disability progression at week 108. Although both doses trended positive, neither had a statistically significant benefit. Teriflunomide 7 mg reduced risk by 25.0% (p=0.1459) and teriflunomide 14 mg reduced risk by 25.1% (p=0.1259)] over placebo.

Reviewer’s Comments

Preventing the progression of disability is where a difference in treatment effect is clearly seen between the two doses. Although both doses seem to have a similar treatment effect on the ARR, only the 14 mg dose appears to have a significant treatment effect on preventing disability progression for 12 weeks. This is further supported by the sensitivity analysis of the PP population and the various subgroup analyses. Even though disability progression was not delayed for 24 weeks or longer, a delay of disability progression for 12 weeks is recognized as being clinically significant for an MS drug.

The fact that the treatment effect for prevention of disability progression was not seen in those in the Americas is noted, although in this same population both doses did work to prevent relapse. All three regions, the Americas, Eastern Europe and Western Europe were all well balanced for their demographics according to the sponsor, although they were noted by this reviewer to be slightly older, heavier, have a higher BMI and be more of Hispanic ethnicity. (See Table 9) This issue was explored further by the agency statistician and it was confirmed that baseline EDSS was similar for all three regions. (See Table 19) Since it is possible that the practice of medicine in the Americas region (Chile and Canada) may not be referable to that practiced in the US, the significance of this finding and the explanation for it are unclear. It may be that there are regional differences in enrollment, treatment, an unknown variable or even the difference in patient characteristics such as age and ethnicity that account for the findings. The study was not powered to assess this and these regional differences were not felt to be of significance in determining approvability.

Other secondary endpoints

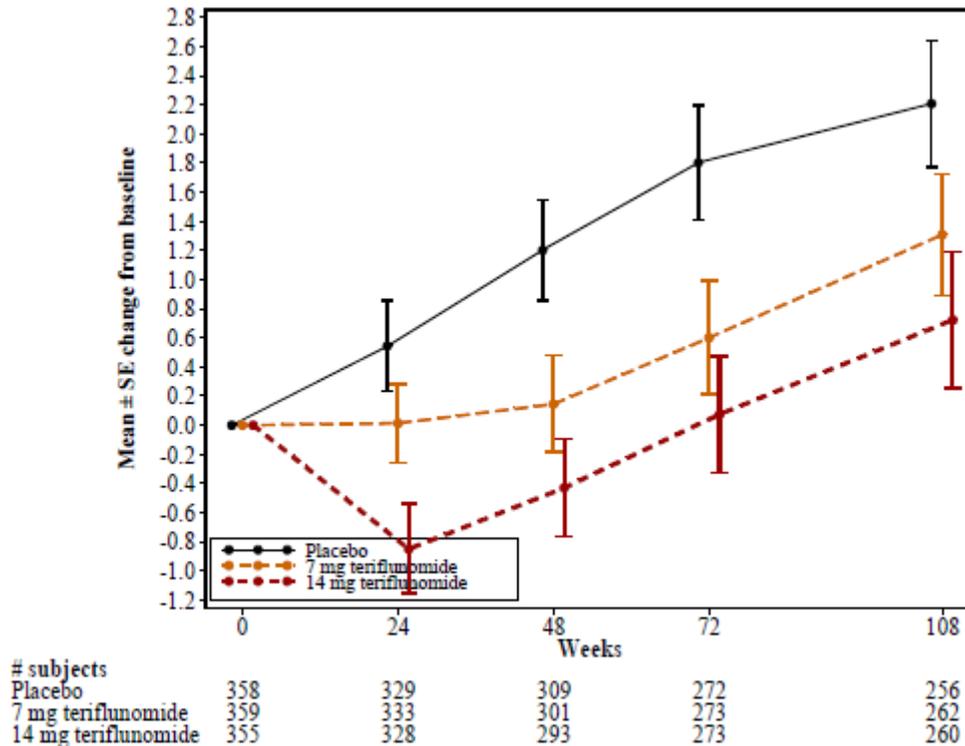
MRI variables

Burden of Disease (BOD) is the total volume of the T1 gadolinium enhanced lesions and the T2 lesions and is thought to represent past disease activity. Due to skew distribution, as stated in the statistical analysis plan the BOD was measured by evaluating the mean change in the absolute value of the cubic root transformed from baseline. The BOD at every time point including 108 weeks was lower in both teriflunomide treatment groups compared with placebo as seen in Figure 6. At the study conclusion, week 108, the mean change in absolute value of cubic root transformed BOD from baseline was 0.111 for the placebo group, 0.072 for the teriflunomide 7 mg group and 0.045 for the teriflunomide 14 mg group. The mixed-effect model with repeated measures (MMRM) using cubic root volume data as provided by the agency statistician is seen in Table 21. The change from baseline was robust for the 14 mg dose ($p = 0.0003$).

Table 21 TEMSO trial MMRM analysis of BOD using cubic root volume data

	Teriflunomide		
	Placebo N=363	7 mg N=365	14 mg N=355
Baseline			
N	358	359	355
Mean (SD)	2.383 (0.892)	2.437 (0.890)	2.359 (0.825)
Median	2.336	2.409	2.314
Week 108			
N	258	265	261
Mean (SD)	2.465 (0.873)	2.503 (0.862)	2.383 (0.801)
Median	2.471	2.518	2.385
Change from baseline (MMRM)			
N	256	262	260
LS Mean (SE)	0.132 (0.018)	0.080 (0.018)	0.043 (0.018)
LS mean difference vs. placebo		-0.053	-0.089
p-value		0.0317	0.0003

Figure 6 TEMSO Plot of change from baseline in BOD over time in ITT population



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Number of gadolinium-enhanced T1 lesions

This is a measure of acute inflammatory change and indicates the breakdown of the blood-brain barrier. This measurement is felt to have predictive value regarding the short-term disease course of MS. The measurement is obtained by adding the number of Gd-enhancing lesions at each post-baseline visit for a patient and dividing by the number of scans. At 108 weeks both doses of teriflunomide were highly significant in their effect on the number of Gd-enhancing T1 lesions ($p < 0.0001$). The adjusted Gd-enhancing T1 lesion/scan was 1.331 (95% CI 1.059 to 1.673) in the placebo group, 0.570 (95% CI 0.434 to 0.748) in the 7 mg teriflunomide group and 0.261 (95% CI 0.167 to 0.407) in the 14 mg teriflunomide group as seen in Table 22.

Table 22 TEMSO trial Number of T1 gadolinium-enhancing lesions/MRI scan in the ITT population

	<i>Placebo</i>	<i>Teriflunomide 7 mg</i>	<i>Teriflunomide 14 mg</i>
Baseline			
<i>Number patients</i>	359	359	355
<i>Mean (SD)</i>	1.663 (3.552)	1.507 (3.969)	1.808 (5.173)
<i>Median</i>	0.000	0.000	0.000
<i>Min: Max</i>	0.00: 26.00	0.00: 38.00	0.00: 50.00
108 weeks			
<i>Number of patients</i>	363	365	358
<i>Adjusted lesions/scan</i>	1.331	0.570	0.261
<i>Estimate (95% CI)</i>	(1.059, 1.673)	(0.434, 0.748)	(0.167, 0.407)
<i>Relative risk</i>		0.428	0.196
<i>95% CI</i>		(0.310, 0.592)	(0.120, 0.321)
<i>P value</i>		<0.0001	< 0.0001

Volume of T1-hypointense lesions

These lesions are thought to represent irreversible axonal loss, gliosis and loss of intracellular matrix. Due to skew distribution these also were evaluated as the change from baseline to week 108 in cubic root transformed volume. As seen in Table 23 only the change in volume of the T1 hypointense lesions for the teriflunomide 14 mg dose was significant and not for the 7 mg dose.

Table 23 TEMSO trial Volume change of T1-hypointense lesions in the ITT population

	<i>Placebo</i>	<i>Teriflunomide 7 mg</i>	<i>Teriflunomide 14 mg</i>
Baseline			
<i>Number patients</i>	358	359	355
<i>Mean (SD)</i>	1.278 (0.541)	1.290 (0.546)	1.251 (0.493)
<i>Median</i>	1.232	1.270	1.208
<i>Min: Max</i>	0.25: 2.72	0.00: 2.87	0.17: 3.08
108 weeks			
<i>Number of patients</i>	258	265	261
<i>Mean (SD)</i>	1.341 (0.528)	1.365 (0.547)	1.321 (0.497)
<i>Median</i>	1.293	1.341	1.273
<i>Min: Max</i>	0.33: 2.76	0.17: 2.98	0.22: 3.10
<i>Change from baseline</i>			

<i>Number of patients</i>	256	262	260
<i>LS mean (SE)</i>	0.096 (0.009)	0.079 (0.009)	0.066 (0.009)
<i>LS mean difference from placebo (SE)</i>		-0.016 (0.012)	- 0.0030 (0.013)
<i>95% CI</i>		(-0.041 to 0.008)	(-0.055 to -0.006)
<i>P value</i>		0.1916	0.0161

Clinical Study Report EFC6049 Appendix 14.2.6.

Volume of T2 lesions

Due to skew distribution these were evaluated as the change from baseline to week 108 in cubic root transformed volume. As seen in Table 24 there was a treatment effect for both doses of teriflunomide in the change in volume of the T2 lesions over 108 weeks which was of greater statistical significance with the 14 mg dose.

Table 24 TEMSO trial Volume of change of T2 lesions in the ITT population

	<i>Placebo</i>	<i>Teriflunomide 7 mg</i>	<i>Teriflunomide 14 mg</i>
Baseline			
<i>Number patients</i>	358	359	355
<i>Mean (SD)</i>	2.240 (0.840)	2.295 (0.838)	2.222 (0.782)
<i>Median</i>	2.219	2.315	2.161
<i>Min: Max</i>	0.41: 4.11	0.50: 5.01	0.58 : 4.21
108 weeks			
<i>Number of patients</i>	258	265	261
<i>Mean (SD)</i>	2.312 (0.823)	2.346 (0.804)	2.226 (0.753)
<i>Median</i>	2.272	2.354	2.200
<i>Min: Max</i>	0.60: 4.52	0.42: 4.94	0.56: 4.26
<i>Change from baseline</i>			
<i>Number of patients</i>	256	262	260
<i>LS mean (SE)</i>	0.116 (0.018)	0.065 (0.018)	0.026 (0.018)
<i>LS mean difference from placebo (SE)</i>		-0.051 (0.025)	- 0.089 (0.025)
<i>95% CI</i>		(-0.100 to -0.002)	(-0.139 to -0.040)
<i>P value</i>		0.0404	0.0004

Clinical Study Report EFC6049 Appendix 14.2.6.

Other MRI measures

Brain atrophy

According to the sponsor there was not a significant treatment effect with either dose of teriflunomide over the 108 week period of time.

Volume of white matter

According to the sponsor there was a significant treatment effect for change in white matter volume only for the 14 mg dose (LS mean difference from placebo (6.146, p = 0.002) and not for the 7 mg dose (3.106, p = 0.0609).

Volume of gray matter

According to the sponsor there was no significant treatment effect for change in gray matter volume with either dose.

Number of unique active lesions/MRI scan

This endpoint has been validated as a measure supporting efficacy for other drugs but was only an exploratory endpoint in this study. Unique active lesions include new T1 gadolinium-enhancing lesions, new T2 non-enhancing lesions or enlarging lesions, and those with both without double-counting/subject/scan at 108 weeks in each treatment group. According to the sponsor the relative risk reduction of developing unique active lesions was reduced on drug by 47.7% (p<0.0001) in the 7 mg group and by 69.4% (p<0.001) in the 14 mg group as shown in Table 25.

Table 25 Total number of unique active lesions/MRI scan in the ITT population

	<i>Placebo</i>	<i>Teriflunomide 7 mg</i>	<i>Teriflunomide 14 mg</i>
<i># patients</i>	363	365	358
<i>Total # unique active lesions</i>	3360	1810	1199
<i>Total # scans</i>	2294	1208	1178
<i>Unadjusted unique active lesions/scan</i>	2.814	1.498	1.018
<i>Adjusted unique active lesions/scan</i>	2.463	1.288	0.754
<i>Estimate (95% CI)</i>	(2.102, 2.886)	(1.075, 1.543)	(0.576, 0.987)
<i>Relative Risk (95%CI)</i>		0.523 (0.420, 0.650)	0.306 (0.228, 0.411)
<i>P value</i>		<0.0001	< .0001

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Other clinical endpoints

Fatigue Impact Scale

According to the sponsor there were no statistically significant treatment differences at week 108 with either dose of teriflunomide.

MSFC

The MSFC is a validated test of functional outcome in MS that was performed at screening, baseline, and weeks 24, 48, 72 and 96. The test is a composite which includes 3 components, the T25FW, the 9HP, and the PASAT. All three tests are used to compute the composite Z score. The Z score is based on the number of standard deviation units from the mean of a reference population. The test is thought to be more sensitive at capturing disability at the lower ranges than the EDSS and to also capture cognitive dysfunction contributing to disability. As the three components that comprise the MSFC have been independently validated, they can be assessed independently in addition to looking at the global MSFC score. Although it was noted that no significant treatment differences were seen on the MSFC for either dose of teriflunomide compared with placebo at the last measurement at 96 weeks there were significant findings on the PASAT, the cognitive subpart. On the MSFC, the difference in MSFC z-score change from baseline p value was greater than 0.05 for both doses of teriflunomide, and not statistically significant (see Table 26). This was also the case for the T25FW and the 9-hole peg test. There was a statistically significant treatment difference observed in cognitive function on the PASAT at week 96 for both doses (p values between 0.037-0.043 for both doses), but not for the timed 25-foot walk or the 9-hole peg test where p values were >0.05 as seen in Table 26. See also Figure 7 which graphically shows the difference in treatment effect in the PASAT for those on both doses of drug vs. those on placebo.

Figure 7 PASAT Score, Imputed TEMSO

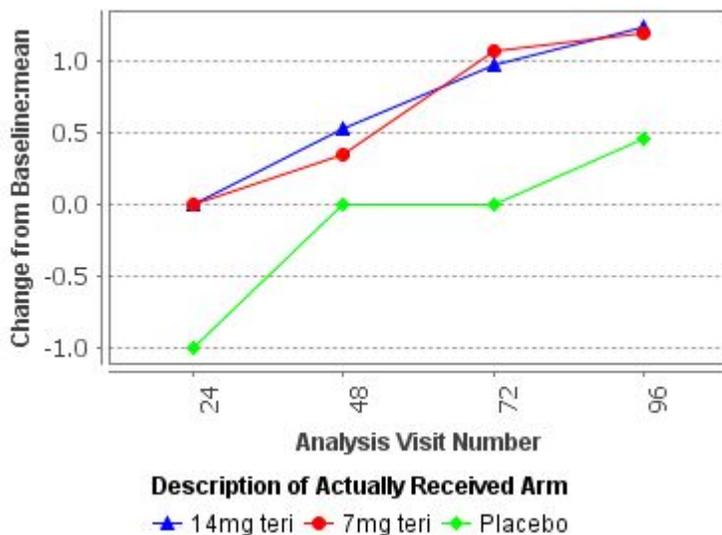


Table 26 MSFC Z score change from baseline to 96 weeks in ITT population

	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
MSFC composite			
Number	260	269	265
LS Mean (SE)	-0.130 (0.039)	-0.096 (0.038)	-0.082 (0.039)
LS Mean Diff from Pb (SE)		0.034 (0.053)	0.048 (0.053)
95% CI		(-0.070 to 0.137)	(-0.056 to 0.152)
P value		0.5219	0.3646
PASAT			
Number	257	265	262
LS Mean (SE)	-0.022 (0.035)	0.075 (0.034)	0.073 (0.035)
LS Mean Diff from Pb (SE)		0.097 (0.47)	0.095 (0.047)
95% CI		(0.005 to 0.189)	(0.003 to 0.187)
P value		0.0379	0.0435
25 ft. Timed walk			
Number	259	268	264
LS Mean (SE)	-0.341 (0.102)	-0.275 (0.101)	-0.202 (0.102)
LS Mean Diff from Pb (SE)		0.066 (0.141)	0.139 (0.141)
95% CI		(-0.219 to 0.343)	(-0.139 to 0.417)
P value		0.3253	0.3253
9-hole peg test			
Number	260	269	265
LS Mean (SE)	-0.100 (0.037)	-0.113 (0.037)	-0.143 (0.038)
LS Mean Diff from Pb (SE)		-0.013 (0.050)	-0.043 (0.051)
95% CI		(-0.112 to 0.86)	(-0.143 to 0.056)
P value		0.7971	0.3933

Clinical Study Report EFC 6049 Appendix 14.2.6

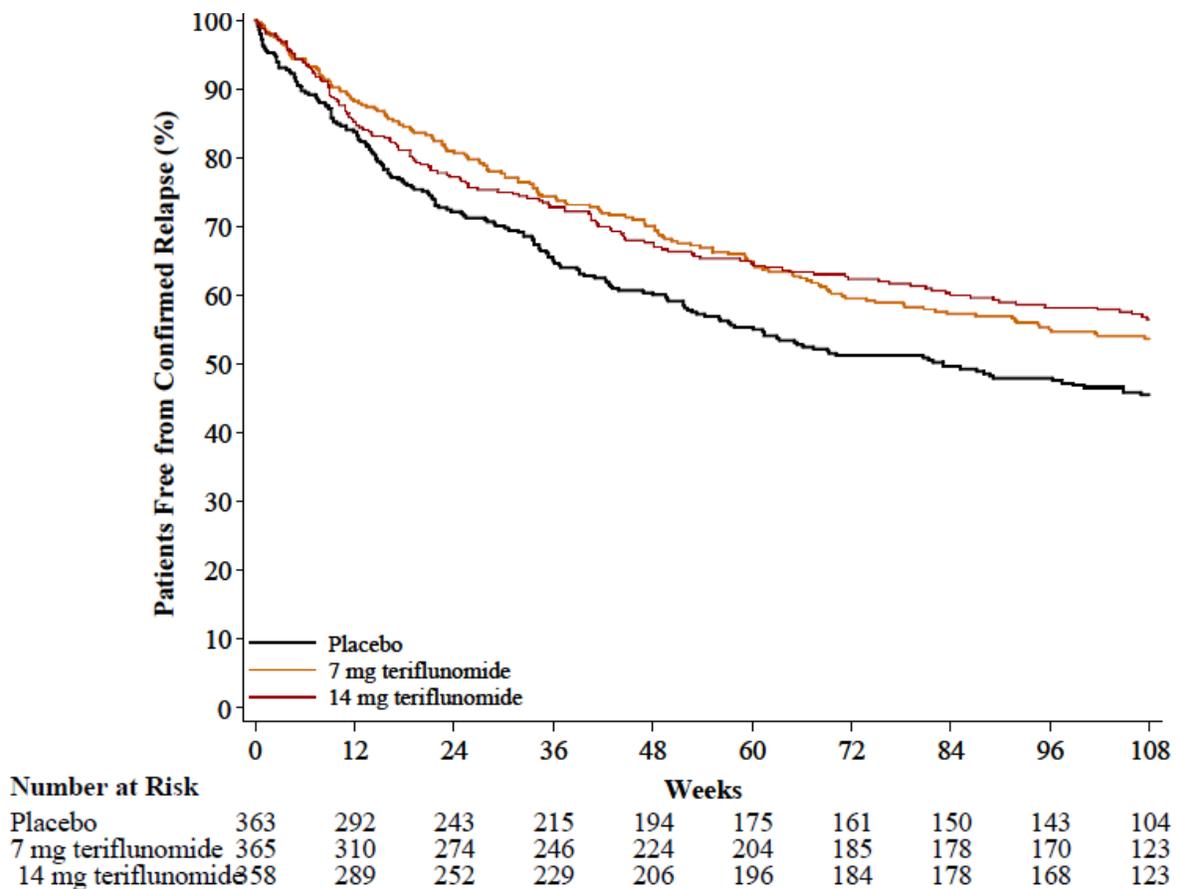
Reviewer's Comment

The MSFC at 96 weeks was chosen as an exploratory endpoint as it has been shown in a study with beta interferon to correlate with brain atrophy and clinically significant disability after 6-8 years. In this trial the MSFC did not substantiate delay in disability with teriflunomide. However a component of the MSFC did demonstrate a significant treatment effect. The PASAT-3 is a task that measures cognitive function by assessing calculation ability as well as mental dexterity in processing a series of numbers. It is acknowledged that the PASAT-3 was not specified as an exploratory endpoint by the sponsor. Since it is known that the PASAT-3 and the EDSS typically have a weak correlation, and since the EDSS is poor at assessing cognitive function, the PASAT-3 is felt to capture an aspect of global function more than what is seen on the EDSS alone. Patients and clinicians are eager to find therapy that can delay cognitive decline, and these findings are suggestive that teriflunomide may do that for MS subjects.

Time to First MS relapse

This was a tertiary efficacy endpoint that was analyzed by log-rank test and which was in support of the primary endpoint. Both doses had a statistically significant effect on delaying the time to first relapse as is seen in the Kaplan-Meier plot provided by the sponsor (Figure 8). Specifically, at the end of 108 weeks, 45.6% of those on placebo were relapse-free, 53.7% of those on 7 mg of teriflunomide were relapse-free, and 56.7% of those on 14 mg of teriflunomide were relapse-free with a hazard ratio of 0.756 ($p = 0.01$) for teriflunomide 7 mg and 0.719 ($p = 0.003$) for teriflunomide 14 mg.

Figure 8 Kaplan-Meier plot of time to first MS relapse ITT population TEMSO



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5.3.2 Phase 2 Study 1726/2001

Study title

A Study of the Safety and Efficacy of Teriflunomide in Multiple Sclerosis with Relapses

Objectives

Primary

- To determine the safety and efficacy of teriflunomide in Multiple Sclerosis with Relapses

Secondary

- To determine the effect of teriflunomide on MRI variables as well as clinical and quality of life measures
- To investigate the following pharmacokinetic and pharmacodynamic relationships:
 - Comparison of population pharmacokinetics of teriflunomide in MS and rheumatoid arthritis patients
 - Investigation of relationships between teriflunomide plasma concentrations and average number of unique active lesions per MRI scan (the primary efficacy variable)
 - Determination of plasma concentrations of trimethylfluoroaniline (TFMA) under steady-state conditions

Study Design

This trial was a randomized placebo controlled, double-blind, and parallel-group trial in adults with clinically definite MS with relapses comparing the efficacy of two doses of teriflunomide with placebo. Subjects were randomized (1:1:1) into one of three treatment groups, placebo, teriflunomide 7 mg, and teriflunomide 14 mg. In the first week of therapy a loading dose was given which was twice the usual dose. After the first week of a loading dose the patients took the maintenance dose for the remainder of the study. After a 4-week treatment-free run in phase there was a 36-week double-blind phase, followed by a 6-week post-treatment observational period with a final MRI at week 42. An extension trial followed the conclusion of this trial. The trial was conducted between April 26, 2001 and March 17, 2003.

Assessment Schedule

The study is divided into two phase:

Baseline included visits 1, 2 and 3

Treatment included visits 4- 11.

The visits are described below.

Visit 1 Screening

Physical exam (PE), Vital Signs (VS), Neurologic exam, Blood draw
Urinalysis (U/A), ECG, CXR
EDSS, Scripps NRS, MSFC, Fatigue Impact Scale, MSQOL-54, MRI

AE, Concomitant medications

Visit 2 Run-in

Training MSFC

Visit 3 Baseline

PE, VS, Neurologic exam, Blood draw

Urinalysis (U/A), ECG, CXR

EDSS, Scripps NRS, MSFC, Fatigue Impact Scale, MSQOL-54, MRI

AE, Concomitant medications

At this point all screening information reviewed, and if deemed appropriate for the study, randomized and given loading dose blister pack and maintenance dose blister pack.

Visit 4 (2 weeks after initiation of dosing)

PE, VS, Neurologic exam, Blood draw, ECG

AE, Concomitant medications

Reminder blood to be drawn in 2 weeks

Visit 5 (six weeks after initiation of dosing)

PE, VS, Neurologic exam, Blood draw, U/A, MRI

AE, Concomitant medications, monitor medication compliance

Reminder blood to be drawn every 2 weeks

Visit 6 (12 weeks after initiation of dosing)

PE, VS, Neurologic exam, Blood draw, U/A

EDSS, Scripps NRS, MSFC, Fatigue Impact Scale, MSQOL-54, MRI

AE, Concomitant medications, monitor medication compliance

Reminder blood to be drawn every 2 weeks

Visit 7 (18 weeks after initiation of dosing)

PE, VS, Neurologic exam, Blood draw, U/A, MRI

AE, Concomitant medications, monitor medication compliance

Reminder blood to be drawn every 2 weeks

Visit 8 (24 weeks after initiation of dosing)

PE, VS, Neurologic exam, Blood draw, U/A

EDSS, Scripps NRS, MSFC, Fatigue Impact Scale, MSQOL-54, MRI

AE, Concomitant medications, monitor medication compliance

Reminder blood to be drawn every 2 weeks

Visit 9 (30 weeks after initiation of dosing)

PE, VS, Neurologic exam, Blood draw, U/A, MRI

AE, Concomitant medications, monitor medication compliance

Reminder blood to be drawn every 2 weeks

Visit 10 (36 weeks after initiation of dosing)

PE, VS, Neurologic exam, Blood draw, U/A, ECG

EDSS, Scripps NRS, MSFC, Fatigue Impact Scale, MSQOL-54, MRI

AE, Concomitant medications, monitor medication compliance

Visit 11 (6 weeks after drug discontinuation)

PE, VS, Neurologic exam, Blood draw, MRI

AE, Concomitant medications

Study Population

This study took place between April 26, 2001 and March 17, 2003. The subjects were between the ages of 18-65. They all had RRMS. There were 60 patients/treatment group for a total of 180 subjects.

Key Inclusion Criteria

- Men and women aged between 18 and 65 years
- Clinically definite MS as defined by the Poser criteria
- At least two documented relapses in the three years prior to screening
- At least one relapse had to be in the year preceding screening
- EDSS between 0-6

Key Exclusion Criteria

Were similar to those in the TEMSO trial.

Treatment Administered

Subjects received a loading dose for the first 7 days of two tablets a day followed thereafter with one tablet a day. The three treatment arms included:

- Placebo: 0 mg
- 7 mg teriflunomide: loading dose 14 mg/day; maintenance dose 7 mg/day
- 14 mg teriflunomide: loading dose 28 mg/day; maintenance dose 14 mg/day

Concomitant Therapy/ Prohibited Medication

The same restrictions applied that were described in the prior two trials

Randomization and Controls

The treatment allocation was determined according to the randomization code provided by sponsor. There was a 1:1:1 randomization to placebo, teriflunomide 7 mg and 14 mg with blocks of six. Randomization was stratified by the subjects' baseline EDSS score. Subjects with a score ≤ 3.5 were randomized in ascending order beginning with the highest number and those with scores > 3.5 were randomized in descending order beginning with the highest number. Access to the randomization code was restricted to the Biometrics Department, Clinical Supplies and Laboratoire of Aventis Pharma and shared with the independent statistician of the DSMB for performing the interim analysis. In addition the bioanalyst who analyzed drug concentrations was unblinded.

Premature patient withdrawals and study drug discontinuations

Upon study withdrawal, if due to a suspected drug-related toxicity, an accelerated elimination of study medication was recommended with cholestyramine over 11 days. All patients who withdrew were to be followed up with to establish cause of withdrawal. If subjects had not withdrawn consent, but had just stopped the study medication then they were encouraged to continue the trial with its assessments. Data from these subjects would be included in the ITT analysis. Subjects who stopped prematurely were not replaced.

Primary efficacy outcome measure

To determine the safety and efficacy of teriflunomide in MS with relapses by evaluating the average number of unique active lesions/MRI scan for the double-blind portion of the trial. The value was calculated as the sum of uniquely new active lesions and unique persistent active lesions for all scans divided by the number of scans on which the sum was based during the double-blind treatment period.

Other outcome measures

To determine the effect of teriflunomide on:

- Other MRI variables
- EDSS
- MSFC
- Clinical relapse rate
- FIS
- Multiple Sclerosis Quality of Life Questionnaire (MSQOL-54) this is a 54 question self-administered instrument which is disease specific and validated to allow the comparison of the quality of life with MS to other diseases in the general population as well as an assessment of health issues related to those with MS. The answers are rated with a score of 1-4, 1.6, 1.7, or 1-20, whereby higher scores indicate a poorer quality of life and a lower score a better quality of life. The combined score is normalized and rated from 0-100.

Investigation of pharmacokinetic and pharmacodynamic relationships:

- Comparison of population pharmacokinetics of teriflunomide in MS and RA patients
- Investigation of relationships between teriflunomide plasma concentrations and average number of unique active lesions per MRI scan
- Determination of plasma concentrations of TFMA under steady-state conditions

Protocol Amendments

Original Protocol (December 1, 2000)

Amendment 1 (January 4, 2001)

- Blood pressure monitoring was made more stringent. Subjects with blood pressure elevations were to be withdrawn from the study if they did not respond to modification of their concomitant medications.

Amendment 2 (March 26, 2001)

- To update the safety information of leflunomide and teriflunomide (i.e., hepatic safety) in the Informed Consent.
- To modify safety assessments and procedures relating to liver enzymes and bilirubin following availability of postmarketing data obtained with leflunomide

- To clarify the processing of pharmacokinetic samples
- To provide the centers with more detailed instructions for performing MRI
- To modify the list of alert terms for expedited reporting
- To modify GCP requirements: The original protocol had assumed that the sponsor would be submitting an IND application to the Food and Drug Administration (FDA) in the USA. As this was not the case, abidance with GCP as described in 21 CFR parts 50, 54, 56, 312, and 314 was no longer required.

Amendment 3 (October 19, 2001)

- To update the safety information regarding severe infections in the IC
- To clarify the information regarding the processing of the pharmacokinetic samples
- To expedite inclusion of subjects who had participated in the CORAL oral Copaxone study

Statistical Methods

As documented in the sponsor's prespecified Statistical Analysis Plan (SAP) the primary efficacy variable studied was the average number of active lesions/MRI for the double-blind treatment period of the study. The value calculated was the sum of unique newly active lesions and of unique persistently active lesions for all scans divided by the number of scans on which the sum was based. The null hypothesis to be tested was that there was no treatment difference between 14 mg and placebo or the 7 mg and the placebo for the average number of unique active lesions/scan. The null hypothesis was tested against the alternative hypothesis with an $\alpha = 0.05$. To preserve α at the 0.05 level for both the 14 mg and the 7 mg group comparison, the critical value for the Dunnett's test for two groups compared with a control was used. The hypothesis was tested using a rank analysis of covariance (ANCOVA) on the ranked average number of unique active lesions/scan during the double-blind treatment period with treatment, baseline EDSS stratum, and the pooled center as fixed effects and the ranked average pre-randomization number of unique active lesions as a covariate. Differences between the treatment groups in the ranked average pre-randomization number of unique active lesions were compared by analysis of variance (ANOVA).

In order to check for consistency of effect an exploratory analysis of the primary efficacy variable was checked in the following subgroups: sex, age, diagnosis, duration of illness, pooled site, prior treatment using ANCOVA with treatment, center as fixed effect and average pre-randomization number of unique lesions as covariate.

No specific endpoint was considered "key secondary". Endpoints analyzed included multiple MRI and clinical endpoints. All secondary efficacy variables were analyzed in the efficacy-evaluable and completer populations. MRI count variables were analyzed using the ANCOVA model and MRI changes from the baseline variables were analyzed with ANCOVA on change from baseline to endpoint with treatment, stratum and pooled center as fixed effects and the baseline score as a covariate.

Clinical assessments include change from baseline using ANCOVA with treatment, stratum and pooled center as fixed effects and the baseline score as a covariate. For the subjects that progressed on the basis of EDSS and for the subjects with relapses, the Cochran-Mantel-Haenszel procedure controlling for pooled center was used. All safety analyses were descriptive.

The sponsor identified four analysis groups:

- Efficacy-evaluable: (EE) All randomized subjects for whom there were at least one on-treatment MRI assessment. All efficacy and quality of life evaluations were based on this population, even if they discontinued therapy
- Completer Population (CP): Those who completed all 231 days of the treatment and had an MRI scan at visit 10. A completer analysis was performed for all efficacy and quality of life variables.
- Per Protocol population (PP): Included all of the ITT population except those with major protocol violations. This was only performed if those with major protocol violations exceeded 10%. Data collected after the drug was stopped was censored and not used for this analysis.
- Safety-evaluable (SE): All randomized subjects who received at least one dose of study medication.

Sample size justification

A total of 54 evaluable subjects/treatment group was felt sufficient to detect with 90% power an effect size of 32% using a 2-sided Wilcoxon rank-sum test and an α -level of 0.05. The effect size for the Wilcoxon rank-sum test corresponds to a parametric effect size of 0.67. It was assumed that there would be a 10% dropout rate and that randomizing 60 patients/treatment arm would be adequate.

Missing data

Missing data was imputed. For missing date of first intake it was assumed to be the same as date of randomization. For missing date of last intake it was assumed to be the date of withdrawal from the study. For other missing dates it was assumed to be July 1 for the available year if the day and month were missing and it was assumed to be the 15th of month if only the day was missing. If the date of an adverse event was missing it was assumed to have occurred after the first intake of study medication.

Relapse and disability progression definitions

Assessment was to be done by a qualified investigator based on neurological examination, Scripps Neurological Rating Scale (NSR) and an EDSS assessment. In this trial relapse symptoms had to persist for at least 48 hours to be counted.

EDSS assessments made to qualify relapses were excluded from measuring disease progression. An EDSS progression was considered an increase by at least 1 point in subjects with baseline EDSS score ≤ 5.5 or an increase in EDSS score by at least 0.5 for those with baseline > 5.5 . The time to progression by EDSS score was measured as well as the change in EDSS progression. Change from baseline to endpoint in MSFC score was also be calculated.

MRI efficacy variables

New lesion –

A count of all lesions that appeared on the current T2 scan but were not visible on any previous T2 scans

Newly enlarging lesion –

A count of all lesions that appeared enlarged on the current T2 scan but were stable on the previous T2 scan

Persistently enlarging lesion –

A count of all further enlarged lesions on the current T2 scan that were categorized as new or enlarging on the previous T2 scan

Newly enhancing lesion –

A count of all lesions that were enhanced on the current T1 scan and were not classified as newly enhancing in a previous T1 scan

Persistently enhancing lesion –

A count of all lesions that were enhanced on the current T1 scan and that were enhanced on the previous T1 scan

Unique newly active lesion –

A count of all unique T1 and T2 lesions that were identified 1 or more times but that were not in the previous scan and had not been classified as unique newly active in any previous scan

Unique persistently active lesion –

A count of all unique T1 and T2 lesions that were identified one or more times that were also in the previous scan

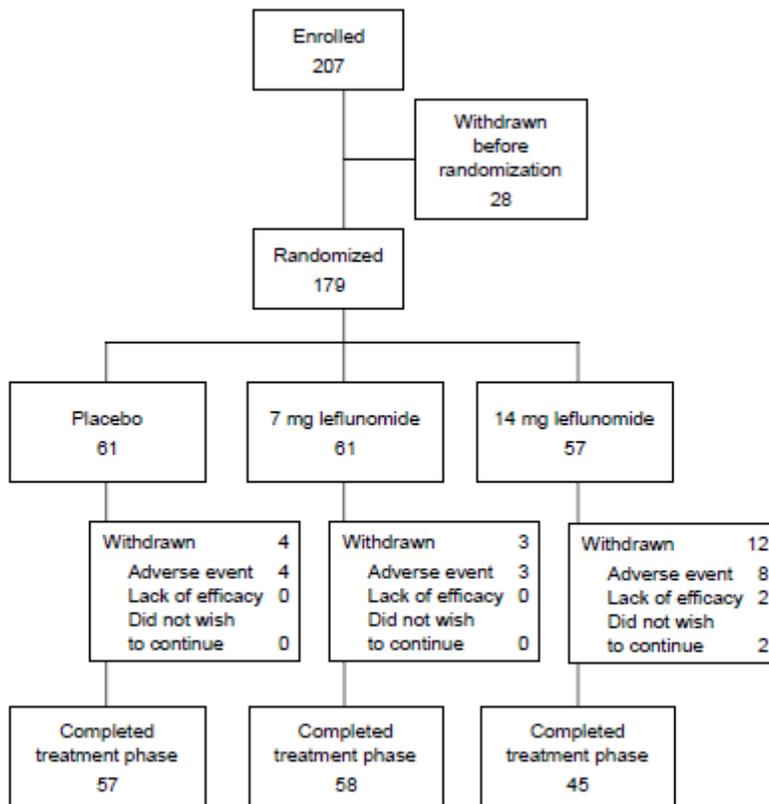
Burden of disease –

Sum of all regions of interest identified on T2 scans

Trial Population, Enrollment and Patient Disposition

A total of 207 subjects were screened for enrollment from 16 centers and 28 subjects were screening failures most of whom did not meet the criteria for the study. Of the 179 subjects that were randomized into three treatment groups in a 1:1:1 randomization scheme, only 177 were in the evaluable population as two were withdrawn before completing any efficacy evaluation. Of these a total of 160 completed the study and 19 (11%) discontinued the study prematurely. (See Figure 9) The discontinuations were not balanced among treatment groups and there were far more discontinuations on 14 mg of teriflunomide (12/57, 21.1%) than on placebo (4/61, 6.6%) or 7 mg teriflunomide (3/61, 4.9%). All discontinuations in the teriflunomide 7 mg and the placebo group were due to adverse event, but in the 14 mg teriflunomide group two patients discontinued due to lack of efficacy and two because they did not wish to continue. Only one subject was unblinded prematurely and this was after all their data was collected.

Figure 9 Trial 2001 Patient Disposition Flow Chart



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Clinical Study Report Study HMR 1726/2001 page 94 (sponsor who refers to teriflunomide in this chart as leflunomide)

Applicability of Foreign Data

All patients were enrolled from either ten centers in Canada or six centers in France. The bulk of the patients, or 65% came from just four of the Canadian centers. There was less racial diversity compared with the US population.

Treatment Compliance

Compliance was measured by tablet counts performed at each center. No subject had compliance less than 83%. The median percentage of days that subjects in the safety-evaluable population took the prescribed dose of medication was 99.2% for placebo subjects, 99.2% for 7 mg teriflunomide subjects and 98.8% for teriflunomide 14 mg subjects according to the sponsor.

Protocol Deviations

Major protocol deviations were found in 30 (16.9%) of the efficacy-evaluable population. The placebo group had 8/61 subjects with deviation (13.1%), the teriflunomide 7 mg dose had 9/60 (15.0%) and the teriflunomide 14 mg had 13/56 (23.2%). Despite the imbalance among groups, the cause of deviation among groups was balanced. The predominant cause was steroid use which had impact on the MRI scan or failure to meet the entry criteria by having too few relapses in the year preceding the trial.

Demographics

Almost all subjects enrolled in the study were Caucasian. Age and BMI was relatively well matched but the ratio of males: females were noted to be higher on placebo than on teriflunomide and higher than is seen in the general population. (See Table 27)

Table 27 Study 2001 Demographic Baseline Characteristics Efficacy –evaluable population

Demographic Characteristic	Placebo N = 61	Teri 7 mg N = 61	Teri 14 mg N = 57
Age (years)			
Mean (SD)	39.2 (8.70)	40.1 (9.28)	40.1 (9.05)
Median	40.0	39.0	41.0
Min Max	19 : 55	19 : 61	21 : 64
Sex (n, %)			
Male	20 (32.8%)	15 (24.6%)	12 (21.1%)
Female	41 (67.2%)	46 (75.4%)	45 (78.9%)
Race (n, %)			
Caucasian	59 (96.7%)	56 (91.8 %)	52 (91.2%)
Black	0	1 (1.6%)	1 (1.8%)
Asian	0	2 (3.3%)	2 (3.5%)
Other	2 (3.3%)	2 (3.3%)	2 (3.5%)
BMI (kg/m2)	26.9	25.8	25.8
SD	7.38	(6.22)	(4.79)

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Baseline Disease Characteristics

As seen in Table 28 approximately 87.5% of patients in the study had RRMS and 12.5% had SPMS. The median baseline EDSS was approximately 2.3. Most patients had 1 relapse in the preceding year and had suffered from MS symptoms for 9 years. Almost half had been treated with corticosteroids in the preceding year. The patients were reasonable well balanced for previous treatment with immunomodulators, approximately 10% had been on glatiramer acetate and 13% had been on interferon beta.

Table 28 Study 2001 MS History in Evaluable Population

Characteristic	Statistic	Placebo (N = 61)	Teriflunomide	
			7 mg (N = 60)	14 mg (N = 56)
Time since diagnosis of MS (years)	Mean (±SD)	4.4 (±5.66)	6.0 (±5.60)	5.3 (±6.22)
Duration of symptoms (years)	Mean (±SD)	8.6 (±7.92)	10.4 (±8.19)	8.5 (±7.21)
Type of MS				
Relapsing-remitting	n (%)	53 (86.9)	53 (88.3)	49 (87.5)
Secondary progressive	n (%)	8 (13.1)	7 (11.7)	7 (12.5)
Baseline EDSS	Median (min-max)	2.5 (0.0-6.0)	2.5 (0.0-6.0)	2.0 (0.0-6.5)
Number of relapses				
In last 3 years	Median (min-max)	3 (1-9)	2 (2-5)	3 (2-6)
In last 12 months	Median (min-max)	1 (0-3)	1 (0-4)	1 (0-3)
Subjects treated with systemic corticosteroids within the past year				
No	n (%)	33 (54.1)	33 (55.0)	28 (50.0)
Yes	n (%)	28 (45.9)	27 (45.0)	28 (50.0)

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Reviewer's Comment

This was a small proof of concept supportive study and the results are descriptive, so the imbalances seen among treatment groups are felt to be immaterial.

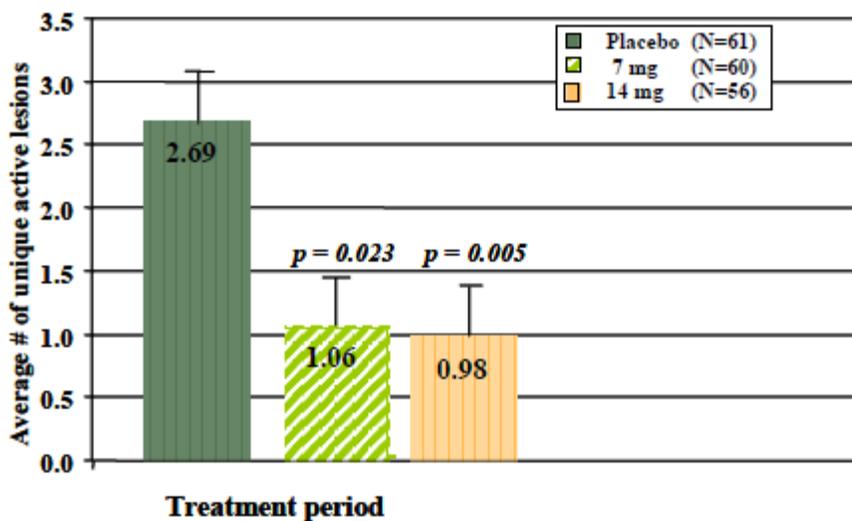
Outcome of Efficacy Analysis

Primary Efficacy Endpoint

As prespecified, an analysis of covariance (ANCOVA) was used on the ranked average number of unique active lesions/scan during the double-blind phase with treatment, stratus and pooled center as fixed effects and the ranked pre-randomized number of unique active lesions as a covariate, as the baseline average number of unique active lesions were not balanced among treatment groups.

According to the sponsor's analysis both doses of teriflunomide showed a significantly lower average number of unique active lesions compared with placebo in the evaluable population. (See Figure 10) The average number of unique lesions was 2.69 (n = 61) with placebo, 1.06 (p = 0.0234; n = 60) with teriflunomide 7 mg, and 0.98 (p = 0.0052, n = 56) with teriflunomide 14 mg. This analysis was based on minimal missing data. Out of the 160 subjects analyzed, only 7 subjects had a single missing scan and 1 subject had 2 missing scans.

Figure 10 Average number of unique active lesions/MRI scan in Study 2001



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Reviewer's Comment

Not only were the number of unique lesions significantly less with both doses of teriflunomide compared with placebo, but there was a decrease in the number of lesions over time from baseline for both doses of teriflunomide whereas for placebo there was an increase in unique active lesions from baseline to study completion. Sensitivity analyses were done of the primary endpoint. Each of the ITT, PP and completer analyses confirmed the results of the Efficacy-evaluable population as displayed in Table 29. Results were more robust for the 14 mg dose compared with the 7 mg dose in all populations.

Table 29 Analysis of Unique Active Lesions/MRI scan for various Populations

Population/ time period	Adjusted mean (±SEM)			Comparison			
	Placebo	Teriflunomide		7 mg – placebo		14 mg – placebo	
		7 mg	14 mg	p-value ^a	(95% CI)	p-value ^a	(95% CI)
Efficacy-evaluable	N = 61	N = 60	N = 56				
Screening period	2.22 (0.62)	1.21 (0.60)	2.44 (0.61)	0.2312	(-2.70, 0.68)	0.9972	(-1.49, 1.94)
Treatment period	2.69 (0.39)	1.06 (0.38)	0.98 (0.39)	0.0234	(-2.70, -0.55)	0.0052	(-2.79, -0.63)
Intent-to-treat	N = 61	N = 60	N = 56				
Screening period	2.22 (0.62)	1.21 (0.60)	2.44 (0.61)	0.2312	(-2.70, 0.68)	0.9972	(-1.49, 1.94)
Treatment period	2.62 (0.39)	1.04 (0.37)	0.98 (0.38)	0.0291	(-2.64, -0.53)	0.0092	(-2.71, -0.58)
Completer	N = 57	N = 58	N = 45				
Screening period	2.20 (0.70)	1.22 (0.64)	2.57 (0.72)	0.5074	(-2.80, 0.84)	0.9906	(-1.58, 2.31)
Treatment period	2.37 (0.40)	0.98 (0.37)	0.69 (0.41)	0.0476	(-2.44, -0.34)	0.0069	(-2.79, -0.56)
Per-protocol	N = 53	N = 51	N = 43				
Screening period	2.15 (0.69)	1.20 (0.65)	2.46 (0.71)	0.2622	(-2.78, 0.88)	0.9485	(-1.60, 2.22)
Treatment period	2.89 (0.48)	1.04 (0.45)	1.00 (0.49)	0.1099	(-3.12, -0.58)	0.0490	(-3.21, -0.57)

The calculation of the p-value for the comparison between treatment groups is based on a rank analysis of covariance. Clinical Study Report HMR 1726/2001 page 103

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Analysis of Secondary Endpoints

MRI endpoints

Table 30 demonstrates the findings for numerous secondary MRI endpoints obtained in this study. For enhancing T1 lesions the greatest effect was seen with the 14 mg dose of teriflunomide compared with the 7 mg dose. For newly enhancing lesions and combined newly enhancing and persistently enhancing lesions both doses were significantly superior to placebo and the 14 mg dose was superior to the 7 mg dose. For persistently enhancing T1 lesions only the 14 mg dose was significantly superior to placebo. For T2 lesions including new lesions, newly enlarging lesions, combined T2 lesions, the lower dose, teriflunomide 7 mg was in generally superior to the 14 mg dose. The only MRI outcome studied that did not reach statistical significance for both doses was that of persistently enlarging T2 lesions. Another measure assessed was the percent change from baseline to endpoint of the BOD in the evaluable population. According to the sponsor there was a statistically significant decrease for those on 14 mg of teriflunomide (-2.5%, p = 0.0215) compared with placebo which increased 5.2% and teriflunomide 7 mg which increased 2.9% (p = 0.0959).

Table 30 An analysis of other MRI endpoints in the Evaluable population

Type of lesion	Adjusted mean (\pm SEM)			Comparison			
	Placebo (N = 61)	Teriflunomide		7 mg – placebo		14 mg – placebo	
		7 mg (N = 60)	14 mg (N = 56)	p-value ^a	(95% CI)	p-value ^a	(95% CI)
T1 lesions							
Newly enhancing	1.83 (0.25)	0.73 (0.24)	0.72 (0.25)	0.0410	(-1.78, -0.41)	0.0108	(-1.80, -0.42)
Persistently enhancing	0.44 (0.11)	0.16 (0.11)	0.10 (0.11)	0.1362	(-0.58, 0.01)	0.0173	(-0.64, -0.04)
Combined T1	2.27 (0.33)	0.89 (0.32)	0.79 (0.33)	0.0331	(-2.29, -0.48)	0.0123	(-2.39, -0.56)
T2 lesions							
New	1.07 (0.19)	0.29 (0.18)	0.42 (0.19)	0.0033	(-1.30, -0.27)	0.0078	(-1.17, -0.14)
Newly enlarging	0.37 (0.06)	0.12 (0.05)	0.22 (0.06)	0.0080	(-0.41, -0.10)	0.0874	(-0.31, 0.00)
Persistently enlarging	0.07 (0.02)	0.02 (0.02)	0.04 (0.02)	0.3514	(-0.11, 0.02)	0.5541	(-0.09, 0.04)
Combined T2	1.51 (0.24)	0.44 (0.23)	0.68 (0.24)	0.0029	(-1.72, -0.42)	0.0184	(-1.49, -0.18)
Unique newly active lesions (T1 and T2)	2.16 (0.31)	0.88 (0.30)	0.84 (0.30)	0.0312	(-2.12, -0.44)	0.0051	(-2.17, -0.47)
Unique persistently active lesions (T1 and T2)	0.53 (0.12)	0.18 (0.11)	0.16 (0.12)	0.0409	(-0.66, -0.03)	0.0700	(-0.69, -0.05)
Unique active lesions (T1 and T2)	Primary efficacy variable (see Section 7.1 Analysis of primary efficacy variable (pg. 000103))						

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Reviewer’s Comments

The sponsor has summarized the average number of MRI lesions for the treatment period in the efficacy-evaluable population as shown in Table 30. Measures of active inflammation such as newly enhancing T1 lesions, new T2 lesions, newly enlarging T2 lesions all showed a statistically significant treatment effect with teriflunomide which was greater with the 14 mg dose. A measure of chronic disease such as persistently enlarging T2 lesions did not show a treatment effect.

MS Relapse Rate

This outcome was evaluated in a qualitative fashion. Although the study was to have evaluated relapses qualified by an examiner this was not done and relapses reported were not qualified. Nonetheless, subjects experiencing relapse were fewest on the 14 mg dose of teriflunomide and fewer subjects required treatment with steroids as seen in 31.

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Table 31 MS Relapse Rate in the evaluable population

Variable	Statistic	Placebo (N = 61)	Teriflunomide	
			7 mg (N = 60)	14 mg (N = 56)
Subjects with MS relapse	n (%)	23 (37.7)	21 (35.0)	13 (23.2)
Subjects with MS relapse requiring treatment with steroid	n (%)	14 (23.0)	13 (21.7)	8 (14.3)
Annual relapse rate ^a	Mean(±SD)	0.81 (1.22)	0.58 (0.85)	0.55 (1.12)

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Measures of Disability

EDSS

According to the sponsor there was no clinically relevant change in EDSS for any of the treatment groups during this study as very few subjects progressed over 36 weeks. For the few that did progress, the progression took place between months 6-9. A total of 4 (7.4%) subjects showed progression on the 14 mg of teriflunomide, 17 (28.8%) on 7 mg of teriflunomide and 13 (21.3%) on the placebo.

MSFC

According to the sponsor there were no relevant changes in functioning on the MSFC with any of the treatments in this study.

Reviewer's Comment

The time period of treatment of this study was brief, and hence the trial was not suited to measure disability progression.

5.3.3 Pivotal trial Protocol EFC10531 TOWER Interim analysis

An interim analysis of this partially completed pivotal trial was requested by the Agency to evaluate the primary endpoint or effect of teriflunomide on relapse rate to ensure that there was at least a trend supporting efficacy. Secondary and supportive analyses of the primary endpoint were requested (such as confirmed relapses including those that took place after treatment discontinuation, all relapses, and analysis of per protocol population).

There were no plans to stop the trial based on the interim results. This study was initiated on August 26, 2008. The interim analysis took place on all patients randomized as of November 30, 2010. The cutoff date for the analysis was February 28, 2011 and the database lock for this analysis took place on May 13, 2011.

The study is now complete and a study report is scheduled to be released as a separate efficacy supplement with a submission date anticipated after the product's approval in 2012.

Protocol EFC 10531 TOWER

Study title

A multi-center double-blind parallel-group placebo-controlled study of the efficacy and safety of teriflunomide in patients with RMS

Objectives

Primary and key secondary objectives

- To assess the effect of two doses of teriflunomide in comparison to placebo on frequency of multiple sclerosis (MS) relapses in patients with relapsing MS
- To assess the effect of two doses of teriflunomide in comparison to placebo on disability progression in patients with relapsing MS as assessed by EDSS

Other objectives

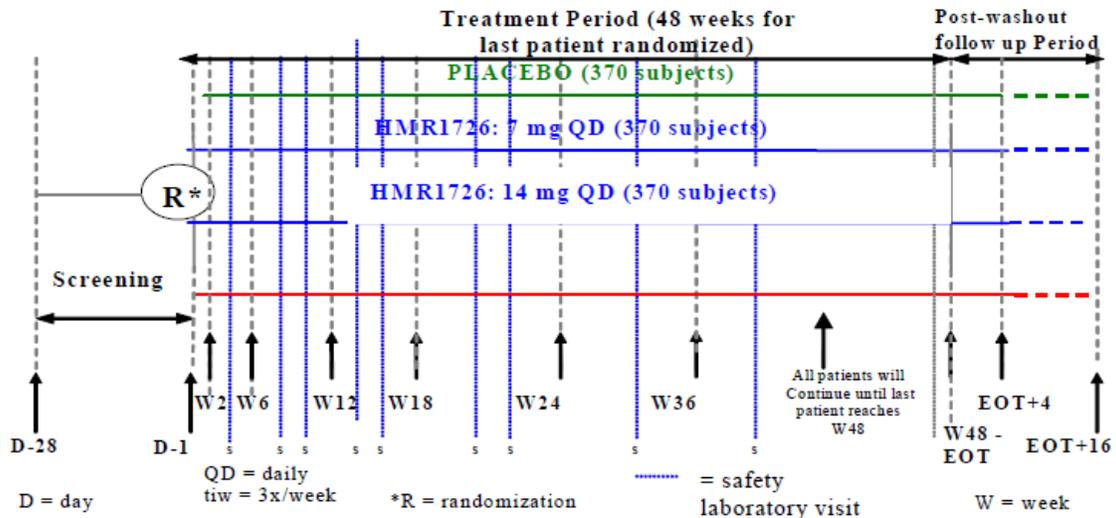
- To assess other measures of efficacy of two doses of teriflunomide in comparison to placebo on:
 - Fatigue as assessed by the FIS
 - Time to First Relapse
 - Proportion of patients without relapse
 - Proportion of patients free of disability progression at 6 months, 1 year and 2 years
 - Change from baseline EDSS
 - Health-related quality of life, a measure of the impact of the patient's health on his or her overall well being
- To evaluate the safety and tolerability of teriflunomide
- To assess the association between the main enzyme systems of teriflunomide metabolism and hepatic safety and other potential associations between gene variations and clinical outcomes (optional pharmacogenomic testing)

Study Design

This was a multicenter study conducted in 26 countries. For the interim analysis the last patient included had a minimum of 3 months of follow-up, and the expected average exposure was 1 year.

This study was a randomized, double-blind, parallel group placebo-controlled study with three treatment groups. The treatment duration was a minimum of 48 weeks for the last patient recruited but longer for those recruited earlier. The treatment period had a fixed end for all patients. The design and schedule of the double-blind portion of the study is shown in Figure 11 and Table 32.

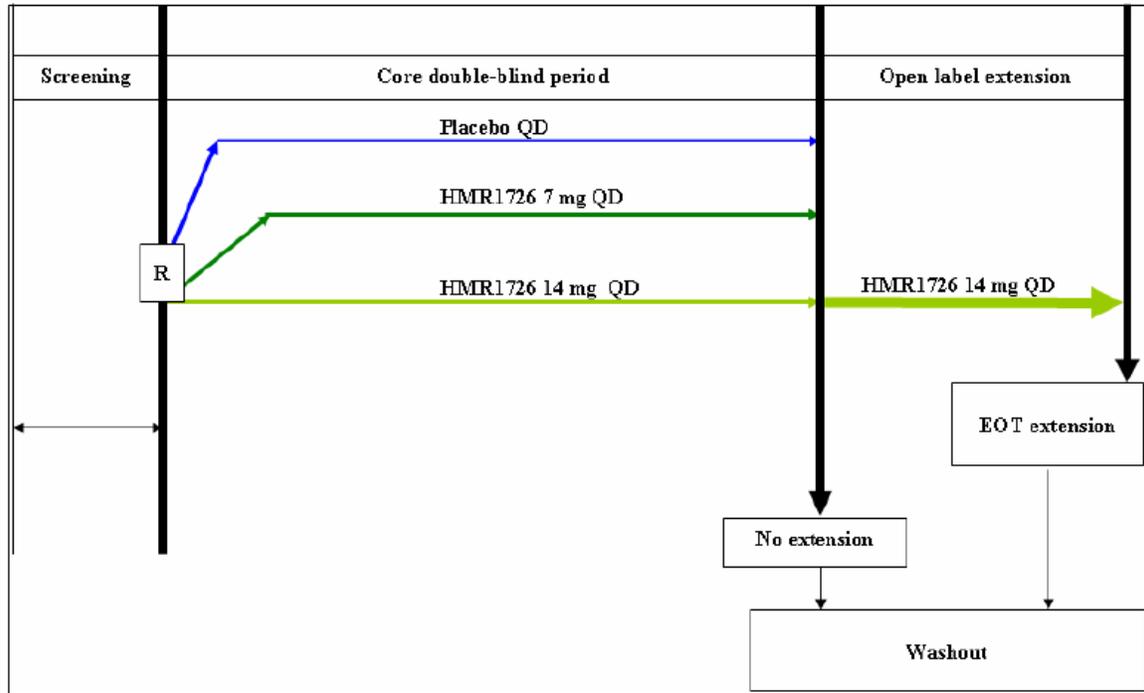
Figure 11 Double-blind portion of the study



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For those patients who completed the treatment period, an open-label extension study of 48 weeks was proposed (See Figure 12 and 33). All patients who withdrew from the study or who completed the study but did not elect to participate in the open-label extension study were to undergo a washout procedure to accelerate teriflunomide elimination. The recommended procedure was 8 g cholestyramine administered every 8 hours for 11 days (24 g daily); alternatively, 50 g activated charcoal powder every 6 hours for 11 days (200 g daily) could be administered.

Figure 12 Additional Extension portion of the study



EOT = end of treatment; R = randomization

Table 32 Assessment Schedule double-blind portion of the study

Day (D) / Week (W) ^a	Screening		Treatment period															Postwashout follow up			Unscheduled				
	W-4	Rand ^b	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W30	W36 and every 12 weeks ^c	W42 and every 12 weeks ^c	EOT	EOT +2	EOT +4	Progression confirmation visit ^d	Relapse visit	EPTD		
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 odd	16 even	17.01	18 ^e	19 ^f	20 ^f				
Entry procedures																									
Informed consents ^g	X ^h																					X ^g	X ^g		
Review inc/excl criteria	X	X																							
Demographics	X																								
Medical/surgical history	X																								
Prior medications	X	X																							
FSH test ⁱ	X																								
HIV testing ^j	X																								
Randomization		X																							
Efficacy																									
EDSS/FS	X	X						X						X		X	X		X				X	X	X
FIS/SF-36		X						X						X		X ^j			X					X	X
Safety																									
Adverse event reporting ^k	X	X	X		X			X						X		X	X		X	X	X		X	X	X
Vital signs ^l	X	X						X						X		X	X		X	X				X	X
Physical examination	X	X												X		X ⁿ			X						
PFT (at selected sites)	X	X												X		X ⁿ			X						
ECG 12-leads		X																	X	X ^m					
Chest X-ray ^o	X																								
Abdominal ultrasound ^p (of the pancreas)	X													X					X						
Clinical laboratories ^{q,r}	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X				
Treatments																									
Concomitant medications		X	X		X			X						X		X	X		X	X	X			X	X

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Day (D) / Week (W) ^a	Screening		Treatment period															Postwashout follow up			Unscheduled				
	W-4	Rand ^b	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W30	W36 and every 12 weeks ^c	W42 and every 12 weeks ^c	EOT	EOT +2	EOT +4	Progression confirmation visit ^d	Relapse visit	EPTD		
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 odd	16 even	17.01	18 ^e	19 ^f	20 ^f				
Dispense study drugs		X						X						X		X	X								
Accountability/ Compliance			X		X						X			X		X	X		X						
PK sampling ^s		X ^t						X ^u											X ^u	X ^v	X ^v				
Pharmacogenomic sampling (optional) ^x		X																							

EOT = End of Treatment, EDSS = Expanded Disability Status Scale, FS= functional score, FIS = Fatigue Impact Scale, FSH = follicle stimulating hormone, SF-36 = Short Form generic health survey (36 items), PFT = Pulmonary Function Testing, PK= pharmacokinetic, EPTD = early premature treatment discontinuation

Table 33 Assessment Schedule extension portion of the study

Day (D) / Week (W) ²	W0 ^b EXT	W4 EXT	W8 EXT	W12 EXT	W16 EXT	W20 EXT	W24 EXT	W30 EXT	W36 EXT	W42 EXT	W48/EOT ^c EXT	EOT +2 EXT	EOT +4 EXT	Progression confirmation visit ^d	Relapse visit
Visit Number	21	22	23	24	25	26	27	28	29	30	31	32	33		
Entry procedures															
Informed consent ^e	X													X ^e	X ^e
Review selec. criteria	X														
HIV testing ^f															
Efficacy															
EDSS / FS							X				X			X	X
FIS / SF-36							X				X				X
Safety															
Adverse event reporting ^g	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs ^h	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical examination											X				
ECG 12-leads											X				
Clinical laboratories ⁱ	X	X	X	X	X	X	X	X	X	X	X	X	X		
Treatments															
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Dispense study drugs	X			X			X		X						
Accountability/compliance				X			X				X	X			
PK sampling												X	X		

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Breaking of the Blind

There was no plan to terminate the study based on the interim analysis. The unblinded interim analysis was conducted by an independent group that had no involvement in the teriflunomide project.

Study Centers

Multicenter study in 26 countries (Australia, Austria, Belarus, Belgium, Canada, Chile, China, Czech Republic, Estonia, France, Germany, Greece, Mexico, Netherlands, Philippines, Poland, Romania, Slovakia, Spain, Sweden, Thailand, Tunisia, Turkey, Ukraine, United Kingdom, and US) with a total of 190 sites.

Study Population: The study population consisted of patients that were ambulatory with an EDSS of ≤ 5.5 with a relapsing form of MS meeting the McDonald criteria. A total of 1096 patients were randomized (366 on placebo, 379 on 7 mg teriflunomide and 351 on 10 mg teriflunomide).

Key Inclusion criteria:

- A diagnosis of relapsing MS as defined by the McDonald criteria and EDSS ≤ 5.5 at the screening visit
- Age 18-55
- Had to have at least 1 relapse over the preceding 12 months or 2 relapses over the preceding 24 months and no relapses in the 30 days prior to randomization

Key exclusion criteria:

Criteria were similar to those for the TEMSO trial

Best
Available
Copy

Treatment Administered

There were 3 treatment arms in the proportion of 1:1:1

- Teriflunomide 7 mg capsule for oral administration once in morning
- Teriflunomide 14 mg capsule for oral administration once in morning
- Placebo in capsule for oral administration once in morning

Concomitant Therapy

All concomitant medication will be recorded and minimized. Medications with a low therapeutic index such as digoxin needed to be monitored carefully. Steroids could only be used to treat an acute MS relapse per protocol specifications.

Prohibited medication:

- Similar to those in the TEMSO trial.

In addition other preventive MS medications were not to be used in the six months preceding the study as well as during the study including glatiramer acetate, intravenous immunoglobulins, natalizumab, cladribine, mitoxantrone, or other immunomodulatory agents such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate, teriflunomide or leflunomide. Other interferons or cytokine therapy was not to be used during the study or for the four months that preceded the study.

Randomization and Controls

The subjects were randomized in a 1:1:1 ratio to one of three treatment groups (placebo, 7mg teriflunomide, 14 mg teriflunomide) and treated in a double-blind fashion. The subjects were stratified by baseline EDSS and by site.

Premature patient withdrawals and study drug discontinuations

All subjects who were prematurely withdrawn or who stopped drug underwent a washout procedure. If a subject discontinued before month 24 then all assessments were at a close-out visit scheduled as soon as possible after drug discontinuation. All such subjects were asked to enter an early permanent treatment discontinuation and adverse events were reported. Follow-up included visits at week 4 after therapy ended and thereafter every 12 weeks until the end of the study.

Amendments to Protocol

Amendment #/Date	Protocol changes Made
Amendment 1 6/27/2008	<ul style="list-style-type: none">· Eliminated the interferon calibrator arm from the study design, and formal assessment of mood disorders· Addition of HIV testing at screening and annually· Revised inclusion criteria to assure that patients are properly informed of alternate available treatment options· Updated the contraception requirements

	<ul style="list-style-type: none"> · Clarified the required qualifications for the examining neurologist · Clarified the method for collecting symptoms related to MS relapses · Revised the statistical methodology to update the procedure for handling premature withdrawals for time to disability progression analysis and to modify the multiplicity control
Amendment 2 7/01/2009	<ul style="list-style-type: none"> · Implemented pulmonary function testing in a subset of patients · Added optional pharmacogenomic testing with aims at assessing the association between the main enzyme systems of teriflunomide metabolism and hepatic safety, and other potential associations between gene variations and clinical outcomes · Clarified the procedure for handling patients who are screen failures and who are not randomized
Amendment 3 10/07/2009	<ul style="list-style-type: none"> · Expanded the population of patients who may opt to participate in the pharmacogenomic testing
Amendment 4 1/19/2011	<ul style="list-style-type: none"> · Changed the time point for confirmation of disability progression to 12 weeks instead of 24 weeks to be in alignment with the other Phase 3 pivotal trial EFC6049 · Added an interim analysis to provide additional evidence on the benefit/risk of teriflunomide for regulatory purposes · Specified the methods of the extension study to include dose of teriflunomide duration of extension, and frequency of liver and pancreatic monitoring · Shortened the washout period from 16 weeks to 4 weeks · Modified the exclusion criteria and concomitant medication restrictions based on updated drug interactions data · Added peripheral neuropathy confirmed by electrophysiological tests as an alert term to provide better documentation on the cases · Added an exploratory investigation of specific cell surface marker expression on T-cell and B-cell lymphocytes populations

Efficacy Outcome Measures Trial 10531

Primary efficacy outcome measure

- Annualized Confirmed Relapse Rate

Key secondary efficacy outcome measure

- Time to disability progression confirmed after at least 12 weeks

Analysis Plan:

Primary endpoint analysis

This is calculated by counting the number of confirmed relapses with onset between the randomization date and the treatment discontinuation or completion date divided by the sum of the study duration in years (last dose intake date-randomization date +1)/365.25. Data is censored after the discontinuation date.

The primary analysis for the ARR was performed using a Poisson regression model with robust error variance to accommodate the potential over-dispersed data appropriately.

The model included the total number of confirmed relapses with onset between the randomization date and the last dose date as the response variable. Covariates were a 3-level treatment group (placebo, teriflunomide 7 mg, and teriflunomide 14 mg), EDSS strata (baseline EDSS score ≤ 3.5 versus > 3.5) and the 4 regions (Eastern Europe, Western Europe, Asia/Australia and Americas). To account for different treatment durations among patients, the log-transformed standardized treatment duration was included in the model as an “offset” variable for appropriate computation of relapse rate. The robust error variances were estimated by specifying the patient identifier in the repeated statement using SAS PROC GENMOD, which is equivalent to the Generalized Estimating Equation (GEE) model. Two-sided 95% confidence intervals (CI) of the rate ratio were calculated for the comparisons of each active treatment versus placebo. The estimated relapse rates and 2-sided 95% CI and the gross estimates of ARR were generated for each treatment group. Subgroup analysis will be done for each of these variables: gender, race, age category, region, territory, baseline EDSS strata, and number of relapses in past 1 year, number of relapses in past 2 years without any statistical testing.

Key secondary endpoint analysis

Time to disability progression must be sustained for at least 12 weeks using the EDSS as defined in the TEMSO trial. No relapses can intervene during the 12 week period of time. If the disability progression occurs toward the end of the study it is only counted if it can be confirmed in 12 weeks during the follow-up visits. A supportive analysis will be sustained disability progression for 24 weeks.

The time to disability progression (sustained for at least 12 weeks) was analyzed using the log-rank test with time to disability progression as the dependent variable, the treatment group as test variable, and region and baseline EDSS strata as stratification factors. Hazard ratios were estimated using Cox regression model with treatment group, region, and baseline EDSS strata as covariates. The Kaplan-Meier graphs were generated and Kaplan-Meier method was used to estimate the disability progression rate and its 95% CI at 6 months, 1 year, and 2 years for each treatment group.

Pooling of centers for statistical analysis

Due to small sample size in some centers/countries centers will be pooled into regions. The regions include:

- America: Brasil, Canada, Chile, Mexico, Peru and USA
- Eastern Europe: Belarus, Czech Republic, Estonia, Greece, Poland, Romania, Slovakia and Ukraine
- Western Europe and Africa: Austria, Belgium, France, Germany, Netherlands, Spain, United Kingdom, Morocco, South Africa, Tunisia, Turkey and Sweden
- Asia and Australia: China, India, Malaysia, Philippines, Thailand and Australia

Sample size justification

The sample size is based on what is known from Tysabri where the placebo 2-year relapse rate in a clinical trial was 1.48. A 25% risk reduction would lead to an ARR for teriflunomide of 0.55. Assuming that the number of relapses followed a Poisson distribution with a common standard deviation (SD) of 1.252, a study with 370 randomized subjects/treatment arm, or 1100 randomized subjects will have a 94% power to detect a 25% relative risk reduction in the 2-year relapse rate at the 2-tailed significance level of $\alpha = 0.050$. This assumes a 20% dropout rate. This size will lead to a 75% powered Log-rank test to detect a 37% hazard ratio reduction of an assumed placebo disability progression hazard ratio of 0.1783 for placebo, 0.1116 for teriflunomide or a 30% probability to disability progression for placebo and a 20% probability for teriflunomide patients at the end of 2 years. The sample size is also adjusted for a 20% drop-out rate.

Handling of dropouts/missing data

For the primary outcome measure subjects who discontinue treatment will have the ARR calculated as last dose date-randomization date +1/365.25. The total number of relapses occurring during the study before discontinuation will be used as response and log transformation of the standard study duration will be used as offset variable.

For the secondary measure of disability progression subjects who discontinue will be considered to be free of progression until the date of the last measurement during treatment and all visits after Visit 23 will be censored. If the visit after disability is recorded is missing and confirmation cannot take place then the patient is recorded as not having sustained progression.

Relapse and disability progression definitions

MS relapse

MS relapses are defined as in the TEMSO trial.

Confirmed relapse

Each episode of relapse must be confirmed by the treating neurologist within 7 days of the event based on the objective assessments of the examining neurologist with similar documentation as in the TEMSO trial.

Disability progression

- The Kurtzke Disability Status Scale (EDSS) is the primary assay of disability. A persistent increase for at least 24 weeks of at least 1.0 points from baseline (or at least 0.5 points when baseline EDSS is > 5.5) is used for the first sustained disease progression. For subsequent progressions the progression must be sustained for another 24 weeks to be counted, at least 1.0 point except for those with an EDSS > 5 where just 0.5 points is adequate.
- When patient is observed to have experienced a sustained disability progression they will require a re-consent in order to continue in the study.

Other secondary efficacy analyses

Subject reported outcomes

- Fatigue Impact Scale (FIS) - see section 5.3.1 for description
- The Medical Outcome Study SF-36 - see section 5.3.1 for description
- Hospital Anxiety and Depression Scale (HADS) this is a validated scale based on 14 self assessment questions to detect anxiety and depression.
- Suicidality Tracking Scale (STS) This is a module in the Mini International Neuropsychiatric Interview and is used to detect risk of suicide in clinical trials.

Interim analysis

The interim efficacy analysis is performed to confirm the primary endpoint, ARR. No formal statistical tests will compare the treatment groups. Simple summaries will compare the various sub-populations of patients. The final database lock is planned for May 2, 2012.

Trial Population, Enrollment and Patient Disposition

Subject Disposition and Discontinuation

A total of 1418 patients were screened and 1096 were randomized as of the cut-off date. Of those, four patients who were randomized did not get drug as they ended up being screening failures and they were not included in the intent to treat population. The most frequent reason for study discontinuation was AE in those on teriflunomide and lack of efficacy in those on placebo (see Table 34). Other reasons included those that simply withdrew consent, refused to return to site, and had other personal reasons such as pregnancy. The total number of withdrawals appeared to be well-balanced among the treatment groups. Discontinuations rose steadily over time but appeared to plateau after 84 weeks. Countries that contributed to the high discontinuation rate included Belarus with 50 subjects or 4.6% of the discontinuations, Canada with 26 (2.4%), Germany with 75 (6.8%), Netherlands with 44 (4%), Poland with 48 (4.4%), Turkey with 60 (5.5%), United States with 204 (18.6%), and China with 128 (11.7%).

Table 34 Disposition of patients Trial EFC10531 randomized population

Disposition	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	Total	
Randomized	366	379	351	1096	
Randomized, not treated	1	1	2	4	
Treated	365	378	349	1092	
Ongoing	293 (80.1%)	293 (77.3%)	275 (78.3%)	861 (78.8%)	
Discontinuation	72 (19.7%)	85 (22.4%)	74 (21.1%)	231 (21.2%)	
Reasons For stopping	AE	16 (4.4%)	40 (10.6%)	40 (11.4%)	96 (8.8%)
	Lack of Efficacy	24 (6.6%)	17 (4.5%)	7 (2.0%)	48 (4.4%)
	Poor Compliance	12 (3.3%)	2 (0.5%)	3 (0.9%)	17 (1.6%)
	Lost to follow-up	0	0	2 (0.6%)	2 (0.2%)
	Other	20 (5.5%)	26 (6.9%)	22 (6.3%)	68 (6.2%)

Clinical Trial Report Trial 10531 Table 4

Treatment Compliance

The compliance rates were similar in all three arms, 77.6% to 80.3%, according to the sponsor. Compliance was highest among those on placebo compared to either dose of drug product. Until the time of the interim analysis the rate of protocol violations was reported as 27 out of 1096 subjects or 2.5%. (35)

Table 35 Major Protocol Violations of Randomized Population

	Placebo (N=366)	teriflunomide	
		7 mg (N=379)	14 mg (N=351)
Any Major Efficacy-Related Protocol Deviation	6 (1.6%)	6 (1.6%)	15 (4.3%)
Major deviation which excludes patient from ITT population	1 (0.3%)	1 (0.3%)	2 (0.6%)
Did not take any study medication	1 (0.3%)	1 (0.3%)	2 (0.6%)
Major deviation resulting in exclusion of the patient from the PP population but not ITT population	5 (1.4%)	5 (1.3%)	13 (3.7%)
Having onset of a relapse in the 30 days prior to randomization	0	0	2 (0.6%)
EDSS score >5.5 at baseline	0	0	0
Less than 2 clinical relapses in the last 2 years and less than 1 clinical relapse in last 1 year prior to randomization	1 (0.3%)	0	0
Treatment compliance <80%	2 (0.5%)	4 (1.1%)	8 (2.3%)
Taking prohibited medication, which may confound patient relapse outcome or EDSS score	0	1 (0.3%)	3 (0.9%)
Received unplanned or more than one study treatment	2 (0.5%)	1 (0.3%)	0
Randomized more than once	0	0	0

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Applicability of Foreign Data

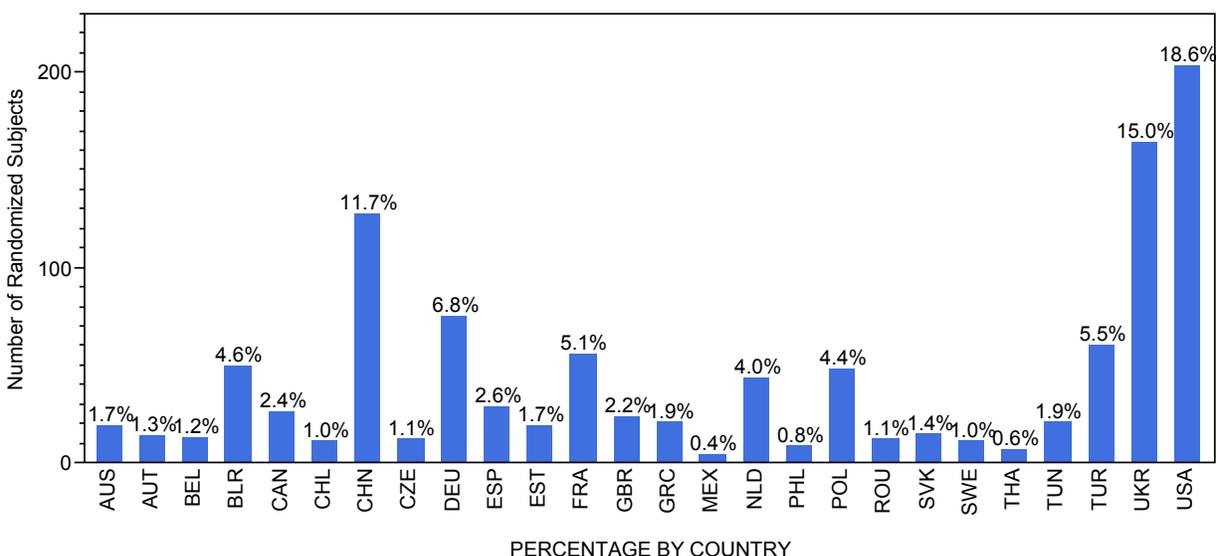
This was truly a multinational study and US subjects were well represented. US patients represented 18.6% of the subjects in the study, the greatest contribution of any country, and a total of 22.4% were from the Americas overall. Eastern Europe accounted for 31.1% of subjects, Western Europe and Africa for 31.7% of subjects and Asia and Australia 14.9% of subjects. (See Figure 13) As seen in Table 37 subjects were well balanced for the three arms.

Table 36 Regional Demographics at Baseline for ITT population EFC 10531

US	Eastern Europe	Western Europe and Africa	Asia and Australia	Americas including US
All N= 204 (18.6%)	All N= 339 (31.0%)	All N= 346 (31.7%)	All N= 162 (14.8%)	All N= 245 (22.4%)
Placebo N = 70 (19.1%)	Placebo N = 111 (30.4%)	Placebo N = 116 (31.8%)	Placebo N = 56 (15.3%)	Placebo N = 82 (22.4%)
Teri 7 mg. N = 71 (18.7%)	Teri 7 mg N = 115 (30.4%)	Teri 7 mg N = 118 (31.2%)	Teri 7 mg 57 (15.1%)	Teri 7mg 88 (23.3%)
Teri 14 mg N = 63 (17.9%)	Teri 14 mg N = 113 (32.4%)	Teri 14 mg 112 (32.1%)	Teri 14 mg 49 (14.0%)	Teri 14 mg 75 (21.5%)

Clinical Trial Report EFC 10531 adapted from Table 8

Figure 13 Percentage of subjects from various countries in the ITT population EFC 10531



Using the sponsor's definition, the analysis sets by treatment category were specified as displayed in Table 37.

Table 37 Analysis populations- Randomized population EFC 10531

Analysis set	Placebo n (%)	Teri. 7 mg n (%)	Teri. 14 mg n (%)
Randomized	366 (100%)	379 (100%)	351 (100%)
ITT set	365 (99.7%)	278 (99.7%)	249 (99.4%)
Safety set	363	379	350

Demographics

General Demographics

Of those randomized to the 1:1:1 randomization scheme, 365 were randomized to placebo, 378 to low dose teriflunomide and 349 to high dose teriflunomide. As of the cut-off date (February 28, 2011) treatment was ongoing for 861 subjects. The groups appeared well balanced for general demographic features including age, sex, race, weight and BMI. Patients were characteristic of those with MS; they were predominantly Caucasian and female with a mean age of 37.9. (See Table 38)

Table 38 General Demographics Trial EFC 10531 randomized population

Demographic Characteristic	Placebo (n=366)	Teriflunomide 7 mg (n = 379)	Teriflunomide 14 mg (n = 351)	All (n = 1096)
Age (years)				
Number	366	379	351	1096
Mean (SD)	38.1 (9.2)	37.4 (9.4)	38.1 (9.5)	37.9 (9.4)
Median	39.0	38.0	38.0	38.0
Min Max	18:56	18:55	18:56	18:56
Sex (n, %)				
Number	366	379	351	1096
Male	113 (30.9%)	99 (26.1 %)	106 (30.2%)	318 (29.0%)
Female	253 (69.1%)	279 (73.9%)	245 (69.8%)	778 (71.0%)
Race (n, %)				
Number	366	379	345	1092
Caucasian	306 (83.6%)	311 (82.1%)	298 (84.9 %)	912 (83.5%)
Black	6 (1.6%)	8 (2.1%)	6 (1.7%)	20 (1.8%)
Asian	50 (13.7%)	52 (13.7%)	44 (12.8%)	146 (13.4%)
Other	4 (1.1%)	8 (2.1%)	2 (0.6%)	14 (1.3%)
Weight (kg)				
Number	365	378	247	1090
Mean (SD)	70.91 (17.57)	71.19n(17.40)	72.13 (17.12)	71.39 (17.36)
Median	67.60	68.0	69.0	68.0
Min Max	42.0: 130.7	38.2: 167.0	43.5:142.8	38.2:167.0
BMI (kg/m2)				
Number	355	370	339	1064
Mean (SD)	25.19 (5.82)	25.20 (5.42)	25.52 (5.33)	25.30 (5.52)
Median	23.98	24.13	24.84	24.22
Min: Max	14.9: 52.7	16.5: 53.9	17.0: 49.6	14.9:53.9

Clinical Study Report EFC10531 adapted from Table 8

Baseline disease characteristics

Baseline disease characteristics were also well balanced for all three groups, although it is noted that MRI measurements were not part of the baseline assessment. The mean length of disease duration before entering the study was 5.15 years. Approximately 65% of subjects had a relapse in the year preceding study entrance. About 75% of the patients in the study had an EDSS < 3.5 and the remainder had one ≥ 3.5. The trial predominantly had RRMS subjects (97%) with the remainder having either SPMS or PRMS. Treatment naïve patients constituted 67.2% of the patients. For the 32.8% who had been treated in the preceding two years, 24.8% were treated with one of the interferons. (see Tables 39 and 40) Treatment naïve was defined as those who had not been on an immunomodulator or immunosuppressant for the preceding two years prior to randomization.

Table 39 Baseline disease characteristics- ITT population

Characteristic	Statistics	Placebo (N= 365)	Teriflunomide 7 mg (n=378)	Teriflunomide 14 mg (n=349)	All N = 1092
Disease duration in years	N	365	378	348	1091
	Mean (SD)	4.87 (5.69)	5.30 (5.42)	5.27 (5.77)	5.15 (5.62)
	Median	2.75	3.50	3.25	3.17
	Min; Max	0.1:33.8	0.0: 29.1	0.0: 32.7	0.0: 33.8
Time since last attack prior to study Day 1 (in months)	N	365	378	348	1091
	Mean (SD)	5.28 (3.39)	5.22 (3.42)	5.31 (3.23)	5.27 (3.35)
	Median	5.00	4.00	5.00	4.00
	Min; Max	1.0: 23.0	1.0 : 20.0	1.0 : 20.0	1.0 : 23.0
Baseline EDSS (N, %)		365	378	349	1092
	Mean (SD)	2.66 (1.35)	2.75 (1.35)	2.70 (1.35)	2.70 (1.35)
	Median	2.50	2.50	2.50	2.50
	Min : Max	0.0 : 5.5	0.0: 5.5	0.0 : 5.5	0.0 : 5.5
	≤ 3.5	283 (77.5%)	283 (74.9%)	257 (73.6%)	823 (75.4%)
	≥ 3.5	82 (22.5%)	95 (25.1%)	92 (26.4%)	269 (24.9%)
Relapse in Prior 12 months (N, %)		364	378	348	1090
	0	7 (1.9%)	9 (2.4%)	4 (1.1%)	20 (1.8%)
	1	237 (65.1%)	243 (64.7%)	225 (64.7%)	705 (64.7%)
	2	99 (27.2%)	95 (25.1%)	96 (27.6%)	290 (26.6%)
	3	12 (3.3%)	26 (6.9%)	18 (5.2%)	56 (5.1%)
	≥ 4	9 (2.5%)	5 (1.3%)	5 (1.4%)	19 (1.7%)
	Mean	1.4 (0.8)	1.4 (0.7)	1.4 (0.7)	1.4 (0.7)
MS subtype (n, %)		365	378	349	1092
	RRMS	355 (97.3%)	364 (96.3%)	344 (98.9%)	1063 (97.4%)
	SPMS	4 (1.1%)	3 (0.8%)	2 (0.6%)	9 (0.8%)
	Prog. Relapsing	6 (1.6%)	11 (2.9%)	2 (0.6%)	19 (1.7%)

Clinical Study Report EFC 10531 Appendix Table 14.2.4.2.2.

Prior Disease Modifying Therapy Characteristics

In this study the groups were well balanced for past history of treatment with an immunomodulator. Roughly 67% were treatment naïve and 33% were previously treated in the preceding 2 years with immunomodulators. (Table 40) Previous treatment was almost totally confined to one of the interferons or Copaxone.

Table 40 History of prior disease modifying medications- ITT population

Category of past treatment	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	Total
Previously treated N	366	379	351	1096
Treatment -naive	241 (65.8%)	264 (69.7%)	231 (65.8%)	736 (67.2%)
Previously treated	125 (34.2%)	115 (30.3%)	120 (34.2%)	360 (32.8%)
Interferon β -1a	54 (14.8%)	59 (15.6%)	61 (17.4%)	174 (15.9%)
Interferon β -1b	35 (9.6%)	25 (6.6%)	33 (10.3%)	93 (8.5%)
Copaxone	50 (13.7%)	46 (12.1%)	36 (10.3%)	132 (12.0%)
Mitozantrone	0	0	0	0
Tysabri	1 (0.3%)	0	0	1 (<0.1%)
Fingolimod	1 (0.3%)	1 (0.3%)	3 (0.9%)	5 (0.5%)

Analysis of Primary Endpoint

The analysis of the primary endpoint, the ARR, included both patients continuing drug treatment as well as those who discontinued treatment. For the later, the relapse rate was calculated as the last value while they remained on the trial medication and the missing data was not imputed. As this was an interim analysis only, a population analysis for the ITT population could be performed. A sensitivity analysis was done for those with all relapses and not just qualifying relapses. Relapses were evaluated in the aggregate for the ITT population and were descriptive.

The median duration of treatment for subjects in this study was 313 days for the placebo group, 302 for teriflunomide 7 mg group and 317.5 for the teriflunomide 14 mg group. Approximately 44% of all three treatment groups received the intended 48 weeks of treatment. Despite the abbreviated treatment captured in this analysis, both doses of teriflunomide showed a treatment effect over placebo for the ARR. The 7 mg dose of teriflunomide reduced the relapse rate by 30% and the 14 mg dose reduced the relapse rate by 42.7%. The adjusted ARR was 0.531 (95% confidence interval [CI]: 0.444 to 0.636) in the placebo group, 0.371 (95% CI: 0.300 to 0.459) in the teriflunomide 7 mg group, and 0.321 (95% CI: 0.258 to 0.400) in the teriflunomide 14 mg group as seen in Table 41. Additionally the unadjusted ARR where the total number of relapses was divided by the total number of patient-years was consistent with the adjusted primary analysis.

Table 41 ARR of confirmed relapses for the Interim Analysis of EFC 10531 (ITT)

ARR Confirmed relapses for the Interim Analysis of EFC 10531 ITT population			
Relapses	Placebo N = 365	Teriflunomide	
		7 mg N = 378	14 mg N = 349
Number of relapses	172	122	100
0	241 (66.0%)	289 (76.5%)	269 (77.1%)
≥ 1 relapse	124 (34.0%)	89 (23.5%)	80 (22.9%)
Unadjusted ARR	0.507	0.359	0.303
Adjusted ARR	0.531	0.371	0.321
95% CI	(0.444, 0.634)	(0.300, 0.459)	(0.258, 0.400)
Relative risk reduction		30%	42.7%

Clinical Study Report EFC 10531 Appendix Table 14.2.6.1.1

Sensitivity analysis

A sensitivity analysis was performed to evaluate all relapses, both those confirmed and not confirmed. Both doses reduced the overall risk of all relapses as displayed in 42.

Table 42 Sensitivity analysis of ARR all relapses for Trial EFC 10531 (ITT)

ARR of All relapses for the Interim Analysis of EFC 10531 ITT population			
Relapses	Placebo N = 365	Teriflunomide	
		7 mg N = 378	14 mg N = 349
Number of relapses	196	137	110
0	230 (63.0%)	279 (73.8%)	262 (75.1%)
≥ 1 relapse	135 (37.0%)	99 (26.2%)	87 (24.9%)
Adjusted ARR	0.601	0.413	0.350
95% CI	(0.505, 0.714)	(0.339, 0.504)	(0.284, 0.432)
Relative risk reduction		33%	42.8%

Clinical Study Report Trial EFC10531 Appendix 14.2.6.1.3

Subpopulations

A qualitative analysis was done of various subgroups. In all subgroups large enough to be evaluated, teriflunomide worked better than placebo with the exception of those previously treated with immunomodulators in the preceding two years as seen in Table 44.

Table 43 Subgroup analysis of the Interim Trial 10531- ITT population

Subgroup	Statistic	Placebo (N = 365)	Teriflunomide	
			7 mg (N = 378)	14 mg (N = 349)
Male	N	112	99	105
	Adjusted ARR	0.576	0.299	0.331
	(95% CI)	(0.415, 0.799)	(0.190, 0.471)	(0.228,0.480)
Female	N	253	279	244
	Adjusted ARR	0.527	0.401	0.317
	(95% CI)	(0.426, 0.652)	(0.317, 0.507)	(0.242,0.416)
< 38 years	N	166	186	164
	Adjusted ARR	0.703	0.492	0.378
	(95% CI)	(0.555, 0.892)	(0.363, 0.667)	(0.275, 0.519)
≥ 38 years	N	199	192	185
	Adjusted ARR	0.419	0.296	0.290
	(95% CI)	(0.321, 0.547)	(0.217, 0.402)	(0.213, 0.394)
EDSS ≤ 3.5	N	280	282	260
	Adjusted ARR	0.507	0.345	0.276
	(95% CI)	(0.416, 0.617)	(0.270, 0.440)	(0.210, 0.362)
EDSS > 3.5	N	85	96	89
	Adjusted ARR	0.510	0.399	0.398
	(95% CI)	(0.358,0.727)	(0.271, 0.589)	(0.282, 0.560)
RRMS	N	355	364	344
	Adjusted ARR	0.515	0.371	0.307
	(95% CI)	(0.428, 0.620)	(0.299, 0.461)	(0.246, 0.383)
Prior tx	N	125	115	120
	Adjusted ARR	0.572	0.585	0.402
	(95% CI)	(0.431,0.759)	(0.419,0.815)	(0.290,0.558)
No prior tx	N	240	263	229
	Adjusted ARR	0.494	0.278	0.265
	(95% CI)	(0.391,0.624)	(0.210,0.369)	(0.195,0.361)

Clinical Study Report TOWER Adapted from Tables 12, 14, 17, and 21.

Reviewer's Comment

In this incomplete study it is noted that teriflunomide did not work well on those previously treated with immunomodulators. This may be of relevance to US subjects who generally would have been treated with an immunomodulator prior to starting teriflunomide. Little weight is ascribed to this finding, however, due to the incomplete nature of this trial and because teriflunomide did work well in this subgroup in the completed study.

5.3.4 Trial LTS 6048

This open-label extension trial provided additional safety data to the NDA. Interim efficacy data was provided by the sponsor but was not requested to support efficacy.

Study Title

Extension of Protocol HMR1726D/2001, A Phase II Study of the Safety and Efficacy of Teriflunomide (HMR 1726) in Multiple Sclerosis with Relapses

Study objective

Two doses of teriflunomide, 7 mg and 14 mg, were compared for safety and efficacy in subjects suffering from MS for up to 8 years. The primary efficacy variable was the MS relapse rate.

Study design

This trial was a randomized, parallel-group design of up to 8 years duration. Subjects previously randomized to placebo in study 2001 were re-randomized in a 1:1 ratio to either 7 mg or 14 mg of teriflunomide and subjects previously treated with teriflunomide remained on the same dose as before. Although all were on active drug, none knew their dose. This study had open-ended treatment duration up to 8 years.

Efficacy assessments

The efficacy variables being studied included EDSS, MSFC, BOD, brain atrophy, and other MRI parameters all assessed yearly as well as ARR, time to first relapse and proportion of relapse-free subjects. In addition safety parameters included AE, laboratory data, vital signs, abdominal ultrasound, ECG as well as MSQOL-54 and Fatigue Impact Scale. PK was further studied as well.

Statistical analysis

Descriptive statistics were performed for safety data and MRI data. Other interim efficacy data was analyzed using the Poisson regression model for ARR and Kaplan-Meier for time to first relapse and proportion of relapse-free subjects.

Table 44 Overall patient disposition for Extension trial to study 2001

	Placebo/7mg (N=29)	7mg/7mg (N=52)	Placebo/14mg (N=26)	14mg/14mg (N=40)
Randomized and not treated	0	0	0	0
Randomized and treated	29 (100%)	52 (100%)	26 (100%)	40 (100%)
Completed study treatment period	0	0	0	0
Did not complete study treatment period	13 (44.8%)	30 (57.7%)	16 (61.5%)	18 (45.0%)
Ongoing in the study	16 (55.2%)	22 (42.3%)	10 (38.5%)	22 (55.0%)

Reason for study treatment discontinuation

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Study status

The study enrolled its first patient on January 28, 2002 and is currently ongoing. An interim analysis of the study was performed with cut-off date of February 24, 2011. As of the cut-off date, no subjects had completed the study. Table 44 shows patient disposition. Of the 160 subjects who completed Trial 2001, a total of 147 entered the extension trial. Of those, 77 have discontinued the trial before reaching 8 years.

Efficacy Results

Interim descriptive analysis revealed no significant dose dependent benefit for the adjusted ARR and disability progression. Both doses of teriflunomide worked and according to the sponsor minimal disease progression was noted. The adjusted ARR was 0.252 (95% CI: 0.149, 0.425) in the placebo/7 mg group, 0.316 (95% CI: 0.209, 0.477) in the 7 mg/7 mg group, 0.212 (95% CI: 0.195, 0.428) in the placebo/14 mg group and 0.200 (95% CI: 0.114, 0.352) in the 14 mg/14 mg group. At week 336 the mean change in EDSS was 1.10 in the placebo/7 mg group, 0.30 in the 7 mg/7 mg group, -0.13 in the placebo/14 mg group and 0.63 in the 14 mg/14 mg group. According to the sponsor several MRI parameters showed a possible trend toward a dose-dependent benefit of 14 mg over the 7 mg dose. One such measurement was the mean change (SD) of BOD which from baseline to week 336 was 5714.79 (9740.56) mm³ in the placebo/7 mg group, 3846.58 (6415.27) mm³ in the 7 mg/7 mg group, 2039.98 (2649.14) mm³ in the placebo/14 mg group, and 1674.11 (1623.53) mm³ in the 14 mg/14 mg group.

Reviewer's Comment

Only preliminary efficacy results are available in this small open-label study that was not designated to support efficacy. It was noted that both short duration and long duration treatment seemed to decrease relapses and delay disease

progression compared to what one would expect over eight years for untreated patients as described in the literature.

5.3.5 Trial LTS 6050

This open-label extension trial provided additional safety data to the NDA. Interim efficacy data was provided by the sponsor but was not requested to support efficacy.

Study Title

Long-term extension of the multinational, double-blind, placebo controlled study EFC6049 to document the safety of two doses of teriflunomide (7 and 14 mg) in patients with multiple sclerosis with relapses.

Study objective

In this extension trial 7 mg and 14 mg of teriflunomide were compared in patients suffering from MS with relapses. The primary objective was to document the long-term effect on disability progression, annual relapse rate, and MRI variables as well as the safety of the drug.

Study design

This trial was a multinational, multi-center parallel group study. Subjects previously randomized to placebo were re-randomized to either 7mg or 14 mg of teriflunomide and subjects previously treated with teriflunomide remained on the same dose as before. All were on active treatment, but were blinded as to the dose.

Efficacy assessments

The primary efficacy variable was the time to disability progression as measured in the TEMSO trial. Secondary efficacy variables included ARR, proportion of patients free of disability progression, time to first relapse and other measures including MRI measures. The analysis of ARR was calculated only from the data collected from the extension period, but the analysis of disability was calculated from the data collected from both the extension period and the core period.

Statistical analysis

A log-rank test was used to compare placebo/7 mg to 7mg/7mg and placebo/14 mg to 14 mg/14 mg as well as 7 mg/7 mg to mg/14mg. The dependent variable was time to disability progression and the treatment group was the test variable. The region, baseline EDSS were the stratification factors. Hazard ratios were estimated using Cox regression model with treatment group, region, and baseline EDSS strata as covariates. The Kaplan-Meier graphs were generated and Kaplan-Meier method was used to estimate the disability progression rate and its 95% confidence intervals (CIs) at yearly time points since randomization in EFC6049/TEMSO for each treatment group. Secondary efficacy analyses include estimates of the proportion of patients free of

disability at selected time points using the Kaplan-Meier method. Additionally the adjusted ARR was performed using a Poisson regression model with robust variance to accommodate the potential over-dispersed data appropriately. To account for different treatment durations the log-transformed standardized treatment duration was included in the model as an “offset” variable for computation of the relapse rate.

Study status

The study initiated on October 16, 2006 and the last subject enrolled on April 29, 2010. An interim analysis took place on January 10, 2011. The study is scheduled for completion in the spring of 2012. The study has an open-ended duration and most patients are intended to be treated for up to 6 years. At the time of the interim analysis subjects had maximum treatment duration of 5 years (288 weeks) since the original randomization into study EFC 6049. A total of 129 subjects were treated with placebo/7 mg, 252 were treated with 7 mg/7mg, 108 were treated with placebo/14 mg and a total of 251 were treated with 14 mg/14 mg.

Efficacy results

The interim analysis of the primary outcome measure for the risk of disability progression sustained for 12 weeks can be found in Table 45. As noted the risk was numerically lower in the 7 mg/7mg group compared to the placebo/7 mg group and in the 14 mg/14 mg group compared with the placebo/14 mg group. Although duration of therapy appeared to be a factor in prevention of disease progression dose did not.

Table 45 Analysis of time to disability progression sustained for at least 12 weeks- ITT population)

	Placebo/7mg (N=129)	7mg/7mg (N=252)	Placebo/14mg (N=108)	14mg/14mg (N=251)
Number of patients with disability progression	50 (38.8%)	83 (32.9%)	40 (37.0%)	84 (33.5%)
Number of patients who were censored	79 (61.2%)	169 (67.1%)	68 (63.0%)	167 (66.5%)
25% quartile time to disability progression (days) (95% CI) ^a	596.0 (428, 930)	932.0 (673, 1277)	769.5 (489, 1101)	1080 (756, 1260)
Kaplan-Meier estimates of probability of disability progression (95% CI) since EFC6049 randomization				
1 year	0.163 (0.099, 0.226)	0.139 (0.096, 0.182)	0.130 (0.066, 0.193)	0.120 (0.079, 0.160)
2 years	0.279 (0.202, 0.356)	0.210 (0.160, 0.261)	0.250 (0.168, 0.332)	0.195 (0.146, 0.244)
3 years	0.352 (0.269, 0.436)	0.297 (0.239, 0.354)	0.310 (0.222, 0.398)	0.274 (0.219, 0.330)
4 years	0.420 (0.326, 0.513)	0.329 (0.268, 0.391)	0.372 (0.276, 0.468)	0.345 (0.283, 0.408)
5 years	0.420 (0.326, 0.513)	0.371 (0.303, 0.439)	0.418 (0.309, 0.526)	0.375 (0.307, 0.443)
Hazard ratio (95% CI) ^b		0.785 (0.552, 1.115) ¹		0.854 (0.585, 1.247) ² 0.986 (0.728, 1.336) ³
P-value ^c		0.1877 ¹		0.4132 ² 0.9387 ³

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Reviewer's Comment

Although this is an interim analysis of an open-label extension trial most subjects were near completion of the trial and have had five years of treatment since the original randomization. The data suggests that both doses of teriflunomide had similar effects on delaying disability prevention which may be related to duration of treatment, but not to dose.

5.3.6 Trial PDY 6045

This phase 2 trial with teriflunomide as adjuvant therapy provided additional safety data to the NDA. Efficacy data was provided by the sponsor but was not requested to support efficacy.

Study Title

A randomized, multinational, double-blind, placebo-controlled, parallel-group pilot study to estimate the tolerability, safety, pharmacokinetics, and pharmacodynamic effects of teriflunomide for 24 weeks when added to treatment with interferon- β in subjects with multiple sclerosis.

Study objectives

To estimate the tolerability, safety, pharmacokinetics and pharmacodynamic effects of 7 mg and 14 mg of teriflunomide for 24 weeks when added to treatment with interferon-beta in subjects with one of the relapsing forms of MS. Secondary objectives included evaluating BOD, ARR, and Fatigue Impact scale over the 24 week period.

Study design

This was a randomized, multinational, double-blind, placebo-controlled parallel-group pilot study which had three treatment arms which included placebo, 7 mg teriflunomide and 14 mg of teriflunomide each added to interferon-beta. The patients were randomized 1:1:1. The patient population included ambulatory MS subjects ages 18-55 with EDSS \leq 5.5 who had a stable clinical course in the four weeks prior to randomization, and no relapses in the preceding 60 days. Subjects were on stable doses of IFN-beta for at least 26 weeks.

Efficacy assessment

The key efficacy variables were burden of disease (BOD), other MRI variables (total number and total volume of gadolinium enhancing T1-lesions, volume and change from baseline volume, and percentage change from baseline of hypointense post-gadolinium T1 lesion and of T2 lesion component), and annualized relapse rate.

Statistical analysis

Results were descriptive. There were exploratory statistical analyses.

Study status

The study is currently complete and data from this study was used as part of the safety database. Treatment lasted for 24 weeks and observation was for a total of 44 weeks which included also a screening period of 4 weeks and a 16 week follow-up period. A total of 116 patients were randomized and treated in the study (41 in the placebo group, 36 in the 7 mg group and 39 in the 14 mg group).

Efficacy results

This was a small phase 2 trial. Although the results of this phase 2 study were descriptive, according to the sponsor there did appear to be a trend in reducing the number and volume of the T1-Gd lesions over 24 weeks that was dose related on drug compared with placebo. Compared to beta-interferon alone, those also on adjuvant treatment with teriflunomide had a 54.6% reduction in the number of lesions (7 mg dose) and a 81.3% reduction in lesions in those on 14 mg of teriflunomide (both with $p < 0.001$). Of those on interferon alone, 5/41 had relapses during the treatment period, 5/36 of those on 7 mg teriflunomide had further relapses and 2/39 subjects on teriflunomide 14 mg had further relapses.

5.3.7 Trial PDY 6046

This phase 2 trial with teriflunomide as adjuvant therapy provided additional safety data to the NDA. Efficacy data was provided by the sponsor but was not requested to support efficacy.

Study Title

A randomized, multinational, double-blind, placebo-controlled, parallel-group pilot study to estimate the tolerability, safety, pharmacokinetics, and pharmacodynamic effects of teriflunomide for 24 weeks when added to treatment with GA in subjects with multiple sclerosis.

Study objectives

To study the tolerability and safety of a 7 mg and a 14 mg dose of teriflunomide as an adjuvant to GA in comparison to those on a stable dose of GA alone. Secondary outcomes measures included ARR and MRI outcomes.

Study design

This was a randomized, multinational, double-blind, placebo-controlled parallel-group pilot study to estimate the tolerability, safety, pharmacokinetics and pharmacodynamic effects of teriflunomide for 24 weeks when added to treatment with GA in subjects with one of the relapsing forms of MS. The study had three treatment arms which included placebo, 7 mg teriflunomide and 14 mg of teriflunomide each added to GA. The patient population was ambulatory MS subjects ages 18-55 with an EDSS ≤ 5.5 who had a

stable clinical course in the four weeks prior to randomization, and no relapses in the preceding 60 days. They needed to be on a stable dose GA for at least 26 weeks.

Efficacy assessment

The primary outcome of this study was to assess safety. Efficacy as measured by MRI measures such as the total number of gadolinium enhancing T1-lesions and the BOD were estimated as was the ARR. Since there was no primary efficacy endpoint only descriptive statistics were provided over the 24 weeks of therapy.

Study status

The study is currently complete and data from this study was used as part of the safety database. There was a study treatment of 24 weeks. A total of 41 subjects were randomized to placebo, 42 subjects were randomized to 7 mg/day and 40 subjects were randomized to 14 mg/day.

Efficacy results

No clear cut trend in effectiveness was evident in this small study which lacked a primary clinical outcome measure and in which subjects had unbalanced baseline MRI findings.

5.3.8 Trial LTS 6047

This was an extension safety trial for teriflunomide as adjuvant therapy which provided additional safety data to the NDA. Efficacy data was provided by the sponsor but was not requested to support efficacy.

Study Title

Long-term extension of the multinational, double-blind, placebo controlled studies PDY6045 and PDY6046 to document the safety of teriflunomide when added to treatment with interferon- β or GA in patients with multiple sclerosis with relapses.

Study objectives

To evaluate the long-term safety and tolerability of teriflunomide when added to treatment with interferon- β or GA in patients with multiple sclerosis with relapses.

Study design

This was the long-term extension trial of two phase 2 studies, PDY6045 and PDY6046, whose purpose was to document the safety of teriflunomide when added to treatment with either interferon-beta or GA in patients with one of the relapsing forms of MS. The study was an international, multi-center trial with parallel, double-blind treatment of two-fixed doses of teriflunomide (7mg and 14 mg) as an adjuvant or placebo where the double-blind status was maintained for a minimum of 24 weeks. This was followed by a 16 week follow-up period. Treatment was the same as in the prior study and stable

doses of either INF-beta or glatiramer acetate were continued for the duration of the study in those both on placebo and teriflunomide.

Efficacy assessment

As a secondary outcome measure the long-term effect on relapse rate, disability progression and MRI variables were studied. Since there was no primary efficacy endpoint, only descriptive statistics were provided over the 24 week treatment period.

Study status

This study is now complete and ran between October 17, 2007 and April 14, 2010. Data from this study contributed to the safety database. A total of 241 patients were randomized into this study for 24 weeks of treatment and a total of 166 completed the study, with a total of six treatment arms.

Efficacy results

The study was not formally designed to study efficacy and had multiple small treatment arms without consistent results for teriflunomide as an adjuvant to GA and with a trend in those on teriflunomide as an adjuvant to interferon- β .

6 Review of Efficacy

Efficacy Summary

In this application the sponsor submitted a single large well-controlled pivotal trial, TEMSO, which provided substantial evidence of efficacy for the reduction of the ARR and the delay in the accumulation of physical disability in those with relapsing multiple sclerosis. TEMSO was a large phase 3 trial with 1088 patients. The vast majority of subjects in the study had RRMS (92.8%) while the remainder had SPMS or RPMS. The 108 week trial was performed at foreign sites and had <1% US subjects. The study was statistically powered to evaluate both the ARR and the effect of drug on delaying the accumulation of physical disability as assessed by the EDSS confirmed at 12 weeks. Subjects were stratified by baseline EDSS and by center. MRIs were evaluated at baseline weeks 24, 48, 72 and 108. Relapses were qualified. Two doses of teriflunomide were tested, 7 mg and 14 mg, and both proved efficacious for preventing relapses, but only the 14 mg dose proved efficacious at delaying disability as measured by the EDSS.

The results of the pivotal trial were further supported by MRI evidence from a phase 2 trial 1726/2001. The supportive trial was small with 179 randomized subjects that were treated for only 36 weeks. In this study 87.5% had RRMS and 12.5% had SPMS. MRI findings were the primary outcome measure; MRI was assessed at baseline, week 6, week 12, week 18, week 24, week 30 and week 36. The primary endpoint of average change in number of unique active lesions on MRI was significantly less with both doses of teriflunomide. A decrease in the number of lesions at the end of 36 weeks compared

with baseline was observed for both doses of teriflunomide as well, and this was not seen in those on placebo. Relapses were not qualified in this study and hence could not be meaningfully assessed.

Finally, in the TOWER trial, a phase 3 trial for which the sponsor provided interim results, the primary outcome measure was ARR and the secondary outcome measure was time to disability progression confirmed after 12 weeks. The 14 mg dose appeared to be more efficacious than the 7 mg dose, but it is noted that only descriptive results were provided for the primary outcome measure due to the interim nature of the report. This study included 1092 subjects with 18.6% from the US.

Relapse Rate

Demonstration of efficacy of the primary endpoint ARR was based on the pivotal trial (TEMPO) as the phase 2 trial (1726/2001) was of shorter duration where confirmed relapses were not assessed. The sponsor did show robust evidence of relapse reduction in patients with RRMS (p values <0.0002) reducing relapses by 31% with both the 7 mg and 14 mg dose of teriflunomide compared with placebo. These efficacy findings were corroborated by multiple sensitivity analyses which included the PP population, those who continued to have relapses even after treatment was discontinued, and those with all relapses including non-qualifying relapses.

At least for the primary endpoint, the reduction in the ARR was consistent for both doses of teriflunomide. In this study both the primary analysis of the ARR in the ITT population as well as the supportive sensitivity analyses showed evidence for efficacy. The 14 mg dose appeared to reduce the risk of relapse by 42.7% compared with placebo and the adjusted ARR was 0.321 on 14 mg of teriflunomide compared to 0.531 for placebo. Review of the Interim analysis of the TOWER study, though descriptive, lent further support that relapse rate is reduced by teriflunomide. Further details of trial design and findings are presented in section 5.3.1 and section 5.3.3.

Disability Progression

Reduction in disability progression was assessed as a secondary endpoint in the TEMPO trial and was not assessed in the Interim analysis of the TOWER trial nor in the 1726/2001 study. Specifically, delay in disability progression sustained over a 12 week period as measured by the EDSS was a secondary endpoint and exploratory endpoints included delay in disability progression sustained over 24 weeks and change in the MSFC.

In the TEMPO trial only the 14 mg dose demonstrated substantial evidence of efficacy (p=0.0279); the 7 mg dose showed a trend toward efficacy but not a statistically significant result (p=0.0835). The risk of disability progression was decreased by 29.8% in the ITT population for those on the 14 mg dose compared with placebo and by 23.7% for those on the 7 mg dose. This finding was further supported by the sensitivity analysis for the PP population where a clear cut difference was seen between the two

doses. There were statistically significant results for the 14 mg dose (RR reduction of 30.1%, $p=0.0258$) but not for the 7 mg dose (RR reduction of 21.7%, $p=0.1144$). For those on the 14 mg dose of teriflunomide at 108 weeks, only 20.2% of those had progression whereas 27.3% of those on placebo had progression and risk of progression was reduced by 25.1% ($p = 0.1259$).

An analysis of reduction of disability progression measured by EDSS sustained for 24 weeks did not support efficacy with either dose, nor did an analysis of the exploratory endpoint, MSFC, over time. A subpart of the MSFC, the PASAT-3, a test of cognitive function, did however show evidence of treatment effect with both doses of teriflunomide.

MRI lesions

Further evidence that substantiated the superiority of the 14 mg dose of teriflunomide came from multiple MRI endpoints in the TEMSO trial as well as the phase 2 trial 1726/2001. Endpoints included those that were thought to measure either new disease, active disease or chronic disease. Specifically, in the TEMSO trial, Burden of Disease (BOD) was evaluated as a secondary endpoint. This measure is generally thought to measure past disease activity. At every time point in the trial, including the trial conclusion at week 108, the BOD was less in the group treated with teriflunomide 14 mg than in those treated with placebo. The mean change in the absolute value of the cubic root transformed BOD was 0.111 for placebo and 0.045 for teriflunomide 14 mg.

In the 1726/2001 trial the primary efficacy endpoint was the average number of unique active lesions/MRI during the blinded portion of the study. MRI was assessed at baseline, week 6, week 12, week 18, week 24, week 30 and week 36. Not only were the absolute number of lesions decreased over time from baseline on teriflunomide 14 mg compared with placebo, but during this same period of time there was an increase in the number of such lesions for those on placebo but not for those on drug. For the entire 36 week treatment period there was an average of 2.69 unique active lesions/scan on placebo and 0.98 unique active lesions/scan on teriflunomide 14 mg ($p = 0.005$). As a proof of concept trial many other MRI measures were obtained which included a significant effect on gadolinium-enhanced T2 lesions with the 14 mg dose and BOD.

The number of gadolinium-enhanced T1 lesions is thought to indicate short-term disease activity and robust findings for their reduction was present with both doses of teriflunomide ($p<0.0001$) in the TEMSO trial. No MRI measurements collected in the TOWER trial were analyzed in this NDA.

6.1 Indication

The sponsor's proposed labeling for teriflunomide is for the treatment of patients with the relapsing forms of multiple sclerosis (RMS [REDACTED] (b) (4) [REDACTED])

6.2 Methods

In the pivotal trial TEMSO, a double-blind, placebo-controlled trial, patients with the relapsing forms of MS were treated with teriflunomide 7 mg, teriflunomide 14 mg or placebo once/day. After screening, subjects were stratified by center and by baseline EDSS (≤ 3.5 or > 3.5). Entry criteria included having a diagnosis of MS that met the McDonald criteria, experienced at least one relapse over the preceding year or two relapses over the preceding two years, and an EDSS score ≤ 5.5 . Subjects were randomized and treated in a 1:1:1 fashion for 108 weeks. They were seen monthly for 6 months and then every 6 weeks until the completion of the study. At the end of the 108 weeks the ARR was computed using only confirmed relapses that occurred between the randomization date and the last study medication intake date.

A Poisson regression model with robust error variance was used. The model included the total number of confirmed relapses with onset between randomization date and last dose date as response variable and treatment group, EDSS strata (baseline EDSS score ≤ 3.5 versus > 3.5), and region as covariates. Time to disability progression sustained for 12 weeks, the key secondary endpoint was also assessed in this study using a log-rank test with time to disability progression as the dependent variable, treatment group as the test variable, and region and baseline EDSS strata as strata factors. Hazard ratios were estimated using a Cox regression model with treatment group, region, and baseline EDSS strata as covariates.

Both endpoints were assessed in a hierarchical order with a step-down testing procedure was used to control for Type-I error. The two doses of teriflunomide were compared sequentially (teriflunomide 14 mg first) with placebo to analyze ARR, and then for time to disability progression. Each hypothesis was tested only if the preceding one was significant at the 5% level.

Several MRI endpoints were evaluated in the pivotal trial. The main MRI endpoint was burden of disease (BOD) defined as the total volume of abnormal brain tissue on MRI calculated as the sum of the total volume of T2 lesions and T1 hypointense lesions. The BOD was assessed at 24, 48, 72 and 108 weeks and compared to baseline. Patient reported outcomes such as the impact of fatigue was assessed in the pivotal trial as well as other tertiary disability measures such as the MSFC.

In the confirmatory phase 2 trial, 1726/2001, the primary efficacy variable was based on those subjects who had at least one on-treatment MRI assessment. An analysis of

covariance was performed on the average number of unique active lesions per scan during the double-blind treatment period, EDSS strata (baseline EDSS score ≤ 3.5 versus >3.5), and center as fixed effects and the average pre-randomization number of unique active lesions as covariate.

The design of the TOWER trial was similar to the TEMSO trial however, there were no MRI endpoints and the duration was variable. The study was to end when the last subject completed 48 weeks of treatment. By mutual agreement with the agency, the only endpoint analysis that was required for this NDA submission was the ARR and associated sensitivity analyses including confirmed relapses, those that took place after treatment discontinuation, and an analysis of the per protocol population. Statistical analysis followed the method described in the TEMSO study. Patients were randomized into this study in a ratio of 1:1:1. Entry criteria included MS diagnosis meeting McDonald criteria, EDSS ≤ 5.5 , at least one relapse in the 12 months preceding the study or two relapses in the 12 months preceding the study.

6.3 Demographics

Overall, the demographics of the pivotal TEMSO trial was well balanced for baseline patient and disease characteristics, disease burden, MRI findings, prior use of immunomodulators but was notable for containing few US subjects. Study R/1726/2001, the small non-IND study of Canadian and French subjects, had less racial diversity than the other studies and did have some small imbalances between treatment arms felt to be immaterial due to the descriptive nature of the study. The as yet incomplete multinational TOWER trial also appeared to have subjects well balanced for demographic features, although MRIs were not part of the baseline assessment. The remainder of this section will focus on the TEMSO trial since it was the only large completed trial supporting efficacy and other trial data will be mentioned when relevant. Further demographic details of the individual trials can be found in section 5.3.1, 5.3.2, and 5.3.3.

Baseline patient characteristics

Baseline characteristics in the TEMSO trial of the ITT population included 97.5% Caucasian, 72.2% female, 27.8% male, mean age 37.9 (SD 8.8), mean weight 70.04 kg (SD 15.30), mean BMI 24.61 kg/m² (SD 4.74). Whereas most demographic characteristics were representative of the US population, those that were not are cited. There was an underrepresentation of minority groups such as Blacks and Asians in the pivotal trial, but these ethnic groups are often underrepresented in studies when US subjects are studied exclusively. The subjects had on average slightly lower body weights (70.04 kg) and BMIs (24.61 kg/m²) than might be seen in a study with more US subjects, but body weight was not believed to play a significant role in drug metabolism and this was felt to be inconsequential. (See Table 9) The TOWER trial enrollment, though very similar to TEMSO, did have larger Asian ethnicity (13.4%) and were also

heavier (71.39 kg, SD 17.36), but were well balanced across treatment arms. (See Table 38)

Baseline disease characteristics

In the TEMSO trial baseline disease characteristics were in general well matched among treatment arms. It was noted that there was a slightly greater representation of those with RRMS (91.4%) and less of those with SPMS and PRMS than is typically representative of US MS patients. This is of little concern, as the basis of approval for many of the MS products marketed in the US were pivotal trials in subjects exclusively with RRMS and the various relapsing forms of MS are felt to share similar pathophysiology.

Other disease characteristics such as mean disease duration 5.33 years (SD 5.48), mean time since last attack prior to study 6.35 months (SD 3.54), mean baseline EDSS 2.68 (SD 1.30), mean number of relapses in 12 months prior to randomization 1.4 (SD 0.7) all appeared reasonably well balanced among treatment arms and comparable to what would be expected of the US population. (See Table 10) MRI baseline characteristics were also well balanced including mean number of gadolinium enhancing T1 lesions 1.66 (SD 4.28) and mean BOD 19.28 (SD 19.06). (See Table 11).

For the TOWER trial there were fewer subjects with progressive disease (2.6%) and more with RRMS (97.5%), mean baseline EDSS was 2.70 (SD 1.35), disease duration 5.15 years (SD 5.62), time since last attack prior to entering the study 5.27 months (SD 3.35), and mean number of relapses in prior 12 months 1.4 (SD 0.7), that is disease activity appeared quite similar to those in the TEMSO trial, even though baseline MRI was not available.

Prior immunomodulators

There were possibly more treatment naïve patients in the TEMSO trial than is typically reported with US subjects (73%), but this was hard to firmly assess as the sponsor's definition of treatment naïve was different than the usual definition. Subjects considered treatment naïve in this study were those who had not been on an immunomodulator for the preceding two years. The TOWER study had 32.8% that were treatment naïve probably related to the greater US representation.

Applicability of Foreign Data

The population of the TEMSO trial included 7 US subjects (0.7%) out of the 1088 randomized subjects, presumably because enrollment took place primarily while the trial was conducted as a non-IND study. The patients were from 21 different countries with almost half from Western Europe (46.3%). The other half was recruited from either Eastern Europe (31.1%) or from the Americas (22.6%). Those subjects from the Americas were predominantly Canadians (181 subjects) or Chileans (55 subjects). Although the sponsor did not provide any justification of the applicability of foreign data, US subjects were probably reasonably represented by the subjects enrolled in this

study in terms of baseline characteristics. Study 1726/2001 was exclusively a non-IND study with foreign subjects but this was only a small supportive proof of concept trial. The TOWER trial was multinational and included 18% US subjects which is more in line with pivotal trials for other marketed products for MS, but this is as yet incomplete.

6.4 Subject Disposition

Out of the 1088 subjects randomized in the TEMSO trial, 1086 were treated with at least one dose of drug and 796 completed the trial. Discontinuations were higher than the sponsor anticipated with teriflunomide in the pivotal trial (26.7%) but were reasonably well balanced between the treatment groups. Adverse events were the most common cause of drop out (28.7%) particularly in those on drug product (teriflunomide 7 mg 10.1% or teriflunomide 14 mg 10.6% vs. placebo 8%). Almost as common, subjects who did not wish to continue accounted for 25% of dropouts (teriflunomide 7 mg 8.7%, teriflunomide 14 mg 7.2%, and placebo 9.1%). Withdrawal due to treatment failure (lack of efficacy or progressive disease) was a bit higher for those on drug than on placebo. Most notable were those who reported progressive disease as a cause of withdrawal, 11 placebo patients (3%), 32 patients on teriflunomide 7mg (8.7%) and 26 patients on teriflunomide 14 mg (7.2%). (See Table 8) Those on treatment appeared to withdraw earlier than those on placebo. This would not be expected to be a bias toward treatment effect.

In study 1726/2001 a total of 207 were screened and 179 were randomized, but only 177 were in the evaluable population as 2 withdrew before any efficacy evaluation. A total of 160 completed the study and 19 (11%) discontinued prematurely. The discontinuations were not well balanced. A total of 21.1% (12/57 subjects) discontinued on teriflunomide 14 mg whereas on placebo 6.6% or 4/61 discontinued and on 7 mg of teriflunomide 4.9% or 3/61 discontinued. All discontinuation in the placebo group and 7 mg group were due to adverse event, but in the 14 mg group two discontinued due to lack of efficacy. As this study was a small proof of concept study that only served as supportive evidence, not much can be concluded about these imbalances.

Since the TOWER trial is still ongoing only a limited amount can be said about subject disposition. Of the 1096 subjects randomized, 4 did not undergo treatment and a total of 861 are still undergoing treatment. A total of 231 subjects (21.2%) have discontinued treatment to date. Discontinuations appear to be well-balanced.

6.5 Analysis of Primary Endpoint(s)

Confirmed Annualized relapse rate (ARR)

The confirmed ARR was the primary outcome measure for both the TEMSO and TOWER trials and is perhaps the most common primary endpoint for studies demonstrating efficacy for the relapsing forms of MS. In both trials the ARR was confirmed by the independent and treating neurologist and the studies demonstrated robust results for both doses. Of the 1086 patients in the ITT population of the TEMSO trial the adjusted ARR was 0.539 (95% CI: 0.466 to 0.623) in the placebo group, 0.370 (95% CI: 0.318 to 0.432) in the teriflunomide 7 mg group, and 0.369 (95% CI: 0.308 to 0.441) in the teriflunomide 14 mg group. Both doses of drug caused a 31.5% reduction in the ARR. The results of the TOWER interim analysis were also consistent with those of the TEMSO trial as displayed in Table 46. These findings were also confirmed by the independent agency statistical reviewer. To give this a clinical perspective, when teriflunomide is compared to approved products such as the interferons and glatiramer acetate, it is thought to confer a very similar reduction in relapse rate. Natalizumab and fingolimod are thought to confer more benefit, approximately a 50-60% reduction, when one compares across the respective clinical trials used to demonstrate efficacy.

Table 46 Clinical efficacy for the primary outcome measure, confirmed ARR in ITT population in the TEMSO and Interim Studies

Relapses	TEMSO			TOWER Interim Study		
	Placebo N = 363	Teriflunomide		Placebo N = 365	Teriflunomide	
		7 mg N = 365	14 mg N = 358		7 mg N = 378	14 mg N = 349
Number of relapses	335	233	227	172	122	100
0	179 (49.3%)	211 (57.8%)	217 (60.6%)	241 (66.0%)	289 (76.5%)	269 (77.1%)
1	97 (26.7%)	92 (25.2%)	86 (24.0%)			
2	48 (13.2%)	49 (13.4%)	33 (9.2%)			
3	22 (6.1%)	10 (2.7%)	16 (4.5%)			
4	11 (3.0%)	2 (0.5%)	4 (1.1%)			
≥ 5	6 (1%)	1 (0.3%)	2 (0.6%)			
Adjusted ARR	0.539	0.370	0.369	0.531	0.371	0.321
95% CI	(0.466, 0.623)	(0.318, 0.432)	(0.308, 0.441)	(0.444, 0.634)	(0.300, 0.459)	(0.258, 0.400)
Relative risk		0.688	0.685			
P value		0.0002*	0.0005*			

*Based on 2-side statistical significance level of at least 0.05
 Clinical Study Report EFC 6049 adapted from Table 17 p 80

Sensitivity analyses of ARR

Multiple sensitivity analyses were done of the ARR in the TEMSO trial. One such analysis included looking at the ARR in the ITT population but excluding those with major protocol violations (PP). The PP group included those subjects with less than two clinical relapses in the last two years, subjects with a relapse in the month preceding randomization, subjects taking prohibited medications which might confound the results, subjects with poor compliance to the study treatment, and subjects with a baseline EDSS > 5.5. Other sensitivity analyses included those who discontinued treatment but who continued to have relapses including during the follow-up period and in those with both qualifying and non-qualifying relapses. All of the sensitivity analyses confirmed the robust treatment effect with both doses of teriflunomide. In the TEMSO trial the risk of relapse was reduced for both doses by approximately 33% in the PP group, and the risk of confirmed relapses after treatment discontinuation was reduced by 29% for both doses. For those with both confirmed and nonconfirmed relapses the risk was reduced approximately 28.7% for those on 7 mg teriflunomide and 30.7% for those on 14 mg teriflunomide. The only sensitivity analysis that could be completed for the Interim TOWER analysis was that of confirmed and nonconfirmed relapses and this analysis demonstrated a risk reduction of relapse of 42.7% for the 14 mg dose and 30% for the 7 mg dose.

6.5 Analysis of Secondary Endpoints(s)

Prevention of Disability Progression

The TEMSO pivotal trial measured sustained disability progression of EDSS for 12 weeks as a key secondary endpoint. The time to first disability progression was defined as a sustained increase of at least 1.0 points from the baseline on the EDSS or 0.5 points for subjects with a baseline EDSS of 5.5. Sustained disability progression needed to persist for 12 weeks and it was assessed at three month intervals over a 2 year period of time. It was with this endpoint that the clearest differentiation between the 7 mg and the 14 mg dose of teriflunomide was seen. Statistically significant findings were present for the 14 mg dose and only trended positive for the 7 mg dose. At the end of 108 weeks the hazard ratio was 0.702 ($p = 0.0279$) for the 14 mg dose and 0.763 ($p = 0.0835$) for the 7 mg dose. (See Table 18) The estimate of those who had 12-week sustained disability at the end of the study was 27.3% for the 14 mg dose, 21.7% for the 7 mg dose and 20.2% for placebo.

Other exploratory measures of disability progression were assessed in the pivotal trial and did not further substantiate the claim, but these were endpoints that did not undergo adjustments for multiple comparisons and they are described in the next section. Disability progression could not meaningfully be assessed in the 1726/2001 trial or in the Interim analysis of the TOWER study due to the incomplete or short-term nature of the trials.

6.6 Other Endpoints

Other markers of disability progression

MSFC

The Multiple Sclerosis Functional Composite (MSFC) is another widely used disability rating scale that was assessed as an exploratory outcome measure in the TEMSO trial and the 2001 trial. In neither trial was there a significant impact on the MSFC with the use of teriflunomide. Since this is a scale based on a composite of three endpoints all three components were looked at individually. Each of the three subscales is based on deviation from the mean of a reference population from which one computes a z score. The two components that primarily evaluate motor and coordination skills, the T25FW and the 9-HP test, did not show treatment effect with either dose of drug. Only the PASAT-3, primarily a cognitive task, showed evidence that teriflunomide had some beneficial effect with both doses of drug. Since the individual being tested is not being compared to himself but is being compared to a population mean, it may be that the MSFC is relatively insensitive to capturing changes in disability in this study.

Twenty-four week sustained disability progression

Both doses of teriflunomide trended positive in terms of having a treatment effect at week 108 that was sustained for 24 weeks, but neither reached statistical significance. Teriflunomide reduced the risk of having sustained disability for 24 weeks in about 25% of subjects either on 7 mg /day of Teriflunomide or 14 mg/day ($p = 0.1459$ and $p = 0.1259$).

MRI Endpoints

For the TEMSO trial – MRI findings were checked throughout the trial at weeks 0, 24, 48, 72, and 108 weeks. All of these measures were reported as a change from baseline to week 108 with the exception of unique active lesions. The key MRI variable was Burden of Disease.

For the 1726/2001 Trial – The primary efficacy outcome was the average number of unique active lesions/MRI scan for the double-blind portion of the trial.

Burden of Disease (BOD)

The burden of disease was defined as the change from baseline in the transformed BOD at week 108. This MRI measure is thought to be a marker of past disease activity. The BOD was the sum of the total volume of T2 lesions and T1 hypointense lesions (considered the total volume of all abnormal brain tissue) which was a cubic root transformation due to skew distribution of the data. The BOD at every time point measured in the TEMSO trial was significantly lower for both doses of teriflunomide compared with placebo according to the sponsor. (See Figure 6) The model adjusted least square mean difference from the baseline measurement was -0.053 for 7 mg of teriflunomide ($p = 0.0317$) and -0.089 for the 14 mg dose of teriflunomide ($p = 0.0003$). (See Table 21) According to the sponsor in the 1726/2001 trial the BOD difference between placebo and teriflunomide groups did not reach significance for the 7 mg

teriflunomide group ($p = 0.059$), but did reach significance for the 14 mg teriflunomide group ($p = 0.0215$). MRI was not evaluated in the TOWER trial.

Average number of unique active lesions/scan

This was calculated as the sum of unique newly active lesions and unique persistently active lesions/ number of scans performed over the double-blind treatment period. Unique active lesions could be new T1 gadolinium enhanced lesions or new T2 non-enhanced lesions or enlarging lesions. Both doses of teriflunomide had a significant treatment effect over placebo in the TEMSO trial with duration of 108 weeks as well as in the 1726/2001 trial with duration of 36 weeks. In the TEMSO trial the adjusted unique active/lesions/scan was 2.463 for placebo, 1.288 for teriflunomide 7 mg and 0.754 for teriflunomide 14 mg. Both doses had robust findings with a reduction of relative risk of such lesions of 69.4% on the 14 mg dose and 47.7% on the 7 mg dose. In the phase 2 trial, 1726/2001, the findings were statistically significant for both doses of teriflunomide, but robust for the 14 mg dose. The average number of unique lesions was 2.69 for placebo, 1.06 for 7 mg ($p = 0.0234$) and 0.98 for 14 mg ($p = 0.0052$).

Total number of gadolinium-enhanced T1 lesions/MRI scan

Gadolinium-enhanced T1 lesions are thought to be a marker of acute inflammatory changes due to the breakdown of the blood-brain barrier that takes place when disease is active and this MRI marker often correlates with relapse activity or short-term disease activity. The cumulative number of Gd-enhancing T1 lesions at each post-baseline visit up to week 108 was calculated and divided by the number of scans in the TEMSO trial. As would be expected given the treatment effect noted on ARR, the adjusted total number of gadolinium-enhanced T1 lesions was significantly reduced with both doses of teriflunomide at 108 weeks, but greatest with the 14 mg dose. In the 1726/2001 trial the greatest effect was seen with the 14 mg dose of teriflunomide.

Volume of T1 hypointense lesions (black holes)

Black holes are thought to indicate irreversible axonal loss, gliosis and loss of intracellular matrix. As the results also had a skew distribution the values were transformed and represent the change from baseline to week 108 in cubic root transformed volume. Only the 14 mg dose of teriflunomide had a significant effect on this measure in the TEMSO trial.

Volume of T2 lesions

Both doses of teriflunomide were shown to have a treatment effect, but the effect of 14 mg was more robust than that of 7 mg teriflunomide in the TEMSO trial.

Volume of White matter

There was a significant treatment effect of the 14 mg dose of teriflunomide but not of the 7 mg dose in the TEMSO trial according to the sponsor.

Other clinical endpoints

Time to First Relapse

Although this was a tertiary endpoint, this is a common one that is used to judge a drug's effectiveness and it was evaluated in the TEMSO trial.. This variable was analyzed by using a log-rank test and an estimate was made of the subjects relapse-free at week 108. This finding demonstrated efficacy for both doses, but showed a dose effect with more robust findings of the 14 mg dose.

6.7 Subpopulations

The effect of both doses of teriflunomide was investigated in multiple subpopulations in the TEMSO trial. Age, gender, region, type of MS and previous MS treatment were reanalyzed by the agency statistician who confirmed that there was a treatment effect for ARR in all but those with progressive disease on the 14 mg dose although a trend was noted on the 7 mg dose. Whereas those who had RRMS had an adjusted ARR of 0.371 (nominal p value 0.0005) on 7 mg and ARR of 0.355 (nominal p value of 0.0002) on 14 mg, those with a progressive form of MS had an adjusted ARR of 0.305 (nominal p value = 0.2096) on 7 mg and 0.471 (nominal p value = 0.9708) on 14 mg and 0.478 on placebo. It is noted that those with progressive forms of MS represented only 8.6% of the subjects in the trial, and specifically those on 14 mg represented only 26 out of the 1088 randomized subjects, so this descriptive finding is uninterpretable. The TOWER study when complete will not be helpful in further evaluating this group as only 2.6% of the subjects in that trial of 1096 randomized subjects have one of the progressive forms of MS. A higher overall ARR was seen in those under age 38 than in those older across all treatment arms and in those previously treated with immunomodulators for MS as would be expected based on the literature. Relapse rates in the Americas were also lower across treatment groups compared with other regions possibly related to the fact that they were slightly older (See Table 9) or to an unknown factor.

An analysis was also done of subpopulations for the secondary endpoint, time to sustained disability progression. This also showed a treatment effect for the various subgroups analyzed with the exception of those in the Americas. Compared with Eastern Europe and Western Europe, subjects in the Americas had less treatment effect on disability progression with both doses of teriflunomide. The agency statistician confirmed this and demonstrated that there was no baseline imbalance in EDSS that would account for this finding. (See Table 20) Those in the Americas had on average no increase in EDSS scores over time on placebo but did on both doses of teriflunomide. The average number of days before progression was longer for the group on the 14 mg dose than the 7 mg dose as confirmed by the agency statistician.

Those from the Americas were heavily represented by those from Canada and also Chile where the practice of medicine may be different from the United States. Baseline demographic data revealed this population to be a bit older, slightly more Hispanic, and

with higher weight and BMI than the general population, and it is unknown which, if any, of these factors may have played a role in the differences seen.

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Initially dosing with teriflunomide was based on preferred dosing of leflunomide used in the treatment of rheumatoid arthritis. Leflunomide is rapidly metabolized in vivo during first pass metabolism to the active metabolite, teriflunomide. It was found that when a single dose of 20 mg of leflunomide was compared to a single dose of 20 mg of teriflunomide the relative bioavailability of leflunomide was 70% that of teriflunomide. Hence the 20 mg effective dose of leflunomide for rheumatoid arthritis would be the equivalent of the 14 mg dose of teriflunomide and the 10 mg dose of leflunomide would be the equivalent of the 7 mg dose of teriflunomide. Ultimately these were the doses used in 12 completed studies of healthy adults and those with impaired hepatic function and the same doses were then used in phase 1, 2 and 3 trials in MS subjects.

Both the 7 mg and 14 mg dose either trended positive or had statistically significant results for all of the primary and main secondary endpoints of the pivotal trial. Although both doses appeared to have equally significant benefit in terms of lowering the relapse rate, the higher 14 mg dose appeared to have greater effectiveness (greater statistical significance) in reducing disability progression and limiting the MRI findings typically seen in MS. Specifically there were a reduced number of T1-Gd lesions/scan and a reduced BOD and volume of hypointense T1 lesions found in those on the 14 mg dose compared with those on the 7 mg dose. At the time of the filing of this NDA the second pivotal trial was as yet incomplete as were some of the long term extension trials. Based on the data submitted, there was no compelling reason to consider approving a 7 mg dose, and only an approval for the 14 mg dose is being sought.

According to the sponsor a PK/PD analysis was done using trough teriflunomide plasma levels after eight weeks of treatment and the efficacy results from the TEMSO trial. There did not appear to be a relationship between the mean teriflunomide concentration and either the ARR or the BOD measurement at week 108. There did appear to be a relationship between concentration level and risk of disability progression where there was a statistically significant reduction in the risk for disability progression sustained for 12 weeks on the higher dose of 14 mg/day compared with 7 mg/day. Specifically the predicted probability for a MS patient, without any active MS lesions at baseline, to be free of active lesions was 13.2% and 28.4% higher for 7 mg and 14 mg, respectively, compared to placebo. The probability for a MS patient, with at least one active MS lesion at baseline, to be free of active lesions at 108 weeks was 32.2% and 85.5% higher for 7 mg and 14 mg respectively.

6.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The two year TEMSO trial was followed by an extension trial, Protocol 6050, for a total period of approximately 5 years of treatment. The initial trial was a double-blind trial with three treatment arms: placebo, 7 mg of teriflunomide and 14 mg of teriflunomide. After 108 weeks of treatment those on teriflunomide remained on the same dose that they had been on during the double-blind period, but those on placebo were switched to active treatment. The later subjects were re-randomized to either 7 mg or 14 mg of teriflunomide. This meant that some patients had two years of active treatment and others had approximately five years of active treatment with either 7 mg or 14 mg of teriflunomide. According to the sponsor, after 5 years of treatment the risk of disability progression was numerically lower in both groups who received continuous treatment with either 7 mg of teriflunomide or 14 mg of teriflunomide and was greater in those who had received active treatment for a shorter period of time, namely those treated with placebo prior to the extension phase. There was no statistically significant difference in disability progression between those treated with the 7 mg/7mg dose or the 14 mg/14 mg dose for disability progression. This suggests that there was persistence of efficacy for preventing disability progression on teriflunomide.

The adjusted ARR was low in all treatment groups. Specifically the adjusted ARR (95% CI) was 0.251 (0.188 to 0.334) in the placebo/7 mg group, it was 0.234 (0.186 to 0.295) in the 7 mg/7 mg group, it was 0.182 (0.130 to 0.254) in the placebo/14 mg, and it was 0.206 (0.163 to 0.261) in the 14 mg/14 mg group. Since the adjusted ARR was low in all treatment groups this suggested that there was a persistence of effect.

6.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Please see Review of Dr. Lordes Villalba and Dr. Evelyn Mentari.

8 Postmarket Experience

No postmarketing experience exists for this product.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling recommendations are pending at the time of this review.

9.3 Advisory Committee Meeting

Not applicable.

9.4 Pediatric Review Committee (PeRC) Meeting

A meeting with PeRC was held on Wednesday May 2, 2012 to discuss the pediatric studies that would be required to fulfill PREA. The committee agreed that a waiver would be granted to those from birth to age (b) (4) because there are few patients of this age with MS found worldwide and this would make studies impossible or highly impractical to perform. The committee also recommended a deferral for those ages 10 to 17 years until after an acceptable experimental design is determined and a pediatric written request is issued. (b) (4)

The most recent recommendation of the Agency is that the required study should be either a two year placebo-controlled trial with time to first relapse as an endpoint or a study with an open-label active comparator with an MRI endpoint at 6 months. Either study design should be designed to show the superiority of teriflunomide over its comparator in order to provide meaningful information about the treatment of MS in the pediatric population. The protocol should be submitted to the FDA by December 28, 2012 and completed by November 3, 2016. A final study report is required by June 17, 2017.

9.5 Addendum

Clinical Inspection Summary

A clinical Inspection Summary, dated August 9, 2012 has been provided by Antoine, El-Hage, PhD, of the Division of Scientific Investigations, Office of Compliance at the Center for Drug Evaluation and Research. His summary states that data from all sites were considered reliable and supported this application. Although there were some minor regulatory violations noted in the inspections of the Canadian site and French site, they were not felt to critically impact primary efficacy or safety data.

In addition Dr. El-Hage provided specific information about the remaining French site. At this site 38 subjects were screened, 36 were randomized into the study and 29 completed the study. Some deviations from regulatory standards were noted, but none to significantly impact the outcome of the data. The major finding was that the investigator did not save all the source documents; but it was noted that the protocol was vague in its instructions to investigators in this regard. Despite this, most of the source documents regarding primary and secondary endpoints were retained. One exception was that 7 subjects were missing a few EDSS score confirmations in the source documents, but only for a few visits. It was noted that a single subject had his EDSS score changed from a higher to a lower score without explanation in the source documents. Additionally some of the CRFs lacked the signature of the qualifying neurologist, but it was noted that no signature block was provided.

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/s/

JODY E GREEN
09/11/2012

WILLIAM H Dunn
09/11/2012

CLINICAL REVIEW

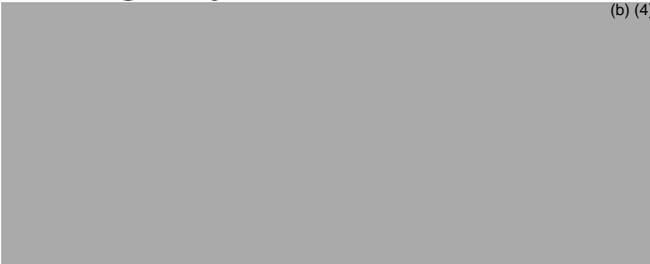
Application Type	NDA
Application Number(s)	202992
Priority or Standard	Standard
Submit Date(s)	August 12, 2011.
Received Date(s)	August 12, 2011. Major amendment April 13, 2012
PDUFA Goal Date	Sept 12, 2012
Division / Office	Division of Neurology Products (DNP) Office of New Drugs
Reviewer Name(s)	Lourdes Villalba, M.D. Evelyn Mentari, M.D., M.S.
Review Completion Date	JULY 12, 2012
Established Name	Teriflunomide
(Proposed) Trade Name	Aubagio
Therapeutic Class	Pyrimidine synthesis inhibitor
Applicant	Sanofi-Aventis
Formulation(s)	Oral tablet
Dosing Regimen	14 mg/day
Indication(s)	 (b) (4)
Intended Population(s)	Adults

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Drs. Lourdes Villalba and Evelyn Mentari

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant proposes marketing teriflunomide 14 mg a day, for the treatment of multiple sclerosis (MS). Teriflunomide is the active metabolite of leflunomide (ARAVA®), a drug approved for the treatment of rheumatoid arthritis since 1998. The major toxicities associated with teriflunomide, which have been described with leflunomide, are liver toxicity (with the potential for liver failure), bone marrow toxicity (with the potential risk for long term immunosuppression, opportunistic infections and malignancies) and potential for fetal harm. Other toxicities observed with the teriflunomide in this application include hypertension, alopecia, peripheral neuropathy and weight loss. Laboratory evaluations showed decreased serum uric acid and phosphorus levels, associated with increased urinary excretion.

The data reviewed in this application has identified a new signal for reversible, acute renal failure, which had not been previously identified with leflunomide but has been described with uricosuric agents, particularly in association with dehydration.

There were five CV deaths (including three sudden deaths, one fatal myocardial infarction and one cardiorespiratory failure), three non-fatal MI and one resuscitated cardiac arrest among approximately 2600 patients exposed to teriflunomide 7 and 14 mg daily in phase 2/3 studies in this database, all in extension studies. No cardiovascular signal has been previously identified with leflunomide. Sudden death has been reported in patients with multiple sclerosis involving the brainstem. However, a causal relationship between teriflunomide and CV death can not be ruled out, perhaps through long term effects on blood pressure and/or acute electrolyte imbalance.

Teriflunomide has a long half life owed to enterohepatic circulation. Plasma levels can be detected for up to 2 years after drug discontinuation in patients who do not undergo washout. Washout with cholestyramine or activated charcoal allows rapid elimination of the drug, if needed or desired.

Overall, there are no safety concerns that preclude the approval of teriflunomide in patients with MS. Adverse events associated with teriflunomide could be addressed through appropriate labeling (which should include WARNINGS AND PRECAUTIONS similar to those of leflunomide), and continuous evaluation through postmarketing studies. For review of efficacy and risk/benefit assessment, please see reviews by Drs. Jody Green and Bill Dunn.

1.2 Risk Benefit Assessment

Please see reviews by Drs. Green and Dunn.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine pharmacovigilance.

Continue to monitor adverse events of special interest that were evaluated in this database, including those for which an increased risk could not be ruled out: pancreatic toxicity, convulsions, hemorrhage, thromboses.

1.4 Recommendations for Postmarket Requirements and Commitments

If approved, I recommend the following:

1.4.1. Given the occurrence of five cardiovascular deaths, including three sudden deaths, in the teriflunomide database, an observational study to evaluate CV death and arrhythmia should be conducted in patients who have received leflunomide (teriflunomide's parent drug, approved in patients with rheumatoid arthritis).

1.4.2. Given the known effect of teriflunomide on increasing urine excretion of uric acid and phosphorus, and the newly identified risk of transient acute renal failure, the following should be conducted

- Systematic collection of additional information in subjects with reported acute renal failure or elevated serum creatinine $\geq 100\%$ of baseline in ongoing studies and postmarketing cases
- Comprehensive evaluation of cases of loin or flank pain in ongoing studies and postmarketing setting

1.4.3. In view of 1.4.1 and 1.4.2 above, the lack of information on serum bicarbonate and magnesium in teriflunomide studies, and the limited information on calcium levels in the teriflunomide database, the following should be conducted:

- Evaluation of the effect of teriflunomide on bicarbonate, magnesium and calcium levels.

1.4.4. An updated Integrated Summary of Safety pooling the TOWER completed study with Study 6049.

2 Introduction and Regulatory Background

2.1 Product Information

Teriflunomide (HMR1726, also referred to as Teri in this review) is an immunomodulator with anti-proliferative and anti-inflammatory activity. It is a potent, selective, and reversible inhibitor of dihydroorotate-dehydrogenase (DHO-DH), a mitochondrial enzyme involved in the de novo synthesis of pyrimidines for deoxyribonucleic acid (DNA) replication. In vitro, Teriflunomide inhibits T cell proliferation, DNA and ribonucleic acid (RNA) synthesis, and expression of cell surface and nuclear antigens involved in T-cell activation and proliferation. In preclinical studies

of experimental autoimmune encephalomyelitis, Teriflunomide delayed disease onset, reduced relapses, and improved neurological findings. Teriflunomide is the active predominant metabolite of leflunomide (Arava®), which has been approved worldwide since 1998 for oral treatment of rheumatoid arthritis.

Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative disorder of the central nervous system (CNS), characterized by inflammation, demyelination, and oligodendrocyte and neuronal loss. MS affects an estimated 2.5 million individuals worldwide. Treatment strategies in MS usually involve symptom management and use of disease modifying therapies to reduce the frequency of relapses and to slow the accumulation of disability. Teriflunomide has been developed for the treatment of relapsing forms of MS, the most frequent clinical presentation of the disease.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following table summarizes available treatments for relapsing forms of multiple sclerosis.

Table 1. Disease-modifying medications approved for use in relapsing forms of multiple sclerosis

Brand Name	Generic Name	Year of FDA Approval	Frequency/Route of Delivery/Usual Dose
Avonex	Interferon beta-1a	1996	Once weekly; intramuscular injection; 30 mcg
Betaseron	Interferon beta-1b	1993	Every other day; subcutaneous injection; 250 mcg
Copaxone	Glatiramer acetate	1996	Every day; subcutaneous injection; 20 mg
Extavia	Interferon beta-1b	2009	Every other day; subcutaneous injection; 250 mcg
Novantrone	Mitoxantrone*	2000	Four times per year; intravenous infusion in a medical facility; lifetime cumulative dose limit of approximately 8-12 doses over 2-3 years (140 mg/m ²)
Rebif	Interferon beta-1a	2002	Three times per week; subcutaneous injection; 44 mcg
Tysabri	Natalizumab	2006	Every four weeks ; intravenous infusion in a registered infusion facility; 300 mg
Gilenya	Fingolimod	2010	Once daily; oral administration; 0.5 mg

*Available as a generic drug as of 2006

2.3 Availability of Proposed Active Ingredient in the United States

Please see Dr. Green's review.

2.4 Important Safety Issues with Consideration to Related Drugs

Safety issues included as Boxed Warnings, Warnings, and/or Precautions in the Prescribing Information for disease-modifying medications approved for use in relapsing forms of MS are summarized below.

Table 2. Safety issues for disease-modifying medications approved for use in relapsing forms of multiple sclerosis

Brand Name/ Generic Name	Safety Issues
Avonex/ Interferon beta-1a	<p>Warnings:</p> <ul style="list-style-type: none"> • Depression and suicide • Anaphylaxis (rare) and other allergic reactions • Decreased peripheral blood counts in all cell lines, including rare pancytopenia and thrombocytopenia • Severe hepatic injury (rare), including hepatic failure, and asymptomatic transaminase elevation • Albumin (a derivative of human blood) in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases or Creutzfeldt-Jakob disease (CJD) <p>Precautions:</p> <ul style="list-style-type: none"> • Seizures – an increased rate of seizures was seen in Avonex-treated subjects in 2 placebo-controlled trials in MS • Cardiomyopathy and congestive heart failure – post-marketing cases were reported in patients without known predisposition to these events • Autoimmune disorders – post-marketing cases of disorders including idiopathic thrombocytopenia, hyper- and hypothyroidism, and autoimmune hepatitis have been reported
Betaseron/ Interferon beta-1b	<p>Warnings:</p> <ul style="list-style-type: none"> • Depression and suicide • Injection site necrosis reported in 4% of patients in controlled clinical trials • Anaphylaxis (rare) and other allergic reactions • Albumin (a derivative of human blood) in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases or Creutzfeldt-Jakob disease (CJD) <p>Precautions:</p> <ul style="list-style-type: none"> • Flu-like symptoms • Abortifacient potential
Copaxone/ Glatiramer acetate	<p>Warnings and Precautions:</p> <ul style="list-style-type: none"> • Immediate post-injection reaction in about 16% of exposed placebo-trial patients (compared to 4% of placebo-treated patients) with symptoms that included at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. These symptoms were generally transient and did not require treatment. • Chest pain (transient) • Lipoatrophy and skin necrosis at injection sites • Potential effects on immune response
Extavia/ Interferon beta-1b	<p>Warnings and Precautions:</p> <ul style="list-style-type: none"> • Depression and suicide • Injection site necrosis reported in 4% of patients in controlled clinical trials • Injection site reactions (injection site inflammation, pain, hypersensitivity, mass, or edema) in 78% of controlled clinical trial subjects • Anaphylaxis (rare) and other allergic reactions • Flu-like symptoms • Leukopenia • Hepatic enzyme elevation • Laboratory tests – in addition to tests normally required for monitoring patients with

Brand Name/ Generic Name	Safety Issues
	<p>MS, complete blood count and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests are recommended at regular intervals. Thyroid function tests are recommended every 6 months in patients with thyroid dysfunction.</p> <p>Albumin (a derivative of human blood) in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases or Creutzfeldt-Jakob disease (CJD)</p>
Novantrone/ Mitoxantrone*	<p>Boxed Warnings:</p> <ul style="list-style-type: none"> • May only be given into a freely flowing intravenous infusion. Severe injury may occur if there is extravasation during administration or if it is given subcutaneously, intramuscularly, intra-arterially, or intrathecally. • Bone marrow suppression, primarily nonlymphocytic leukopenia • Cardiotoxicity – potentially fatal congestive heart failure may occur during or after termination of therapy • Secondary acute myelogenous leukemia <p>Warnings:</p> <ul style="list-style-type: none"> • Safety in patients with hepatic insufficiency has not been established • May cause fetal harm when given to pregnant women
Rebif/ Interferon beta-1a	<p>Warnings:</p> <ul style="list-style-type: none"> • Depression and suicide • Severe hepatic injury (rare), including hepatic failure, and asymptomatic transaminase elevation • Anaphylaxis (rare) and other allergic reactions • Albumin (a derivative of human blood) in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases or Creutzfeldt-Jakob disease (CJD) <p>Precautions:</p> <ul style="list-style-type: none"> • Seizures – an increased rate of seizures has been seen with beta-interferons • Leukopenia • Worsening thyroid abnormalities • Possible abortifacient effects similar to other beta-interferons
Tysabri/ Natalizumab	<p>Boxed Warning:</p> <ul style="list-style-type: none"> • Increased risk of Progressive Multifocal Leukoencephalopathy (PML) • Available only under a special restricted distribution program called the TOUCH Prescribing Program <p>Warnings and Precautions:</p> <ul style="list-style-type: none"> • Hypersensitivity reactions (including anaphylaxis) occurred at an incidence of <1% . Hypersensitivity reactions were more common in patients with antibodies to Tysabri. • Immune system effects may increase the risk for infections. • Hepatotoxicity – clinically significant liver injury has been reported in the post-marketing setting. • Laboratory test abnormalities – Tysabri induces increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells.
Gilenya/ Fingolimod	<p>Warnings and Precautions:</p> <ul style="list-style-type: none"> • Bradyarrhythmia and atrioventricular blocks following the first dose. • Dose-dependent reduction in peripheral lymphocyte count may increase risk of infections. • Macular edema • Respiratory Effects – dose-dependent reductions in forced expiratory volume over 1

Brand Name/ Generic Name	Safety Issues
	second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) <ul style="list-style-type: none"> • Elevation of liver enzymes • Fetal harm - women of childbearing potential should use effective contraception during and for 2 months after stopping Gilenya treatment • Increase in blood pressure

In summary, several drugs/biologic agents are currently approved for the treatment of MS. Each agent has a unique safety profile, although, in general, all of them are associated with potential increase in the risk of infections and malignancies, and some are associated with fetal harm. They are also associated with some degree of hepatotoxicity.

Teriflunomide is the active metabolite of leflunomide. Major safety concerns with leflunomide are liver toxicity, teratogenicity, potential for immunosuppression, skin reactions and peripheral neuropathy. The following are excerpts from the leflunomide (ARAVA®) label:

- BOXED WARNING

CONTRAINDICATIONS AND WARNINGS (bolded and boxed)

Pregnancy
Pregnancy must be excluded before the start of treatment with ARAVA. ARAVA is contraindicated in pregnant women, or women of childbearing potential who are not using reliable contraception. (See CONTRAINDICATIONS and WARNINGS.) Pregnancy must be avoided during ARAVA treatment or prior to the completion of the drug elimination procedure after ARAVA treatment.

Hepatotoxicity
Severe liver injury, including fatal liver failure, has been reported in some patients treated with ARAVA. Patients with pre-existing acute or chronic liver disease, or those with serum alanine aminotransferase (ALT) >2xULN before initiating treatment, should not be treated with ARAVA. Use caution when ARAVA is given with other potentially hepatotoxic drugs.

Monitoring of ALT levels is recommended at least monthly for six months after starting ARAVA, and thereafter every 6-8 weeks. If ALT elevation > 3 fold ULN occurs, interrupt ARAVA therapy while investigating the probable cause of the ALT elevation by close observation and additional tests. If likely leflunomide-induced, start cholestyramine washout and monitor liver tests weekly until normalized. If leflunomide-induced liver injury is unlikely because some other probable cause has been found, resumption of ARAVA therapy may be considered. (SEE WARNINGS – HEPATOTOXICITY).

- **CONTRAINDICATIONS (summarized)**

- Known hypersensitivity to leflunomide or any of the other components of ARAVA.
- Women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

- **WARNINGS**

Hepatotoxicity

Severe liver injury, including fatal liver failure, has been reported in some patients treated with ARAVA. Patients with pre-existing acute or chronic liver disease, or those with serum alanine aminotransferase (ALT) >2xULN before initiating treatment, should not be treated with ARAVA. Use caution when ARAVA is given with other potentially hepatotoxic drugs. Monitoring of ALT levels is recommended at least monthly for six months after starting ARAVA, and thereafter every 6-8 weeks. If ALT elevation > 3 fold ULN occurs, interrupt ARAVA therapy while investigating the probable cause of the ALT elevation by close observation and additional tests. If likely leflunomide-induced, start cholestyramine washout and monitor liver tests weekly until normalized (see **PRECAUTIONS - General - Need for Drug Elimination**). If leflunomide-induced liver injury is unlikely because some other probable cause has been found, resumption of ARAVA therapy may be considered. In addition, if ARAVA and methotrexate are given concomitantly, ACR guidelines for monitoring methotrexate liver toxicity must be followed with ALT, AST, and serum albumin testing monthly.

In clinical trials, ARAVA treatment as monotherapy or in combination with methotrexate was associated with elevations of liver enzymes, primarily ALT and AST, in a significant number of patients; these effects were generally reversible. Most transaminase elevations were mild (≤ 2 -fold ULN) and usually resolved while continuing treatment. Marked elevations (>3 -fold ULN) occurred infrequently and reversed with dose reduction or discontinuation of treatment. Table 8 shows liver enzyme elevations seen with monthly monitoring in clinical trials US301 and MN301. It was notable that the absence of folate use in MN302 was associated with a considerably greater incidence of liver enzyme elevation on methotrexate. (*Table not shown*)

In a 6 month study of 263 patients with persistent active rheumatoid arthritis despite methotrexate therapy, and with normal LFTs, leflunomide was added to a group of 130 patients starting at 10 mg per day and increased to 20 mg as needed. An increase in ALT greater than or equal to three times the ULN was observed in 3.8% of patients compared to 0.8% in 133 patients continued on methotrexate with placebo added.

Immunosuppression Potential/Bone Marrow Suppression

ARAVA is not recommended for patients with severe immunodeficiency, bone marrow dysplasia, or severe, uncontrolled infections. In the event that a serious infection occurs, it may be necessary to interrupt therapy with ARAVA and administer cholestyramine or charcoal (see **PRECAUTIONS – General – Need for Drug Elimination**). Medications

like leflunomide that have immunosuppression potential may cause patients to be more susceptible to infections, including opportunistic infections, especially *Pneumocystis jiroveci* pneumonia, tuberculosis (including extra-pulmonary tuberculosis), and aspergillosis. Severe infections including sepsis, which may be fatal, have been reported in patients receiving ARAVA, especially *Pneumocystis jiroveci* pneumonia and aspergillosis. Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness which, in addition to rheumatoid disease, may predispose patients to infection.¹

There have been rare reports of pancytopenia, agranulocytosis and thrombocytopenia in patients receiving ARAVA alone. These events have been reported most frequently in patients who received concomitant treatment with methotrexate or other immunosuppressive agents, or who had recently discontinued these therapies; in some cases, patients had a prior history of a significant hematologic abnormality. Patients taking ARAVA should have platelet, white blood cell count and hemoglobin or hematocrit monitored at baseline and monthly for six months following initiation of therapy and every 6- to 8 weeks thereafter. If used with concomitant methotrexate and/or other potential immunosuppressive agents, chronic monitoring should be monthly. If evidence of bone marrow suppression occurs in a patient taking ARAVA, treatment with ARAVA should be stopped, and cholestyramine or charcoal should be used to reduce the plasma concentration of leflunomide active metabolite (see **PRECAUTIONS – General – Need for Drug Elimination**).

In any situation in which the decision is made to switch from ARAVA to another anti-rheumatic agent with a known potential for hematologic suppression, it would be prudent to monitor for hematologic toxicity, because there will be overlap of systemic exposure to both compounds. ARAVA washout with cholestyramine or charcoal may decrease this risk, but also may induce disease worsening if the patient had been responding to ARAVA treatment.

Skin Reactions

Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients receiving ARAVA. If a patient taking ARAVA develops any of these conditions, ARAVA therapy should be stopped, and a drug elimination procedure is recommended. (See **PRECAUTIONS - General - Need for Drug Elimination**).

Malignancy

The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppression medications. There is a potential for immunosuppression with ARAVA. No apparent increase in the incidence of malignancies and lymphoproliferative disorders was reported in the clinical trials of ARAVA, but larger and longer-term studies would be needed to determine whether there is an increased risk of malignancy or lymphoproliferative disorders with ARAVA.

¹ There have been 2 published reports of PML in patients treated with leflunomide: 1 report in a patient with RA receiving concomitant treatment with azathioprine and 1 report in a patient receiving extensive immunosuppression prior to leflunomide initiation for unapproved indication (systemic lupus erythematosus).

Use in Women of Childbearing Potential

There are no adequate and well-controlled studies evaluating ARAVA in pregnant women. However, based on animal studies, leflunomide may increase the risk of fetal death or teratogenic effects when administered to a pregnant woman (see **CONTRAINDICATIONS**). Women of childbearing potential must not be started on ARAVA until pregnancy is excluded and it has been confirmed that they are using reliable contraception. Before starting treatment with ARAVA, patients must be fully counseled on the potential for serious risk to the fetus.

The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing and, if positive, the physician and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of the active metabolite by instituting the drug elimination procedure described below at the first delay of menses may decrease the risk to the fetus from ARAVA.

Upon discontinuing ARAVA, it is recommended that all women of childbearing potential undergo the drug elimination procedure described below. Women receiving ARAVA treatment who wish to become pregnant must discontinue ARAVA and undergo the drug elimination procedure described below which includes verification of M1 metabolite plasma levels less than 0.02 mg/L (0.02 µg/mL). Human plasma levels of the active metabolite (M1) less than 0.02 mg/L (0.02 µg/mL) are expected to have minimal risk based on available animal data.

Peripheral Neuropathy

Cases of peripheral neuropathy have been reported in patients receiving ARAVA. Most patients recovered after discontinuation of ARAVA, but some patients had persistent symptoms. Age older than 60 years, concomitant neurotoxic medications, and diabetes may increase the risk for peripheral neuropathy. If a patient taking ARAVA develops a peripheral neuropathy, consider discontinuing ARAVA therapy and performing the drug elimination procedure (see WARNINGS – Drug Elimination Procedure).

Drug Elimination Procedure

The following drug elimination procedure is recommended to achieve non-detectable plasma levels (less than 0.02 mg/L or 0.02 µg/mL) after stopping treatment with ARAVA:

- 1) Administer cholestyramine 8 grams 3 times daily for 11 days. (The 11 days do not need to be consecutive unless there is a need to lower the plasma level rapidly.)
- 2) Verify plasma levels less than 0.02 mg/L (0.02 µg/mL) by two separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L, additional cholestyramine treatment should be considered.

Without the drug elimination procedure, it may take up to 2 years to reach plasma **M1 metabolite**² levels less than 0.02 mg/L due to individual variation in drug clearance.

- **PRECAUTIONS**

General

Need for Drug Elimination

The active metabolite of leflunomide is eliminated slowly from the plasma. In instances of any serious toxicity from ARAVA, including hypersensitivity, use of a drug elimination procedure as described in this section is highly recommended to reduce the drug concentration more rapidly after stopping ARAVA therapy. If hypersensitivity is the suspected clinical mechanism, more prolonged cholestyramine or charcoal administration may be necessary to achieve rapid and sufficient clearance. The duration may be modified based on the clinical status of the patient.

Cholestyramine given orally at a dose of 8 g three times a day for 24 hours to three healthy volunteers decreased plasma levels of M1 by approximately 40% in 24 hours and by 49 to 65% in 48 hours.

Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50 g every 6 hours for 24 hours) has been shown to reduce plasma concentrations of the active metabolite, M1, by 37% in 24 hours and by 48% in 48 hours.

These drug elimination procedures may be repeated if clinically necessary.

Respiratory

Interstitial lung disease has been reported during treatment with leflunomide and has been associated with fatal outcomes (see **ADVERSE REACTIONS**). The risk of its occurrence is increased in patients with a history of interstitial lung disease. Interstitial lung disease is a potentially fatal disorder, which may occur acutely at any time during therapy and has a variable clinical presentation. New onset or worsening pulmonary symptoms, such as cough and dyspnea, with or without associated fever, may be a reason for discontinuation of the therapy and for further investigation as appropriate. If discontinuation of the drug is necessary, initiation of wash-out procedures should be considered. (See **WARNINGS – Drug Elimination Procedure**).³

Tuberculosis Reactivation

Prior to initiating immunomodulatory therapies, including Arava, patients should be screened for latent tuberculosis infection with a tuberculin skin test. Arava has not been studied in patients with a positive tuberculosis screen, and the safety of Arava in individuals with latent tuberculosis infection is unknown. Patients testing positive in

² The M1 metabolite of leflunomide is teriflunomide.

³ In a nested case-control study, the adjusted rate ratio for ILD associated with leflunomide as monotherapy was 1.9 (95% confidence interval [CI]: 1.1 to 3.6), although it is unclear if this was related to channeling bias. (Suissa et al, Arthritis and Rheumatism, 2006.)

tuberculosis screening should be treated by standard medical practice prior to therapy with ARAVA.

Renal Insufficiency

Single dose studies in dialysis patients show a doubling of the free fraction of M1 in plasma. There is no clinical experience in the use of ARAVA in patients with renal impairment. Caution should be used when administering this drug in this population.

Vaccinations

No clinical data are available on the efficacy and safety of vaccinations during ARAVA treatment. Vaccination with live vaccines is, however, not recommended. The long half-life of ARAVA should be considered when contemplating administration of a live vaccine after stopping ARAVA.

Blood Pressure Monitoring

Blood pressure should be checked before start of leflunomide treatment and periodically thereafter.

As noted above, the ARAVA label contains several WARNINGS AND PRECAUTIONS, and a CONTRAINDICATION during pregnancy. Although some of the safety issues identified with leflunomide may not be evident in the teriflunomide database, it is anticipated that the labeling regarding the safety profile of teriflunomide will be similar to that of ARAVA.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Milestones during drug development are summarized below

- 3/30/2004 - Investigational New Drug application (IND 67,476)
- 11/12/2004 - End of Phase 2 meeting
- 6/27/2006 -Clinical Hold because of concerns of genotoxicity and safety monitoring (bone marrow toxicity/immunosuppression, hepatotoxicity, pulmonary function, pancreatic toxicity and peripheral neuropathy).
- 1/18/2007 - Concerns addressed. Clinical Hold was lifted.
- 10/8/2010 – Sponsor proposed to submit NDA for the treatment of patients with relapsing forms of MS (b) (4) based on purported robust results of one phase 3 and one phase 2 monotherapy study and supportive data from adjunctive studies, while a second phase 3 study (TOWER) is ongoing. An interim analysis of TOWER would be submitted with a data cut-off at the end of February 2011. Patients in TOWER who have been on treatment for 3 months at a minimum would be included, which would number approximately 1080 relapsing MS patients (360 patients on each of the teriflunomide 7 and 14 mg groups). This proposal was accepted by DNP on 12/20/2010.
- 3/28/2011 - Pre-NDA meeting
- 8/12/2011 – NDA submission – Original PDUFA date was 8/12/2012

2.6 Other Relevant Background Information

For additional information on pre-submission regulatory activities, the reader is referred to Dr. Jody Green's clinical review of efficacy.

A Major Amendment related to information on renal safety was submitted on April 13, 2012. New PDUFA date: September 12, 2012.

3 Ethics and Good Clinical Practices

Please see review by Dr. Green.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The reader is referred to Dr. Prafull Shiromani's discipline review.

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

The following information has been excerpted from Section 1.4 of the applicant's ISS, "Potential safety issues related to non-clinical data." For a detailed FDA review of the full preclinical program the reader is referred to Dr. Richard Houghtling's review of non-clinical data.

In general, the repeat-dose toxicity of teriflunomide was a reflection of the pharmacologic activity (i.e., inhibition of DNA synthesis). Primary adverse events were seen in bone marrow, lymphoid organs (atrophy), oral cavity / GI tract (epithelial degenerative changes, erosions, ulcers, bleeding), and reproductive organs. Anemia, leukopenia, lymphopenia, decreased platelet counts, effects on the immune system (decreased lymphocytes, white blood cells [WBC], CD3/CD4, CD3/CD8, B cells, IgM and IgG), and secondary infections were related to the effects on the bone marrow and/or lymphoid organs. Hemorrhages in multiple organs (sometimes lethal) occurred secondary to reduced platelet counts. Convulsions were observed in the 3-month toxicity study in 1 high dose animal and were thought to be secondary to a submeningeal hemorrhage. No emboli or thrombi were observed preclinically. The pancreas was identified as a target organ of toxicity in the dog. The human exposure at the target dose of 14 mg teriflunomide is greater than the systemic exposure at the no-observed-adverse-effect-level (NOAEL) in rats and dogs.

No hyperplastic or neoplastic findings were observed in 2-year oral carcinogenicity studies in rats and mice at the highest dosage administered. A decrease in survival was observed in the mid

and high dose male rats and in the high dose mice of both sexes related to non-proliferative findings (bone marrow, lymphoid and thymus atrophy; skin and GI ulcer/inflammation). Teriflunomide is embryo-toxic and teratogenic in rats and rabbits when administered during the period of organogenesis. The exposure in humans at the clinical dose of 14 mg teriflunomide is greater than the exposure at the embryo-fetal NOAEL in pregnant rats and rabbits.

4.4 Clinical Pharmacology

The following information has been excerpted from the applicant's Clinical Overview, Overview of Biopharmaceutics and Overview of Clinical Pharmacology. For a detailed review of the full program the reader is referred to the Clinical Pharmacology team review.

The applicant is seeking market authorization for a film-coated immediate-release (IR) 14 mg teriflunomide tablet formulation, once a day. Various formulations have been used throughout the drug development program. Comparative bioavailability studies among these formulations were conducted and were successful (as per the applicant). A same-dose comparison between leflunomide and teriflunomide showed that the relative bioavailability of teriflunomide after ARAVA was about 70% that of teriflunomide. Therefore, 14 mg teriflunomide is equivalent to 20 mg ARAVA (the daily dose recommended for ARAVA in RA). Hence 7 and 14 mg were chosen for the teriflunomide trials.

The pharmacokinetics (PK) and pharmacodynamics (PD) of teriflunomide were assessed in 18 clinical pharmacology studies involving 232 healthy subjects exposed to a single oral dose (from 7 to 70 mg, including 6 subjects exposed to a single 10 mg intravenous [IV] administration) and 223 subjects exposed to repeated doses of teriflunomide following a suprathreshold regimen (repeated QD oral doses 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 pharmacology studies, either cholestyramine or activated charcoal was administered to accelerate the elimination of teriflunomide in all subjects.

Summary of Pharmacokinetics

Teriflunomide is highly bound to plasma proteins (mostly albumin), has a **long terminal half life (19.4 days)**, it is mostly eliminated through the bile and presents enterohepatic circulation. The PK profile of teriflunomide, as presented by Sanofi, is summarized in the following table.

Table 3. Teriflunomide pharmacokinetic characteristics

Process	Parameters	
Absorption	Steady-state Cmax [Mean, 14 mg] a	45.23 mg/mL
	Steady-state tmax [Median, 14 mg] a	1.2 hours
	Steady-state AUC0-24 [Mean, 14 mg] a	1070 mg.h/mL
	Bioavailability b	~ 100%
	Transport	BCRP c
Distribution	Binding to plasma proteins (in vitro)	99.5 to 99.7%
	Volume of distribution (IV)	11 L
Metabolism	Metabolism pathways	Primary: hydrolysis, with oxidation (minor). Secondary: oxidation, N-acetylation and sulfate conjugation
	Circulating metabolites	None
Elimination	Terminal half-life [Median, 14 mg] a	19.4 days
	Total body clearance (IV)	30.5 mL/h
		37.5% of the administered dose (61.3% after REP)
	Fecal recovery	22.6% of the administered dose (21.9% after REP)
	Urinary recovery	Mostly through biliary and direct intestinal secretion (mostly unchanged drug), leading to enterohepatic recycling due to subsequent reabsorption.
Others	Excretion	
	Time to steady-state [Median]a	~ 100 days (3.5 months)
	Accumulation (AUC0-24, 14 mg) a	~ 34-fold

AUC= area under the plasma concentration versus time curve extrapolated to infinity; AUC0-24= area under the plasma concentration from time 0 to 24 hours; BCRP=breast cancer resistant protein; Cmax= maximum plasma concentration observed; REP= rapid elimination of teriflunomide procedure (cholestyramine treatment); IV= intravenous. *a* Based on population pharmacokinetic analysis in healthy subjects and MS patients (POH0290) *b* Based on cross-study comparison (Studies 1001 and 1024). *c* No significant effect of BCRP genotypes on teriflunomide exposure was found in healthy volunteers and in patients. As a result, no significant effect on teriflunomide exposure is expected with BCRP inhibitors and inducers. Source: Table 1 of Clinical Overview (module 2.5)

The elimination of teriflunomide can be accelerated by oral administration of cholestyramine or activated charcoal, presumably by interrupting the reabsorption processes at the intestinal level. Teriflunomide concentrations measured during an 11-day procedure to accelerate teriflunomide elimination with either 4 g cholestyramine every 8 hours, 8 g cholestyramine every 8 hours, or 50 g activated charcoal every 6 hours following cessation of teriflunomide treatment have shown that these regimens were effective in accelerating teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations, with cholestyramine being faster than charcoal.

The ARAVA® label notes that without cholestyramine or charcoal it may take 2 years to get rid of the M1 metabolite (which is teriflunomide) in the WARNINGS section of labeling, and also the need for rapid elimination in some patients in the PRECAUTIONS section of labeling. The teriflunomide proposed label mentions

that the time to elimination of teriflunomide may take up to 2 years in some patients in the section (b) (4), but the washout procedure is described in the (b) (4) section of labeling.

A substantial number of patients underwent rapid elimination with cholestyramine or charcoal in the premarketing clinical trials (85% of patients who discontinued from study drug in 6049/TEMSO; 100% of subjects in clinical pharmacology studies). That is the way that adverse events were mitigated in premarketing clinical studies. Information regarding the long half life of the drug and need for washout in some patients should be in a separate section in the WARNINGS and PRECAUTIONS section of the Teriflunomide labeling, (b) (4). If rapid elimination is not clearly recommended in labeling, adverse events observed in the postmarketing setting are likely to be more severe than what was observed in premarketing trials.

5 Sources of Clinical Data

The teriflunomide clinical program was targeted at demonstrating the efficacy of teriflunomide as a disease-modifying monotherapy in the treatment of relapsing MS in patients 18 years of age and older. As a supplement to the monotherapy indication, teriflunomide is currently being investigated as adjunctive therapy to interferon-beta (IFN- β) as well as the delay to conversion to clinically definitive MS among patients who had a first episode consistent with MS.

5.1 Tables of Studies/Clinical Trials

The teriflunomide phase 2 and 3 program in MS includes five completed, double-blind (DB), randomized, placebo-controlled studies (two monotherapy studies and two adjunctive to either IFN- β or glatiramer acetate, with a single DB extension study to both adjunctive studies) and six ongoing studies. All phase 2 and 3 studies were multicenter, multinational studies.

The studies used to support the proposed indication are the two completed monotherapy studies (2001 and 6049/TEMSO).

Phase 2/3 studies, including data submitted from each study in this application are summarized in the following table.

Table 4. Summary of phase 2 & 3 studies in NDA 202-992 (Teriflunomide in MS)

Study ID Number of centers¹	Objective/Study design	Treatment	Number of subjects R², Gender: M/F³ Age: mean ± SD (range) Number per treat. group
COMPLETED STUDIES (Full study reports)			
<i>Controlled Monotherapy Clinical Studies</i>			
2001 16 centers Phase 2	Determine safety and efficacy of Teri in relapsing MS. DB, R, PC, parallel-group	Teri 7: 14 mg QD x7 d, then 7mg QD Teri 14: 28 mg QD x 7 d, then 14 mg QD Placebo - 2 tablets QD for 7 d, then 1 tablet QD <i>Duration: 36 wks</i>	R: 179. M/F: 47/132; Age: 40yrs (19 – 64) Placebo: 61 Teri 7-mg: 61 Teri 14-mg: 57
EFC6049 (TEMSO) 126 centers Phase 3	Efficacy and safety of Teri in reducing frequency of relapse/ delaying physical disability in relapsing MS. DB, R, PC, parallel-group, stratified (by center and baseline EDSS)	Teri 7 and Teri 14 mg, QD Placebo <i>Duration: 108 wks</i>	R: 1088. M/F: 303/785; Age 37.9 yrs ± 8.8 (18-55) Placebo: 363 Teri 7: 366 Teri 14: 359
<i>Controlled Adjunctive Clinical Studies</i>			
PDY6045 28 centers Phase 2 Adjunctive with IFN	Safety and tolerability in combination with a stable dose of IFN-β. DB, R, PC, stratified by dose of IFN- β (low- or high dose)	Teri 7 or 14 mg QD, Placebo in addition to IFN-β 1a ⁴ <i>Duration: 24 wks</i>	R:116, M/F: 35/81 Age: 40.1 yrs ± 8.0 (19 – 54) Placebo + IFN-β: 41 Teri 7 + IFN-β: 36 Teri 14 + IFN-β: 39
PDY6046 24 centers Phase 2 Adjunctive with GA	Safety and efficacy in combination with GA in relapsing MS. R, DB, PC, stratified by country	Teri 7 or 14 mg QD, Placebo in addition to GA ⁵ <i>Duration 24 wks</i>	R: 123. M/F: 26/97 Age: 41.4 yrs ± 7.9 (19 – 55) Placebo + GA: 41 Teri 7 + GA: 42; Teri 14 + GA: 40
LTS6047 35 centers Phase 2 Adjunctive with INF or GA	Long-term safety and tolerability when added to treatment with IFN-β or GA Parallel, DB, extension to PDY645 & PDY6046	Teri 7 or 14 mg QD, Placebo in addition to IFN-β 1a or GA <i>Duration: 24 wks</i>	<u>PDY6045 + LTS6047:</u> R: 86, M/F: 28/58 Placebo + IFN-β: 31 Teri 7 + IFN-β: 28 Teri 14 + IFN-β: 27 <u>PDY6046 + LTS6047:</u> R: 96, M/F: 23/73 Placebo + GA: 37 Teri 7 + GA: 30 Teri 14 + GA: 29

Table 4. (cont) Summary of phase 2 & 3 studies in NDA 202-992 (Teriflunomide in MS)

ONGOING STUDIES (Interim analyses)			
<i>Uncontrolled Monotherapy Clinical Studies (extension)</i>			
LTS6048 (D2002) 16 centers Phase 3	Assess long-term safety and efficacy in relapsing MS. Open-label extension to study 2001.	Teri 7 and Teri 14 mg QD <i>Duration: 528 wks</i>	R: 147, M/F: 39/108 Age: 39.9 ± 9.2 (19-64) Placebo/7 mg: 29 7 mg/7 mg: 52 Placebo/14 mg: 26 14 mg/14 mg: 40
LTS6050 (D3004) 116 centers	Document long-term safety/tolerability in patients with relapsing MS Parallel group, DB extension of study EFC6049/TEMSo	Teri 7 or 14 mg QD in the morning <i>Duration: 288 wks</i>	R: 742. M/F: 206/536 Age: 38.4± 8.6 (18-55) Placebo/7 mg: 129 7 mg/7mg: 252 Placebo/14 mg: 108 14 mg/14 mg: 253
EFC10531/TOWER 190 centers Phase 3	Efficacy and safety of Teri in reducing the frequency of relapses in relapsing MS. (Interim report written by independent Sanofi-Aventis group to preserve study integrity)	Placebo-controlled Teri 7 and Teri 14 mg QD <i>Duration: Fixed end for all pts, 48 weeks for last pt randomized.</i>	R: 1092 patients as of the end of November 2010. Placebo: 363 Teri 7: 379 Teri 14: 350 <i>Last patient's visit planned for March 30, 2012.*</i>
OTHER ONGOING STUDIES (Only blinded safety data in original submission)			
Protocol EFC10891 (TENERE) Multicenter Phase 3 Monotherapy	Effectiveness of Teri compared to IFN-β 1a, evaluated by time to Rx failure (relapse or permanent study Rx discontinuation for any cause) in relapsing MS. Open-label (Teri vs. IFN-β 1a), R, rater-blinded, parallel-group study	Teri 7 and Teri 14 mg QD in morning with water IFN-β 1a⁶ <i>Duration: Fixed end for all pts, 48 wks from last pt randomized</i>	R: 300 expected >18 years 100 each group expected <i>Completed after NDA submission. Unblinded safety data in 120-day SUR. Complete study report not submitted.</i>
EFC6260 (D3005) TOPIC Multicenter Phase 3 Monotherapy	Effect in reducing conversion of patients with first clinical episode consistent with MS to definite MS R, DB, PC, parallel group study	Teri 7 and 14 mg QD in the morning Placebo <i>Duration: 108 wks</i>	R: 780 M/F: 137/267 Age: 32.2 ± 8.5 (18 – 5) NA
EFC6058 (D3002) TERACLES Multicenter Phase 3 Adjunctive to IFN-β.	Teri vs placebo on frequency of MS relapses in patients with relapsing MS already treated with IFN-β. DB, PC, parallel-group	Teri 7 or 14 mg Film-coated tablets, QD Placebo QD Taken in the morning, with water With or without food All patients on IFN-β. <i>Planned Duration: at least 48 wks</i>	R: 5 Gender: M/F: 3/2 Age: 34.4 ± 9.9 (25 – 50) First patient enrolled February 2011. Planned 485 per group.

¹All are multicenter, multinational studies. ²R: patients randomized. DB: double blinded. PC: placebo-controlled ³M/F: male/female. ⁴IFN-β dose: Low dose (Avonex® 30 mcg once a week) or High dose (Betaseron® 0.25 mg every other day subcutaneously or Rebif® 44 µg 3 times per week ⁵GA: glatiramer acetate ⁶IFN-β dose: Rebif® 44 µg 3 times per week subcutaneous injection. Source: Module 5.2, Tubular listing of clinical studies, original ISS and interim report for TOWER study.

5.2 Review Strategy

The safety review of this application was conducted by Drs. Lourdes Villalba and Evelyn Mentari, clinical reviewers in the DNP Safety Team. The efficacy of teriflunomide in patients with multiple sclerosis was reviewed by Dr. Jody Green. The CDTL is Dr. Billy Dunn.

This review focuses on completed monotherapy studies but safety data from other phase 2 & 3 studies and clinical pharmacology studies were also reviewed. Narratives and selected CRFs were reviewed for deaths, serious AEs and discontinuations due to AEs.

This review has incorporates data from the 4-month Safety Update Report as well as all responses to FDA requests for clarification submitted to FDA as of June 26, 2012 (including data from a Major Amendment related to renal safety submitted on April 12, 2012).

All adverse event tables in this review refer to number of patients with treatment emergent events. Tables for Safety Pool 2 refer to the information submitted in the original submission, unless noted otherwise.

5.3 Discussion of Individual Studies/Clinical Trials

Characteristics of the studies have been described in Table 4 of this review.

6 Review of Efficacy

The reader is referred to Dr. Green's review of efficacy.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The integrated summary of safety (ISS) of this application focuses on data from the two completed placebo-controlled monotherapy studies (a phase 2 study of 9 months duration [2001] and a phase 3 study of 2 years duration [EFC6049/TEMSO]) and their ongoing extensions (LTS6048 and LTS6050, respectively). Data from completed 24-week combination studies (one with INF- β [PDY6045] and one with glatiramer acetate [PDY6046]) and their 24-week extension [LTS6047]) were submitted with the original NDA separately from the monotherapy studies in the ISS.

An interim analysis of TOWER, a 48-152 week placebo-controlled monotherapy study, prepared by an independent Sanofi-Aventis group to preserve study integrity was submitted separately from the ISS as an amendment to the NDA (s001).

Three additional clinical studies were ongoing at the time of NDA submission (two placebo-controlled – one in CSI [TOPIC], one as adjunctive therapy to INF- β [TERACLES] - and one INF- β - controlled [TENERE]). Blinded safety data (deaths, serious AE and AE leading to discontinuation) were submitted from these three studies in the original NDA. Unblinded data from TENERE were submitted as part of the 120-day SUR.

The interim cut-off date for the ongoing Phase 2 & 3 studies in the original NDA was January 10, 2011. The final cut-off date for inclusion of safety data was 01 June 2011 (source: Table 2 of original ISS). The interim cut-off for TOWER was February 28, 2011.

Clinical pharmacology studies involved approximately 450 subjects in single and repeated dose studies. A summary of clinical pharmacology studies is presented in Appendix 1.

7.1.2 Categorization of Adverse Events

An AE was defined as any untoward medical occurrence in a clinical study subject administered a pharmaceutical product. The MedDRA dictionary (Version 13.1) was used to code adverse events.

The on-study observation period was defined as the time from the initial informed consent to the patient's end of follow-up. The observation periods of safety data consisted of:

- Screening Period: from informed consent to first dose of study medication. In Pool 2, for patients receiving placebo in the base study and switching to active treatment in the extension, from informed consent/enrollment in the extension to first dose of active treatment.
- Treatment-emergent adverse event (TEAE) Period, from first dose of study medication up to 16 weeks (112 days) after last dose of study medication for patients discontinuing treatment and/or not entering a long-term extension.⁴ Otherwise, for Pool 1 the TEAE period is from first dose of study medication up to inclusion in long-term extension and for Pool 2, up to the data cut-off date. The TEAE Period includes the Treatment period and the Washout period.
- Post-treatment Period, from the day after the TEAE period to the end of the follow-up period, where applicable.

The inclusion of safety data up to 16 weeks after drug discontinuation is appropriate, given the long half life of teriflunomide (19.4 days), although, the analysis of treatment emergent AEs included events that may have been related to cholestyramine (mostly transaminase elevations).

⁴ As per info submitted 11/14/11 the duration of collection of adverse events after discontinuation of study treatment (as well as the procedure to accelerate the elimination of teriflunomide) evolved during the teriflunomide clinical development program. At the start of the Phase 2 monotherapy program (Study HMR1726/2001 in the year 2001), adverse events were collected for 6 weeks after last dose of study treatment. This remained the approach until the first half of 2007, when the collection period was extended to 16 weeks in all studies ongoing at this time (LTS6048, EFC6049/TEMSO and its extension LTS6050, PDY6045 and PDY6046) for the purpose of documentation of adverse events over a longer duration. All subsequent studies (LTS6047, EFC6050/TOPIC, EFC10531/TOWER, EFC10891/TENERE) were designed accordingly.

Approximately 2/3 of patients in the phase 2 & 3 studies underwent a washout procedure after study treatment completion/ discontinuations. All subjects in clinical pharmacology studies underwent washout. Analyses of AE in these studies were included up to 1 or 2 weeks after the last dose of study drug.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

7.1.3.1 Pooling strategy in phase 2 and 3 studies

The evaluation of safety data from the teriflunomide Phase 2-3 monotherapy program in relapsing MS patients was based on 2 types of pooled analyses:

- Pool 1 focused on the placebo-controlled segments of studies 2001 and EFC6049/TEMPO.
- Pool 2 included patients who received active treatment in the controlled segments of 2001 and EFC6049/TEMPO plus their non-controlled long-term extensions (LTS6048 and LTS6050, respectively). Some of these patients had more than 8 years follow up. See Table below.

Table 5. Integrated summary of safety pooling strategy for phase 2 & 3 monotherapy studies.

Table 4 - Integrated summary of safety pooling strategy

Pool	Type	Studies	Treatment duration	Number of patients Placebo	Number of patients Teriflunomide		Comparisons
					7 mg	14 mg	
1	Placebo-controlled	EFC6049/TEMPO	2 years	360	368	358	7 mg versus placebo/ 14 mg versus placebo
		2001	9 months	61	61	57	
2	Active treatment ^a	EFC6049+LTS6050 (extension of EFC6049)	Avg. 2.5 years	--	497	465	
		2001+LTS6048 (extension of 2001)	Avg. 5.0 year	--	90	83	

^a Placebo period of main study excluded for placebo switch patients

Note: no pooling of Study PDY6045+LTS6047 or Study PDY6046+LTS6047 adjunct studies; only blinded safety data were available for Studies EFC10891 (TENERE), EFC6260 (TOPIC), and EFC6058 (TERACLES).

Source: (Applicant’s ISS, Table 4)

The pooling strategy for the ISS was discussed and agreed upon at the pre-NDA meeting.

7.1.3.2 Pooling strategy in clinical pharmacology studies

Two pools were analyzed:

- Pool of single-dose studies: teriflunomide dose levels were pooled as follows:
 - Teriflunomide 7 mg (includes the 10 mg dose from Study HWA486-1024)
 - Teriflunomide 14 mg (except the 17 subjects with hepatic impairment [Study POP6507] and the 8 subjects with renal impairment [Study POP11432])
 - Teriflunomide >14 mg (consisting of 20 mg and 70 mg doses)

No subjects received placebo in any of the single dose studies.

- Pool of repeated-dose studies: teriflunomide dose levels were pooled as follows:
 - Placebo (except data from the placebo run-in phase of Study TES10852 that were not included in the repeated-dose pool)
 - Teriflunomide 70 mg ± 14 mg which includes the 70 mg repeated doses of the Study TDR10892 where teriflunomide was administered at 70 mg for up to 14 days, the studies where teriflunomide was administered at 70 mg for 3 or 4 days as a loading dose followed by 14 mg daily for 8 to 11 days and the 100 mg dose from Study 1001.

Regarding interaction studies only the periods or phases where teriflunomide was administered alone were extracted and included in single and/or repeated dose pools. In the pooled analysis, teriflunomide exposure was calculated by dose level, regardless of food regimen or drug formulation.

Pooling of clinical pharmacology studies was discussed and agreed at the pre-NDA meeting.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Extent of Exposure in Phase 2/3 monotherapy studies: Placebo-controlled Pool 1

In Pool 1, similar numbers of patients were exposed to placebo (421), teriflunomide 7 mg (429) or teriflunomide 14 mg (415). The cumulative duration of treatment exposure was **663.52** patient-years for the placebo group, **680.50** patient-years for the teriflunomide 7 mg group, and **649.51** patient-years for the teriflunomide 14 mg group.

Table 6. Exposure to teriflunomide in Phase 2 & 3 monotherapy studies, Pool 1

	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Cumulative duration of treatment exposure (patient-years)	663.52	680.50	649.51
Duration of study treatment (days)			
Number	421	429	415
Mean (SD)	575.66 (250.68)	579.37 (258.20)	571.64 (265.07)
Median	755.00	755.00	755.00
Min : Max	17.0 : 786.0	6.0 : 784.0	1.0 : 801.0
Cumulative duration of study treatment by category [n (%)]			
>48 weeks	303 (72.0%)	305 (71.1%)	292 (70.4%)
>108 weeks	128 (30.4%)	129 (30.1%)	127 (30.6%)

Note: Patients are considered in the group of treatment they actually received. Source: Applicant's ISS, Table 10.

7.2.1.2 Extent of Exposure to teriflunomide in Phase 2/3 Active Treatment, Pool 2

Pool 2 includes all patients who received active treatment (teriflunomide 7 mg or 14 mg) in Study 2001 or in Study EFC6049/TEMSO in addition to patients who switched from placebo to teriflunomide 7 mg or 14 mg in the extension studies (LTS6048 and LTS6050). In Pool 2, the cumulative duration of treatment exposure was 1956.75 patient-years for the teriflunomide 7 mg group, and 1781.34 patient-years for the teriflunomide 14 mg group. The median duration of study treatment was 1143.0 days (3.1 years) and 1162.5 days (3.2 years) in teriflunomide 7 mg and 14 mg, respectively. The duration of study treatment ranged from 1 day to 9.8 years.

Table 7. Exposure to teriflunomide in Phase 2 & 3 monotherapy studies: Active treatment Pool 2 (original submission)

	teriflunomide	
	7 mg (N=587)	14 mg (N=548)
Duration of study treatment (days)		
Number	587	548
Mean (SD)	1217.55 (857.96)	1187.29 (830.81)
Median	1143.00	1162.50
Min : Max	5.0 : 3560.0	1.0 : 3563.0
Cumulative duration of study treatment by category [n (%)]		
>48 weeks	484 (82.5%)	445 (81.2%)
>240 weeks	155 (26.4%)	142 (25.9%)
>408 weeks	44 (7.5%)	35 (6.4%)

Source: Modified from Applicant's ISS, Table 11.

Teriflunomide exposure by dose and duration in clinical trials is presented in the following table:

Table 8. Teriflunomide exposure in clinical studies (original submission)

Study	Investigational Product	All	≥ 3 months	≥ 6 months	≥ 1 year	≥ 2 years
Monotherapy completed and ongoing studies in relapsing MS						
EFC6049/TEMSO + 2001	Teriflunomide 7 mg	429	405	384	303	277
	Teriflunomide 14 mg	415	386	363	289	263
LTS6050 + LTS6048	Placebo to Teriflunomide 7 mg	158	150	141	124	81
	Placebo to Teriflunomide 14 mg	133	128	122	109	70
Adjunct completed Phase 2 studies						
PDY6045+LTS6047	Teriflunomide 7 mg on top of IFN-β	37	36	32	22	--
	Teriflunomide 14 mg on top of IFN-β	38	37	31	23	--
PDY6046+LTS6047	Teriflunomide 7 mg on top of GA	42	37	32	30	--
	Teriflunomide 14 mg on top of GA	41	38	29	27	--
		1293	1217	1134	927	691
Other ongoing studies^b						
EFC6260 (TOPIC) ^a	Blinded	270	227	202	136	57
EFC10891 (TENERE) ^a	Blinded	219	200	164	64	0
		489	427	366	200	57
EFC10531 (TOWER) ^a	Teriflunomide 7 mg	365	338	279	155	15
	Teriflunomide 14 mg	365	338	279	155	15
		730	676	558	310	30

^a Approximate number of patients since the study is still blinded

^b In addition, EFC6058/TERACLES, started in February 2011, is only included in the update for serious treatment-emergent adverse events

Source: Table 9 of Clinical Overview

As shown in this table, the time of NDA submission, approximately 2000 unique patients were treated with teriflunomide in phase 2/3 trials, including 384 patients treated with Teri 14 for at least 6 months and 303 treated for at least 1 year (just in controlled monotherapy studies). These numbers would be sufficient to fulfill minimum ICH guidance recommendations of exposure for a drug intended for chronic use. Moreover, teriflunomide is the active metabolite of leflunomide, and the exposure of Teriflunomide 14 mg is equivalent to that of leflunomide 20 mg. Therefore, the exposure in the available database is sufficient to adequately assess the safety of teriflunomide.

At the time of the original NDA submission, the exposure in TOWER in PYRs was 336.5, 341.2 and 331.9 in the placebo, Teri 7 and Teri14 groups, respectively.

120-day Safety Update Report (SUR)

The 120-day SUR was submitted on 12/9/11. The cut-off date for the SUR was 9/8/11. The report contains data for studies that were on-going at the time of the original NDA. The update included

- Pool 2a (update of active treatment Pool 2 in the initial NDA) updated as of 9/8/11 using Medical Dictionary for Regulatory Activities (MedDRA) version 14.0.

- Unblinded deaths, SAE and discontinuations due to AE for LTS6050 and LTS6048 and the recently completed Phase 3 randomized, active-controlled Study TENERE.
- Blinded data on deaths, serious and non-serious adverse events, and treatment-emergent adverse events leading to drug discontinuation were provided for ongoing Phase 3 studies, i.e., TOWER, TOPIC, and TERACLES.
- Updated analyses of selected intrinsic/extrinsic factors in Pool 1 of the original NDA (called Pool A in this submission) for concomitant hepatotoxic medication use based on an extended list of potentially hepatotoxic drugs.
- A cumulative overview of the pregnancies (for the entire teriflunomide clinical program) recorded in the Pharmacovigilance database at the cut-off date of 9/8/11.
- Full clinical study reports for clinical pharmacology studies [INT11697], [INT11720], and [INT11932].

The total exposure in teriflunomide phase 2/3 clinical trials at the time of the 120-days SUR (September 8, 2011), as per information submitted on 2/7/12, is as follows:

Table 9. Updated total exposure in teriflunomide phase 2/3 trials (SUR)

Study	Investigational Product	All	≥ 3 months	≥ 6 months	≥ 1 year	≥ 2 years	Exposure (patient-years)
Monotherapy completed and ongoing studies in relapsing MS							
EFC6049/TEMSO + 2001	Teriflunomide 7 mg	429	405	384	303	277	1654.4 ^a
	Teriflunomide 14 mg	415	386	363	289	263	1559.7 ^a
LTS6050 + LTS6048	Placebo to Teriflunomide 7 mg	158	150	141	133	97	502.8
	Placebo to Teriflunomide 14 mg	133	128	122	112	87	409.3
EFC10891 (TENERE)	Teriflunomide 7 mg	110	107	102	97	7	137.5
	Teriflunomide 14 mg	110	103	98	84	11	130.8
Adjunct completed Phase 2 studies							
PDY6045+LTS6047	Teriflunomide 7 mg on top of IFN-β	37	36	32	22	--	28.1
	Teriflunomide 14 mg on top of IFN-β	38	37	31	23	--	29.5
PDY6046+LTS6047	Teriflunomide 7 mg on top of GA	42	37	32	30	--	32.0
	Teriflunomide 14 mg on top of GA	41	38	29	27	--	30.2
Sub-total	Teriflunomide 7 mg	776	735	691	585	381	2354.8
	Teriflunomide 14 mg	737	692	643	535	361	2159.5
	Teriflunomide 7 mg + 14 mg	1513	1427	1334	1120	742	4514.3

Study	Investigational Product	All	≥ 3 months	≥ 6 months	≥ 1 year	≥ 2 years	Exposure (patient-years)
Other ongoing studies							
EFC6260 (TOPIC) ^b	Blinded	311	275	238	192	109	459.7
EFC10531 (TOWER) ^b	Teriflunomide 7 mg	388	359	339	267	75	526.4
	Teriflunomide 14 mg	388	359	339	267	75	526.4
EFC6058 (TERACLES) ^b	Blinded	45	17	1	0	0	10.6
Sub-total	Teriflunomide 7 mg + 14 mg	1132	1010	917	726	259	1523.1

Source: Table 1. Sanofi’s 2/7/12 response to FDA request for information.

a The treatment exposure is calculated from the start of study 2001/EFC6049 to the end of the extension study (LTS6048/LTS6050).

b Approximate number of patients based on a 1:1:1 randomization ratio to placebo, teriflunomide 7mg, and teriflunomide 14 mg since the study is still blinded

As per this table submitted 2/1/7/12, at least 531 patients have been exposed to Teri 14 for at least 6 months, and 423 for at least 1 year, with 362 exposed for at least 2 years in completed monotherapy or adjunctive therapy studies. Including completed and ongoing studies, there is a total exposure of approximately 2600 patients (6000 PYRs) to teriflunomide 7 or 14 mg in phase 2/3 studies.

The SUR added little to the information provided in the original submission. It contains mostly blinded safety data from the ongoing studies and new unblinded data from TENERE, a small interferon-controlled study with approximately 100 patients per arm. Updated data from TOWER was not provided.

If approved, TOWER final study report and a pooled analysis of all controlled teriflunomide studies will be requested as a postmarketing requirement.

7.2.1.2 Selection Criteria

Selection Criteria in Completed Core Phase 2/3 Clinical Studies in Patients with Relapsing Multiple Sclerosis are listed in Appendix 9.4.2 of this review. As the target population for this drug is determined, restrictive clinical trial selection criteria will need to be considered, including the following:

1. While monotherapy study 2001 (179 randomized subjects) included subjects up to age 65 years, other core Phase 2/3 studies, including monotherapy study EFC6049 (TEMZO) (1088 randomized subjects) and adjunctive therapy studies PDY6045 and PDY6046, included subjects only up to age 55.

(b) (4)

2. Persons with “significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia” (without specific laboratory value criteria) were excluded from Study 2001. Studies EFC 6049 (TEMSO), PDY6045, and PDY6046 excluded patients with “significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia” with the following criteria:
- Hematocrit <24% and/or
 - Absolute white blood cell count (WBC) <4000 cells/mm³ and/or
 - Platelet count <150000 cells/mm³ and/or
 - Absolute neutrophil \leq 1500 cells/mm³.

While reference ranges for individual laboratories vary, the exclusion criteria for absolute white blood cell count, platelet count, and absolute neutrophil count are similar to the lower limit of commonly used laboratory reference ranges.^{5,6} Thus, a recommended treatment population similar to the subject population in the core Phase 2/3 trials would not include subjects with mild decreases in absolute WBC count, absolute neutrophil count, or platelet count.

(b) (4)

3. Studies EFC 6049 (TEMSO), PDY6045, and PDY6046 excluded patients with “a history of cancer (except for basal or squamous cell skin lesions that had been surgically excised, with no evidence of metastasis).”
- The proposed prescribing information, submitted 8/12/11, does not prove specific recommendations regarding patients with a history of cancer.*
4. Studies 2001, EFC 6049 (TEMSO), PDY6045, and PDY6046 excluded patients with liver function impairment or persisting elevations of serum glutamic pyruvic transaminase (SGPT /ALT) or direct bilirubin greater than 1.5-fold the upper limit of normal (ULN).

(b) (4)

5. Studies 2001, EFC 6049 (TEMSO), PDY6045, and PDY6046 excluded patients with moderate to severe impairment of renal function, as shown by serum creatinine >133

5 Massachusetts General Hospital hematology core lab reference intervals. Accessed on August 19, 2011 at <http://mghlabtest.partners.org/hematology.htm>

6 McClatchey KD. *Clinical Laboratory Medicine*. 2nd ed. Lippincott Williams & Wilkins; 2002.

μmol/L (or >1.5 mg/dL). Two clinical pharmacology studies in patients renal impairment (one with mild to moderate and one with severe renal impairment) were conducted.

(b) (4)

6. Studies EFC 6049 (TEMSO), PDY6045, and PDY6046 excluded patients with persisting elevations of serum amylase or lipase greater than 2-fold the ULN.
The proposed prescribing information, submitted 8/12/11, does not discuss adverse events of teriflunomide affecting the pancreas.

These exclusion criteria are reasonable for the development program of a drug known to be associated with multiple toxicities, including liver and bone marrow toxicity. However, the label should reflect these exclusions. A full list of entry criteria in studies 2001, 6049/TEMSO, PDY6045 and 6046 are included in Appendix 2.

7.2.1.3 Demographics and baseline characteristics of the population in MS studies

In Pool 1, approximately 72% of patients were female, with a mean age of 38 years; 96.9% were Caucasian, followed by Asian/Oriental (1.5%), Black (0.6%) and other races (1.0%). The mean weight was approximately 68 kg. Regarding region, 405 patients (32%) were from the Americas (including 8 patients from the US and 349 from North America other than US), and 860 (68%) from Europe (27% Eastern Europe, and 41% Western Europe).

MS disease characteristics at baseline were similar among treatment groups, within each of the studies. The median duration of MS since first symptoms was 6.9 years and the median EDSS score was 2.5. Overall, approximately 91% had relapsing remitting MS; 6% had secondary progressive MS, and 3% had progressive relapsing MS. With regard to previous MS treatment, in Pool 1, 62 - 67% of patients had received systemic corticosteroids prior to study entry. Additionally, approximately 73% of patients had not received previous MS disease modifying drugs within 2 years prior to randomization. Among the 336 (26.6%) patients who had taken previous MS medications (other than corticosteroids), the distributions of patients within each type of previous treatment was similar across the study treatment groups. The most common prior MS treatment received was INF (beta-1A and IFN beta-1B) (22-24%) followed by glatiramer acetate (7-12%). No patient had received mitoxantrone. Five patients had received natalizumab (2 in the Teri 7 group and 3 in the Teri 14 group).

In clinical pharmacology studies, there was a higher percentage of male (79% and 68% in the single and repeated dose pools, respectively) and a higher percentage of Black subjects (11% and 4.5% in single and repeated dose pools, respectively) than in the phase 2/3 studies. In clinical pharmacology repeat studies, subjects on placebo tended to be older than those on teriflunomide (39.1 years and 35.6 years, respectively).

Regarding prior and concomitant diseases and medications at baseline, there were no major differences among treatment groups in medical/surgical history or prior medications.

At the pre-NDA meeting, the DNP requested analyses of the number of subjects screened, the number of subjects who failed screening, and the reasons for screening failures in Study EFC6049/TEMSO. One hundred fifty five patients failed screening because “failed entrance criteria”. Additional information submitted 11/17/11 indicates that 58 (37.4%) failed to fulfill entry criteria and 112 (72.3%) fulfilled some of the exclusion criteria (mostly because of preexistent elevated liver enzymes, low WBC or platelet count, or recent use of prohibited treatments).

The demographics and disease characteristics of the MS population in the ISS are consistent with those in other applications for MS. Small differences between treatment groups were not clinically meaningful. Of note, there were only 8 patients from the US in the completed monotherapy studies. However, there were 439 patients from North America other than US in Pool 1, and 204 patients (18.7%) in TOWER were from the US.

7.2.2 Explorations for Dose Response

The choice of doses used in the phase 2/3 clinical trials was based on a clinical pharmacology study that showed that 7 and 14 mg of teriflunomide are equivalent to 10 and 20 mg of leflunomide, respectively. No other doses were used in the teriflunomide phase 2/3 trials.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to the pharmacology toxicology review by Dr. Richard Houghtling

7.2.4 Routine Clinical Testing

The safety assessment for each study was based on the monitoring of AEs, clinical laboratory parameters, physical examinations, and vital signs. Because of the concern of severe liver injury and bone marrow disorders, hepatic and hematologic parameters were followed closely in all teriflunomide studies. In studies 2001, EFC6049/TEMSO and TOWER liver enzymes and CBC were done every 2 weeks during the first 6 months and every 6 weeks and end of study thereafter. Laboratory measurements were every 4 weeks during the first 6 months in EFC6058/TERACLES and EFC6260/TOPIC.

Strict stopping rules and follow-up of patients, including those who were withdrawn from treatment were implemented:

- for any confirmed (repeated value within 48 hours) ALT ≥ 3 x ULN with or without increase in total bilirubin level, ALT between 2-3 x ULN with symptoms of hepatitis
- for any occurrence of confirmed neutrophil count of less than 1000 cells/ μ L with or without infection, or
- for any potentially life threatening cytopenia detected during the follow-up of laboratory abnormality as per Investigator's judgment
- severe bullous skin reactions

- serum amylase or lipase >5x ULN or >2x ULN with associated symptoms of pancreatitis, or abdominal CT/MRI consistent with pancreatitis
- if drug-related peripheral neuropathy is diagnosed
- if pulmonary toxicity is diagnosed

Neurological symptoms suggestive of a peripheral neuropathy, such as bilateral numbness or tingling of the feet or hands were followed up with electrophysiological diagnosis including nerve conduction studies (this was implemented in 2006 by an amendment to the protocol of all ongoing studies).

A specific monitoring of pulmonary symptoms with complementary pulmonary tests was put in place for the ongoing studies EFC10531/TOWER and EFC6260/TOPIC in order to detect and assess any potential pulmonary toxicity.

The pancreas was identified as a target organ in non-clinical studies in the dog. Ultrasound imaging of the pancreas was planned at study entry and throughout the study at 6-month intervals for the first 72 weeks, and at the close-out visit (this was implemented in 2006 by an amendment to the protocol of all ongoing studies). Additionally, monitoring of amylase and lipase laboratory values was performed at regular intervals.

Vital sign parameters included pulse rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP), and weight. Blood pressure measurements were to be performed in supine (or sitting) position during scheduled visits. There was no measurement of orthostatic BP in the phase 2/3 studies.

ECGs: In EFC6049/TEMPO and LTS6050 there was no ECG data collection. Thus, ECG data in Pool 1 comes from study 2001 and in Pool 2 from study LTS6048. The EFC19531/TOWER study included ECG at randomization and end of study but the study was not completed at the time of NDA submission.

Since teriflunomide is teratogenic in laboratory animals in 2 species, double contraception was required for all the teriflunomide studies. If pregnancy was suspected, the patient had to notify the physician immediately for β -hCG blood testing. If the decision was made for continuing the pregnancy, then a rapid elimination procedure of the study medication was required.

Studies in this NDA application had an independent DSMB that reviewed unblinded safety data. Their mandate was to look only at the safety data (e.g., adverse events [including MS relapses], serious adverse events, liver function tests above the ULN, and the number of enhancing MRI lesions) to ensure that the safety of the subjects was maintained.

7.2.4.1 Table of assessments

The scheduled protocol safety assessments in EFC6049/TEMPO are summarized in Appendix 3 of this review.

7.2.4.2 Criteria for normal range and notable laboratory abnormalities in NDA

The criteria for normal range and notable laboratory abnormalities in the NDA application are presented in the following tables.

Table 10. Normal range laboratories used for analyses in study 6049/TEM SO

Parameter	Normal range		
Clinical Chemistry			
ALT/SGPT	6 – 34 (U/L)	Lipasemia	0 – 100 (U/L)
AST/SGOT	9 – 34 (U/L)	Amylasemia	28 – 120 (U/L)
AlkP (Alkaline Phosphatase)	35 – 123 (U/L)	Glucose(mmol/L)	3.9 – 6.4
Total Bilirubin	3 – 21 (µmol//L)	Total protein	6.10 – 8.40 (G/L)
Direct bilirubin	0 – 7 (µmol//L)	Albumin	33 – 49 (G/L)
Indirect bilirubin	0 – 21 (µmol//L)		
GGT	7 – 49 (U/L)		
LDH	53 – 234 (U/L)	Hematology	
BUN (urea nitrogen)	1.4 – 8.6 (µmol/L)	Hemoglobin G/L	116 - 164
Creatinine	31 – 101 (µmol/L)	WBC	3.8 – 10.7 (GIGA/L)
Uric Acid	149 - 446 (µmol/L)	Lymphocytes	0.91 – 4.28 (GIGA/L)
Sodium	132 – 147 (mmol/L)	Neutrophils	1.96 – 7.23 (GIGA/L)
Potassium	3.40 – 5.40 (mmol/L)	Monocytes	0.12 – 0.92(GIGA/L)
Chloride	94 – 112 (mmol/L)	Basophils	0 – 0.20 (GIGA/L)
Inorganic phosphorus	0.71 – 1.65 (mmol//L)	Eosinophils	0 – 0.57 (GIGA/L)
Total Cholesterol	4.42 – 7.53 (mmol//L)	Platelets	140 – 400 (GIGA/L)
Triglycerides	0.59 – 2.96 (mmol/L)		

Source: reference lab values in patient profiles. Study 2001 used slightly different values. E.g. for eosinophil count, the normal was up to 0.4 Giga/L.

Potentially Clinically Significant Abnormalities (PCSAs) were defined by the applicant as abnormal values considered medically important according to predefined criteria/ thresholds based on literature review for clinical laboratory tests, vital signs and ECG. PCSAs are summarized as follows:

Table 11. Criteria for potentially clinically significant laboratory abnormalities in study 6049/TEM SO

Parameter	PCSA
Clinical Chemistry	
ALT/SGPT	By distribution analysis : > 3 ULN > 5 ULN > 10 ULN > 20 ULN
AST/SGOT	By distribution analysis : > 3 ULN > 5 ULN > 10 ULN > 20 ULN
ALP (Alkaline Phosphatase)	> 1.5 ULN
Total Bilirubin	> 1.5 ULN > 2 ULN
ALT & Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN
CPK	>3 ULN > 10 ULN
Creatinine	≥ 150 µmol/L (Adults) ≥ 30% change from baseline ≥ 100% change from baseline
Creatinine Clearance (Cockcroft’s formula)	< 30 ml/min (severe renal impairment) ≥ 30 - < 50 ml/min (moderate renal impairment) ≥ 50 - ≤ 80 ml/min (mild renal impairment)
Uric Acid	Hyperuricemia: > 408 µmol/L Hypouricemia: < 120 µmol/L

BUN (urea nitrogen)	≥ 17 mmol/L
Chloride	< 80 mmol/L > 115 mmol/L
Sodium	≤ 129 mmol/L ≥ 160 mmol/L
Potassium	< 3 mmol/L ≥ 5.5 mmol/L
Total Cholesterol	≥ 7.74 mmol/L (3 g/L)
Triglycerides	≥ 4.6 mmol/L (4 g/L)
Lipasemia	≥ 3 ULN
Amylasemia	≥ 3 ULN
Glucose	≤ 3.9 mmol/L and < LLN ≥ 11.1 mmol/L (unfasted), ≥ 7 mmol/L (fasted)
Hematology	
Hemoglobin	Decrease from Baseline ≥ 20 g/L (1.24 mmol/L) Decrease : Males : ≤ 115 g/L (7.14 mmol/L), Females : ≤ 95 g/L (5.9 mmol/L) Increase : Males : ≥ 185 g/L (11.48 mmol/L), Females : ≥ 165 g/L (10.24 mmol/L)
WBC	< 3.0 GIGA/L (non-Black), < 2.0 GIGA/L (Black), ≥ 16.0 GIGA/L
Lymphocytes	> 4.0 GIGA/L
Neutrophils	< 1.5 GIGA/L (non-Black) < 1.0 GIGA/L (Black)
Monocytes	> 0.7 GIGA/L
Basophils	> 0.1 GIGA/L
Eosinophils	> 0.5 GIGA/L or > ULN if ULN ≥ 0.5 GIGA/L
Hematocrit	Males : ≤ 0.37 v/v, ≥ 0.55 v/v Females : ≤ 0.32 v/v, ≥ 0.5 v/v
Platelets	< 100 GIGA/L; ≥ 700 GIGA/L
Vital signs	
HR	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
SBP	≤ 95 mmHg and decrease from baseline ≥ 20 mmHg ≥ 160 mmHg and increase from baseline ≥ 20 mmHg
DBP	≤ 45 mmHg and decrease from baseline ≥ 10 mmHg ≥ 110 mmHg and increase from baseline ≥ 10 mmHg
Orthostatic Hypotension	SBP : St – Su ≤ -20 mmHg DBP St – Su ≤ - 10 mmHg
Weight	≥ 5 % increase from baseline; ≥ 5 % decrease from baseline
ECG	
HR	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
PR	≥ 220 ms and increase from baseline ≥ 20 ms
QRS	≥ 120 ms
QTc (ms)	Absolute values (ms)
	<i>Males</i> <i>Females</i>
Borderline	431-450 ms 451-470 ms
Prolonged	> 450 ms > 470 ms
Additional	≥ 500 ms ≥ 500 ms
Δ QTc (ms)	Increase versus baseline (M and F) Borderline Δ 30-60 ms Prolonged Δ > 60 ms

PCSA: potential clinically significant abnormality. Source: Appendix C. Statistical analysis plan for EFC6049/TEMPO. Criteria used for all Sanofi studies except oncology studies, version January 2009.

The criteria for clinically significant abnormality are acceptable in general. The criteria for identifying potentially relevant hypertension appear rather strict, particularly for diastolic BP. A single value of DBP ≥ 100 mmHg could be a potentially clinically relevant event.

The values were slightly different for study 2001. For instance, PCSA for eosinophil count was an increase of 0.35 Giga/L from baseline; for neutropenia it was a value < 1 Giga/L. The approach in 6049 appears to be more conservative.

7.2.4.3 Reviewer's comments on the adequacy of the application

In general, the demographics of the population were similar to that of other NDAs for the treatment of MS. Only 8 patients in Pool 1 were recruited in the United States. However the application includes approximately 450 patients from Canada.

The strategy for pooling of studies is acceptable. The exposure is sufficient for an adequate assessment of safety, particularly because of the extensive exposure to the parent drug, leflunomide. As per the TOWER interim study report, the median exposure in this study was approximately 300 days per treatment group (313 days for placebo, 302 days for Teri 7 and 317.5 days for Teri 14). I believe that the interim safety information from TOWER, if pooled with study 2001 and TEMSO might contribute to the characterization of the safety profile of this drug. However, the study is almost complete and the full study report is expected in the near future. As per information submitted on 3/29/12, the last visit for the last patient is expected to occur on 3/30/12. Given the extensive available data from leflunomide, the pooled analysis can be requested upon study completion.

Proposed clinical and laboratory monitoring were adequate, especially after year 2006, when several amendments were made to the protocols regarding safety monitoring. The threshold for clinically important laboratory changes was acceptable. Duration of the post-treatment period was short in study 2001 (6 weeks) but adequate after 2007 (16 weeks in all protocols).

The narratives in this application are not very helpful. Results of laboratory, imaging and ECG data were not consistently included in the narratives and were not included in the CRFs. Narratives mention concomitant medications at the time of the event but do not provide information as to how long the patient had been on that medication. There is little description of the AE. For instance, MS relapses were supposed to be reported as adverse events once the possibility of relapse was excluded. However, none of the AE events of MS relapse provides a description as to what the event consisted of or the criterion why it was considered an AE versus lack of efficacy. Most narratives miss a discussion of alternative explanations for the observed AE. The lack of information in the narratives was partially solved by submission of patient profiles, but the safety reviewers often needed to request additional information from tests done outside pre-scheduled visits. Narratives of patients with arrhythmia-related events also contain very limited information.

Because of the known hepatotoxic effects of leflunomide, liver enzymes were closely monitored in the teriflunomide application. However, many patients in the trials were assumed to have a drug-induced increase in liver enzymes without a full work up to rule out other possible cause, such as viral infection or obstruction. When done, liver serologies included mostly Hepatitis A, B and C, but no other viruses/agents (e.g. Hepatitis E, CMV, EBV). Pertinent negatives (alcohol use, exposure to toxic agents, serology for autoimmune disease) were rarely mentioned in the

narratives. Most narratives missed a thoughtful discussion of alternative explanations for liver enzyme elevation.

ECG data comes from study 2001 and its extension. Study 2001 was a 6 month study with approximately 60 patients per treatment group. Additional ECG data is being collected in TOWER, a 2-year controlled study.

There is no measurement/analyses of magnesium or bicarbonate levels in phase 2/3 studies of this application. Calcium levels were measured only in study 2001. Regarding urinalyses, several patients had a microscopic examination “positive” but there was no explanation of what positive meant. The lack of information in this area is relevant given the finding that teriflunomide is associated with increased renal excretion of uric acid and phosphorus, and with events of acute renal failure. A postmarketing study or adding measurements of the missing labs to ongoing studies may address the lack of information in this area.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see clinical pharmacology review by Clinical pharmacology team.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Based on the available preclinical and clinical data and the safety profile of leflunomide, the following events were designated as adverse events of special interest (AESI):

- Hepatic disorders (including enzymes)
- Pancreatic disorders (including enzymes)
- Bone marrow disorders
- Infections
- Hypersensitivity and Skin disorders
- Malignancy
- Hypertension
- Lung disorders (ILD)
- Hemorrhage
- Peripheral neuropathy
- Convulsions
- Alopecia
- Gastrointestinal disorders (nausea and diarrhea)

Additionally, cardiac arrhythmia and thromboembolic events were requested by DNP to be included in the list of AESI for TOWER, based on an apparent excess of such events in phase 2 and 3 studies.

AESI are discussed in section 7.3.4. of this review.

7.3 Major Safety Results

At the time of the 4-month Safety Update Report (SUR) (cut-off of September 8, 2011) approximately 1500 patients were exposed to Teri 7 (n=776) or Teri 14 (n=737) in completed and ongoing phase 2/3 trials. Of those, 1120 had been exposed for at least one year. Additionally there was information from 450 subjects exposed in clinical pharmacology studies and partial data from 1132 exposed in ongoing studies. Overall there were approximately 3100 patients exposed to teriflunomide. Of note, teriflunomide is the active metabolite of leflunomide, approved as ARAVA® in patients with rheumatoid arthritis, with 2 million PYRs of exposure.

As of May 2, 2012, eight deaths occurred in teriflunomide treated patients and one death (suicide) occurred on placebo in an ongoing study. Five of the eight deaths on teriflunomide were cardiovascular/ unknown cause of death during extension studies (four on Teri 7 and one on Teri 14). They were one fatal MI, one cardiac disorder/respiratory failure/unknown cause of death, and three found dead at home several years into teriflunomide treatment. The other deaths were one suicide, one motor vehicle accident and one gram negative sepsis. Cardiac toxicity has not been identified as an adverse event associated with leflunomide in 14 years of postmarketing experience. No evidence of increased risk of arrhythmia or clinically significant QT prolongation was identified in the controlled database. Sudden death has been reported in patients with MS and brainstem involvement. Therefore, it appears unlikely that the cardiac deaths are related to teriflunomide. However, teriflunomide is associated with increase in blood pressure which may have contributed to an increased cardiovascular risk.

The overall risk of serious adverse events (SAE) during the controlled portion of the monotherapy studies (Safety Pool 1) was slightly higher among teriflunomide patients (15.7% for Teri 14) as compared to placebo (12.8 %). The most frequent SAE were in the Investigations SOC (2.9% for Teri 14 and 3.1% for placebo) lead by hepatobiliary investigations, but the SOC with greater % of events as compared to placebo was the Gastrointestinal disorders SOC (1.9 % in Teri 14 and 0.2% on placebo). There was no evidence of increased overall risk of serious infections in the teriflunomide groups in Pool 1 but one fatal gram negative sepsis occurred in one of the ongoing studies and may have been related to teriflunomide. There were no systemic opportunistic infections in Pool 1 or 2. A few opportunistic infections occurred in ongoing studies (3 cases of tuberculosis, one osteomyelitis by anaerobes, one enterococcal endocarditis). There was no imbalance in the risk or rate of malignancies in the controlled studies. However, the controlled database is relatively small and short for assessment of long-term effects of teriflunomide on immune surveillance (risk of serious and opportunistic infections and malignancy). There were no serious ischemic events on teriflunomide in the controlled database. However, there were three non-fatal myocardial infarctions and one resuscitated cardiac arrest in the monotherapy study extensions. These data, along with the CV deaths is difficult to interpret in the absence of a control group.

The overall risk of discontinuations due to AE in the controlled studies was, 11.8% in the Teri 14 group and 7.9% on placebo. The most common AEs leading to drug discontinuation were in the Skin and subcutaneous tissue disorder SOC (3.1% on Teri 14 and 0 on placebo), driven by events of alopecia.

Evaluation of pre-specified Adverse Events of Special Interest confirmed an increased risk of transaminase elevation/hepatotoxicity, bone marrow toxicity, hypertension, peripheral neuropathy, alopecia, nausea and diarrhea for teriflunomide as compared to placebo.

Evaluation of vital signs showed a dose-related increase in systolic and diastolic blood pressure. In Pool 1, the mean changes from baseline to the study endpoint (last non missing value on treatment) for systolic BP were + 2.7 mmHg in the teriflunomide 14 mg group and – 1.3 mmHg on placebo; for diastolic BP were +1.4 mmHg for teriflunomide 14 mg and – 0.9 mmHg on placebo. There was no measurement of orthostatic blood pressure. Teriflunomide was associated with weight loss. Weight decrease was identified as adverse event in 12 (2.4%) patients on Teri 14 and 4 (1%) patients on placebo. The mean change from baseline to the study endpoint was – 1.3 Kg on Teri 14 and +0.7 Kg on placebo.

Chemistry evaluations were notable for increase in liver enzymes and decrease in serum uric acid and phosphorus. In the controlled safety pool 1, the risk of ALT elevation ≤ 3 x ULN was greater for teriflunomide as compared to placebo, but for ALT > 3x ULN, it was similar between active groups and placebo. The great majority of these events occurred without increase in bilirubin and alkaline phosphatase. A total of 8 cases were identified with increased ALT>3xULN and BR >2 xULN in the entire application, including 3 on Teri 7, 2 on Teri 14 and 3 on placebo. Additionally, one patient with diagnosis of toxic hepatitis had ALT 32x ULN and jaundice, but bilirubin was not available at the time of the jaundice. The available total BR peak value in this patient was 1.7xULN. The patient was hospitalized for 5 weeks and treated with plasmapheresis and cholestyramine washout. She recovered. During the trial this patient presented intermittent eosinophilia. Severe drug induced liver injury could not be ruled out in this patient.

The decrease in serum uric acid and phosphorus were associated with increased urinary excretion. A new signal for increased risk of acute, reversible renal failure was identified with teriflunomide in this application. Ten patients on teriflunomide showed increase in creatinine above normal in Pool 1, as compared to none on placebo. Three of the ten had serum K levels greater than 6 mmol/L (and 4 were missing potassium values). Renal failure has been described with other drugs that cause hyperuricosuria, as well as in patients with hereditary hyperuricosuria.

Hematology evaluations in Pool 1 showed an increased risk of neutropenia, lymphopenia, thrombocytopenia and decreased hemoglobin. No serious infections were reported in patients who reported neutropenia. No serious cases of pancytopenia were identified in the application.

A “Thorough QT” study (TES10852) showed no evidence of clinically relevant QT interval prolongation. Controlled ECG evaluations in Pool 1 come from study 2001, a 6-month study, and from preliminary results of TOWER. Analyses of changes from baseline in PR, QRS or QT interval duration and outlier analyses do not indicate a significant effect of teriflunomide on ECG parameters, except for a dose-related shortening in PR interval, of unclear clinical significance. Preliminary results of pulmonary function tests from TOWER did not show evidence of a deleterious effect of teriflunomide on lung function, however, the results do not rule out lung toxicity either.

There were a total of 53 pregnancies in female patients in this application at the time of the SUR, including 12 live births. Of these, eight were on teriflunomide (seven on Teri 7, one on Teri 14), one was on placebo, one was on IFN- β , and two were still blinded. All patients on teriflunomide underwent rapid elimination with either cholestyramine or charcoal. There were no obvious congenital malformations among the babies. The number is small to draw definitive conclusions regarding teratogenicity and fetal toxicity of teriflunomide.

In summary, teriflunomide is the active metabolite of leflunomide. There is no evidence that teriflunomide is less or more toxic than leflunomide, its parent drug. The major toxicities associated with this drug are liver and bone marrow toxicity (with the potential risk for long term immunosuppression, opportunistic infections and malignancies), and potential for fetal harm. There is evidence that teriflunomide is associated with hypertension, alopecia, peripheral neuropathy and weight loss in the application. The absence of certain safety signals in this database does not erase the knowledge acquired through 14 years of experience with leflunomide in the RA population (e.g. lung toxicity, severe skin reactions such as Steven's Johnson syndrome) and does not allow definitive conclusions about other adverse events (arrhythmia, hemorrhage, thrombosis, convulsions, pancreatic disorder). There were no major differences in the overall risk of serious AE or discontinuations due to AE between Teri 7 and Teri 14, but there was evidence of a dose response for some AEs such as diarrhea and alopecia. The data reviewed in this application has identified a new signal for reversible, acute renal failure, likely related to dehydration. There were five CV deaths, three non-fatal MI and one resuscitated cardiac arrest among approximately 2600 patients exposed to teriflunomide in phase 2/3 studies in this database, all in extension studies. A causal relationship between teriflunomide and CV death can not be ruled out.

7.3.1 Deaths

A total of 9 deaths were reported in the Teriflunomide program (8 on teriflunomide, 1 on placebo). Four of the nine occurred in the monotherapy study extensions (3 on Teri 7; one on Teri 14), and five occurred in ongoing studies (4 in the TOWER study [2 on Teri 7, 2 on Teri 14] and one in the TOPIC study [a patient on placebo]). No deaths were reported in Pool 1, adjunctive therapy studies or clinical pharmacology studies. Deaths are listed in Table 12. Narratives are presented in Table 13.

Table 12. Listing of deaths in teriflunomide studies

Study	Randomized Treatment Group	Subject Number	Days on Treatment at start of AE ¹	Days from Treatment Start to Death ²	Cause of Death	Relationship to Study Treatment*
LTS6048	7 mg/7mg	0013/0009	1570 ³	3022	Myocardial Infarction	Likely
LTS6048	Placebo/7 mg	0030/0004	1750	1750	Cardiac disorder Respiratory failure	Possible (Insuf information) No autopsy
LTS6050	7 mg/7 mg	2407/0030	302	302	Unknown. Found dead.	Unknown (Insuf information)
LTS6050	14 mg/14 mg	3203/0010	558	558	Unknown. Found dead.	Unknown (Insufficient information) No autopsy
EFC6260 (TOPIC)	Placebo	8503/0005	365	365	Suicide	Not taking teriflunomide
10531 (TOWER)	14 mg	156012/005	57	71	Suicide	Unlikely related
10531 (TOWER)	7 mg	840074/004	477	477	Motor Vehicle Accident	Unlikely related
10531 (TOWER)	14 mg	764001/003	623	633	Gram negative sepsis/ DIC	Likely related
10531 (TOWER)	Teri 7 mg	3009/0016	3.9 years	3.9 years	Unknown Died on sleep	Unknown (insufficient information)

¹ Days on treatment at the beginning of the adverse event was calculated as minimum (adverse event start date, last dose date) - first dose date + 1. AE=Adverse Event ² Days from treatment start to death was calculated as date of death – first dose date +1. ³ Start of intermittent chest pain and shortness of breath. Sources: Narratives and CRFs, Sanofi ISS Section 3.1.2.1 *Attribution to study drug, per FDA reviewer.

Table 13. Narratives for deaths in teriflunomide studies

Study/ Subject ID/ Treatment Group	Age* Sex Country	Cause of Death	Comment
Monotherapy studies			
LTS6048 0013/0009 7 mg/7 mg Pool 2	54 F Canada	Myocardial Infarction	This subject with relapsing MS was treated with teriflunomide 7 mg for 9 years and died from a myocardial infarction. Past medical history includes <u>hypertension</u> , <u>depression</u> , <u>hyperlipidemia</u> and <u>coronary artery disease</u> . At baseline sitting blood pressure was 107/78 mmHg. Post-treatment with teriflunomide, systolic BP ranged from 110's to 160's. Asymptomatic increase in BP up to 160/108 mmHg was reported after about 2.3 years on teriflunomide, which led to an increased dose of antihypertensive medication. About 2.7 years later the patient reported intermittent chest pain and was diagnosed with diffuse coronary artery disease, and angioplasty with insertion of 3 stents was done. Nine years into the study she died suddenly of a myocardial infarction. No autopsy was performed. Other AEs ongoing at the time of death included sensory disturbance, tonic convulsion, and increased ALT to 1.4x the upper limit of normal. <i>Reviewer comment: This subject experienced increased blood pressure while taking teriflunomide. Since hypertension is a major risk factor for atherosclerotic disease, it is likely that taking teriflunomide contributed, to some degree, to this subject's myocardial infarction and death.</i>
LTS6048 0030/0004 Placebo/ 14 mg Pool 2	57 F France	Cardiac disorder/ respiratory failure	Patient with relapsing MS, treated with teriflunomide 14 mg for 4.8 years. During the study she presented AEs of dyspnea, anxiety disorder, depression/delusions and hypothyroidism. She had one episode of pneumonia requiring hospitalization 2 years into treatment, complicated with tachycardia and respiratory failure on Day 728, from which she recovered. She also had intermittent ALT elevation up to 4xULN with normal BR during the study. As per the CRF, she had lumbar zona (herpes zoster) that resolved five months prior to death with residual lumbar pain and reported asthenia starting 4 months prior to death (day 1617). As per the datasets, treatment was discontinued approx. 2 months prior to death. On Day 1750, the patient asked her personal physician to evaluate at home for reported "malaise". He noted "tachycardia >150 bpm" and "blood pressure "90 mmHg" and advised hospitalization. At admission blood pressure was 100/60 mmHg, pulse rate at 90 bpm, normal temperature, and O2 saturation was 89%. No laboratory tests (ie, complete blood count, biochemistry, urinalysis, urine or blood cultures) were done and no ECG or chest x-ray were performed (all was planned for the following day). The patient was reported to have moderate sinus tachycardia without dyspnea or pulmonary congestion. Paroxetine and propranolol were stopped and the patient was given oxygen and physiologic serum (500 ml) with 3 NaCl in 4 hours. Five hours later, she was administered one pill of bromazepam and developed within 30 minutes an asthma crisis for which she received 2 puffs of salbutamol. She also received amiodarone, furosemide, and clorazepate. One hour later the patient suffered cardiac trouble (coded as cardiac disorder), respiratory failure and died. The cardiac disorder was considered as related to teriflunomide by the Investigator. <i>Reviewer comment: Insufficient information has been provided to fully characterize the cause of this patient's cardiac disorder and respiratory failure. As per additional information submitted on 10/31/11, one year prior to death a cardiologist noted <u>heart murmur of aortic insufficiency and high blood pressure (160/90)</u>; ECG was normal; echo showed left ventricular hyperkinesia without increased ventricular diameter. Hospitalization report on the date of death states that patient had a prior history of asthma. However, she never received any medication for asthma during the several years that she was in</i>

Study/ Subject ID/ Treatment Group	Age* Sex Country	Cause of Death	Comment
			<i>the study. A nurse called a physician for evaluation of a “crisis of asthma”. The patient died approximately one hour after receiving salbutamol, Lasix and amiodarone. No autopsy performed. Additional information does not help with characterization of this death. In my opinion, the cause of cardiorespiratory arrest 4.8 years into teriflunomide treatment reported as “cardiac trouble” remains unknown.</i>
LTS 6050 2407/0030 7 mg/7 mg Pool 2	41 F France	Unknown Found dead	The subject’s medical history includes depression but no CV risk factors. Ten months after starting treatment, on Day 302, the patient was found dead in her apartment. The cause of the death was listed as unknown (event was coded as death). An autopsy report was performed on Day 305. Toxicology analysis showed no study drug overdose. The pathology examination detected modifications in the cerebral tissue consistent with the changes observed during an acute attack of MS; in the opinion of the applicant, these changes could have resulted in death since they were accompanied by diffuse anoxic-ischemic edema with involvement of the amygdala. They were associated with signs of extended circulatory failure with cardiac necroses, acute pulmonary edema, and centrilobular sinusoidal distension. Bronchial-pulmonary lesions were observed that were liable to be involved in death, for which according to the report an inhalation mechanism by neurological damage can also be discussed. Final autopsy report submitted 10/31/11: death of either natural causes or toxic origin. <i>The cause of death for this patient remains unknown. However, neurogenic pulmonary edema and sudden death due to brainstem disease with involvement of cardiorespiratory centers has been reported in patients with MS.</i>
LTS6050 3203/0010 14 mg/14 mg Pool 2	41 M Russian Federa- tion	Unknown (Found dead)	This subject was found by relatives dead in his bathroom 1314 days after the first dose of teriflunomide 14 mg. As per IND safety report he died while taking a bath. No previous CV risk factors. The physician listed the cause of death as “acute heart failure,” but this was written before the autopsy. The patient had a medical history of duodenal ulcer. He had MS for 11 years prior to study entry with an EDSS score of 5.5. No family history of cardiac sudden death. Coronary insufficiency and hypertension were reported for his father. No signs of arrhythmia were reported. At study visits, pulse rates were stable and ranged from 70’s to 80’s (beats per minute). Supine diastolic blood pressure measurements ranged from 70-90 mmHg and showed no upward trend during the treatment period. Supine systolic blood pressures ranged from 110-125 mm Hg and showed no upward trend during the treatment period. <i>Reviewer comment: FDA requested autopsy results. As per 10/31/11 submission, no autopsy report will ever be available; patient died outside of his home country. Cause of death in this patient remains unknown. However, see comment to case above.</i>
Ongoing studies			
10531 TOWER 840074/004 7 mg	47 M United States	Motor Vehicle Accident	Past med Hx included type 2 diabetes mellitus, obesity, <u>hypertension</u> , depression, sleep apnea. On Day 1, the patient was diagnosed with possible <u>Brugada syndrome</u> , by baseline ECG. On Day 477, the patient experienced a fatal motor vehicle accident. He was driving on a country road in a snow storm and collided head on with another vehicle. The Investigator confirmed with his wife that the patient did not complain from any adverse events (including cognitive, syncope, malaise, dizziness) in the morning before he left the day of the fatal accident. There were no witnesses at the time of the accident. <i>Reviewer comment: Given the adverse weather conditions present during the motor vehicle accident, this fatal outcome is unlikely related to teriflunomide.</i>

Clinical Review

Drs. Lourdes Villalba and Evelyn Mentari

NDA 202992 – Teriflunomide Safety

Study/ Subject ID/ Treatment Group	Age* Sex Country	Cause of Death	Comment
EFC6260 8503/0005 Placebo	26 M Ukraine	Suicide	Medical history included glomerulonephritis and major depression. On Day 365, the patient hanged himself and died. There were no neuropsychiatric symptoms, and he had no history of prior suicidal attempt. The patient was in the TOPIC study and received the last dose of placebo on Day 336, 1 month prior to death.
10531 TOWER 156012/0005 14 mg	19 F China	Suicide	This patient had a past history of depression. No adverse events were reported prior to the subject's death. The last dose of study drug was administered on Day 57. On Day 71, the patient committed suicide by carbon monoxide poisoning. She left a letter to her family mentioning death wishes. The death certificate and autopsy report were not available. <i>Reviewer comment: This subject had a history of depression prior to starting treatment with teriflunomide. She had no adverse events reported after starting teriflunomide.</i>
10531 TOWER 764001/003 14 mg	24 F Thailand	Gram neg. sepsis/ DIC	Other than multiple sclerosis, this subject had no notable past medical history. Prior to the adverse events that lead to her death, she had no reported adverse events and no reported abnormal laboratory measurements while on treatment. After 1.7 years of treatment with teriflunomide, she was hospitalized with acute fever and myalgia. Three days after initial hospitalization, blood cultures were positive for gram negative rods (later shown to be Klebsiella pneumoniae). Ceftriaxone was started. Later that day, she became confused and had a generalized seizure. She became hypotensive and tachycardic and was intubated. Antibiotics were switched to meropenem. Later that day she developed a coagulopathy, consistent with disseminated intravascular coagulation, and had massive epistaxis with 1.5 L estimated blood loss. Four days after the onset of fever she had a cardiac arrest and died. <i>Reviewer comment: In the opinion of this reviewer, the death of this young woman with no notable past medical history (other than MS) is likely related to treatment with teriflunomide. Antimetabolite medications like teriflunomide have immunosuppression potential. Leflunomide is known to be associated with immunosuppression.</i>
LTS6050 3009/0016 7 mg	51 M Poland	Unknown (found dead)	Diagnosed with MS 16 years prior to entry. Three years and 11 months into teriflunomide treatment he died at night, during his sleep. EDSS at baseline was 6. BP was 140/90 mm Hg. Weight= 84Kg. He received placebo in the core study. Six months into placebo, he was diagnosed with glossopharyngeal neuralgia treated with gabapentin. During placebo and during the extension study he had several episodes of MS relapse treated with corticosteroids. BP measured at 16 months into teriflunomide treatment was 160/104. BP at 22 months was 166/102. Patient was started on tramadol, rimipril and carbamazepine. At the last visit (3 years and 8 months) his serum Na was 129 mmol/L (nl 132-147), his BP was 140/83 and weight= 68 Kg. <i>Reviewer comment: the cause of death is unknown. He developed hypertension and hyponatremia during the trial, treated with rimipril and salty diet, respectively. Sudden death has been reported in patients with MS with brainstem involvement. However, hypertension and hyponatremia may have contributed to his death. The patient lost 16 Kg (approx. 33 Lbs) since the beginning of the trial.</i>

* Age at time of death.

Reports of brain MRIs of patients who were found dead (# 2407/0030, #3203/0010 and #3009/0016) were submitted at the FDA request on April 12, 2012. These MRIs were read by [REDACTED]^{(b) (4)}. All three patients showed increase in the burden of disease during the course of the trial. All had severely affected brains with nearly confluent periventricular and subcortical lesions in both cerebral hemispheres, scattered lesions in the brainstem and severe central and cortical atrophy. Patient 3203/0010 had the largest brainstem lesions (one in the right pons of 0.25 ml, one in the left anterior pons of 0.60 ml and one in the left pontomedullary area of 1.0 ml).

DISCUSSION: A total of 9 deaths were reported in this development program (8 on teriflunomide and one on placebo). Five of the eight on teriflunomide were CV/unknown cause of death (one myocardial infarction, one cardio-respiratory failure (in the ER) and three were found dead at home). The patient with fatal MI had a prior history of hypertension, hyperlipidemia and coronary artery disease. The patient with cardiorespiratory failure had a history of paroxysmal tachycardia, dyspnea, hypothyroidism, aortic insufficiency and at least one episode of documented hypertension during the study. Two of the 3 patients found dead at home had no prior cardiovascular history or known risk factors but one developed hypertension and hyponatremia during the study. All five CV deaths occurred in uncontrolled studies. Fatal neurogenic pulmonary edema and sudden death have been reported in patients with MS and brainstem involvement.^{7,8} In a case series of autopsies in 50 patients with MS, 9 deaths (18%) were attributed to atherosclerotic CV disease, and other 9 were attributed to MS itself, after eliminating other potential causes. In these cases, the mechanism of death was uncertain, but potentially attributed to demyelinating lesions of neural structures that control cardiovascular and/or respiratory functions (ie, hypothalamus and brainstem).⁹ MRI reports of the three patients who were found dead did show brainstem lesions that could potentially explain autonomic nerve dysfunction and sudden death. No recent laboratory data were available in these patients.

There was no increased risk of arrhythmias in Pool 1. The TQT study showed no evidence of prolonged QT. ECG analyses in Study 2001 and TOWER did not suggest a clinically relevant effect on ECG parameters, except for a small, dose-related shortening of the PR interval. There was a slight increase in the risk of cardiac arrhythmia related terms in TOWER (1.7% on Teri 14 as compared to 0.8% on placebo) mostly due to single AE terms, except for 2 cases of atrial fibrillation on Teri 14, but the numbers are small (6 cases on Teri 14 and 3 on placebo for all cardiac related arrhythmia terms).

Two of the patients (one MI, one found dead at home) had hypertension with documented diastolic blood pressure >100 mmHg during the trial. Perhaps teriflunomide's effect on

⁷ Hengstman GJ, Kusters B. Sudden cardiac death in multiple sclerosis caused by active demyelination of the medulla oblongata. *Mult Scler.* 2011 17.Sep;17(9):1146-8. Epub 2011 May 17.

⁸ Bramow S, Faber-Rod JC, Jacobsen C, Kutzelnigg A, Patrikios P, Sorensen PS, et al. Fatal neurogenic pulmonary edema in a patient with progressive multiple sclerosis. *Mult Scler* 2008; 14: 711–715

⁹ Causes of unexpected death in patients with multiple sclerosis. A forensic study of 50 cases. Riudavets et al. *Am J Forensic Med Pathol* 2005;26: 244-249)

BP increased their CV risk. However, there was no evidence of increased MI and stroke in the controlled database (up to 2 years).

There were two suicides (one on placebo, one on Teri 14) and one fatal motor vehicle accident. Both suicides occurred in patients with past history of depression who did not report neuropsychiatric AEs during the trial. The events do not appear to be drug related. The MVA appeared related to weather conditions (snow storm).

There was one fatal gram negative (Klebsiella pneumonia) sepsis in a young patient without prior relevant medical history or concomitant medications. This case may have been related to the immunosuppressive effects of teriflunomide.

7.3.2 Nonfatal Serious Adverse Events¹⁰

7.3.2.1 Serious adverse events in the ISS (Safety Pools 1 and 2)

Treatment emergent SAE in safety Pool 1, which includes study 2001 and 6049/TEMSo (placebo-controlled studies (9 months and 2 years data, respectively) occurred in 12.8 %, 15.7%, and 12.8%, of patients on Teri 7, Teri 14, and placebo, respectively. Therefore, there was a slight increase in serious AE in the Teri 14 group. The most common SAEs were in the Investigations, Injury, poisoning and procedural complications and Infections and infestations SOCs, with a suggestion of a dose response between the 7 and 14 mg/day doses of teriflunomide for these events. A summary of TE SAEs in Pool 1 is presented in the following table. All AE tables in this review refer to number of patients with treatment emergent events unless noted otherwise.

Table 14. Serious Adverse Events in Pool 1, teriflunomide studies.

Primary System Organ Class	Placebo (N=421) n(%)	7 mg (N=429) n(%)	14 mg (N=415) n(%)
Any class	54 (12.8)	55 (12.8)	65 (15.7)
Infections and infestations	9 (2.1)	6 (1.4)	9 (2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.2)	2 (0.5)	3 (0.7)
Blood and lymphatic system disorders	1 (0.2)	2 (0.5)	3 (0.7)
Metabolism and nutrition disorders	1 (0.2)	0	0
Psychiatric disorders	4 (1.0)	4 (0.9)	2 (0.5)
Nervous system disorders	6 (1.4)	5 (1.2)	7 (1.7)
Ear and labyrinth disorders	1 (0.2)	0	1 (0.2)
Cardiac disorders	2 (0.5)	0	0
Vascular disorders	0	2 (0.5)	4 (1.0)

¹⁰ A serious AE (SAE) is defined as any event that was fatal or immediately life-threatening, resulted in or prolonged an existing hospitalization, was permanently or significantly disabling, was a congenital anomaly, or required medical or surgical intervention to prevent permanent sequelae or any of the previously mentioned outcomes. SAEs included other important medical events that were judged by the investigator as jeopardizing the subject or potentially requiring intervention to prevent one of the previously listed outcomes.

Primary System Organ Class	Placebo (N=421) n(%)	7 mg (N=429) n(%)	14 mg (N=415) n(%)
Respiratory, thoracic and mediastinal disorders	0	0	2 (0.5)
Gastrointestinal disorders	1 (0.2)	8 (1.9)	8 (1.9)
Hepatobiliary disorders	2 (0.5)	9 (2.1)	2 (0.5)
Skin and subcutaneous tissue disorders	1 (0.2)	1 (0.2)	1 (0.2)
Musculoskeletal and connective tissue disorders	4 (1.0)	5 (1.2)	4 (1.0)
Renal and urinary disorders	0	0	2 (0.5)
Pregnancy, puerperium and perinatal conditions	1 (0.2)	0	3 (0.7)
Reproductive system and breast disorders	2 (0.5)	6 (1.4)	2 (0.5)
General disorders and administration site conditions	0	0	1 (0.2%)
Investigations	13 (3.1)	9 (2.1)	12 (2.9)
Injury, poisoning and procedural complications	4 (1.0)	5 (1.2)	9 (2.2)
Surgical and medical procedures	0	1 (0.2)	0

SAE: Serious adverse event. SOC: System organ class. MedDRA version: 13.1. N= patients exposed.
 n (%) = number and percentage of patients with at least one treatment emergent SAE. Note: Table sorted by SOC internationally agreed order. Source: Table 20, ISS.

In Pool 2, 23.9% and 21.2% of patients treated with Teri 7 and 14, respectively, reported at least one serious AE. The most common SAEs were again in the Investigations SOC (4.6% and 4.7% on Teri 7 and 14, respectively). Serious AEs in the Infections and infestations SOC were reported in 3.6% and 4.0% of patients on Teri 7 and 14, respectively. A summary table of SAEs in Pool 2 is as follows.

Table 15. Serious Adverse Events in Pool 2 (original submission)

Primary System Organ Class	Teri 7 (N= 587) n (%)	Teri 14 (N=548) n (%)
Any class	140 (23.9)	116 (21.2)
Infections and infestations	21 (3.6)	22 (4.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (1.9)	7 (1.3)
Blood and lymphatic system disorders	3 (0.5)	5 (0.9)
Immune system disorders	0	1 (0.2)
Endocrine disorders	0	1 (0.2)
Metabolism and nutrition disorders	0	1 (0.2)
Psychiatric disorders	6 (1.0)	3 (0.5)

Primary System Organ Class	Teri 7 (N= 587) n (%)	Teri 14 (N=548) n (%)
Nervous system disorders	14 (2.4)	9 (1.6)
Eye disorders	0	3 (0.5)
Ear and labyrinth disorders	1 (0.2)	2 (0.4)
Cardiac disorders	5 (0.9)	2 (0.4)
Vascular disorders	8 (1.4)	6 (1.1)
Respiratory, thoracic and mediastinal disorders	3 (0.5)	4 (0.7)
Gastrointestinal disorders	13 (2.2)	14 (2.6)
Hepatobiliary disorders	16 (2.7)	3 (0.5)
Skin and subcutaneous tissue disorders	3 (0.5)	1 (0.2)
Musculoskeletal and connective tissue disorders	7 (1.2)	7 (1.3)
Renal and urinary disorders	3 (0.5)	4 (0.7)
Pregnancy, puerperium and perinatal conditions	2 (0.3)	3 (0.5)
Reproductive system and breast disorders	9 (1.5)	9 (1.6)
General disorders and administration site conditions	3 (0.5)	2 (0.4)
Investigations	27 (4.5)	26 (4.7)
Injury, poisoning and procedural complications	16 (2.7)	13 (2.4)
Surgical and medical procedures	2 (0.3)	1 (0.2)

Table 1.5.5.2, Applicant's ISS. N= patients exposed. n (%) = number and percentage of patients with at least one treatment emergent SAE. Note: Table sorted by SOC internationally agreed order.

The overall percentages of SAEs in Safety Pool 2 are higher than those in Safety Pool 1; this is not unexpected given the longer exposure in Pool 2. There was no obvious dose response in terms of SAEs between Teri 7 and 14 mg/day in Pool 2.

The increase in overall risk of SAEs in Pool 2 as compared to Pool 1 was driven by Infections and infestations, Neoplasms and Investigations.

- The risk of Infections and Infestations went from 1.4% and 2.2% for Teri 7 and 14, respectively, in Pool 1, to 3.6% and 4% for Teri 7 and 14, respectively in Pool 2.
- The risk of Neoplasms went from 0.5% and 0.7% for Teri 7 and 14, respectively in Pool 1, to 1.9% and 1.3% for Teri 7 and 14, respectively in Pool 2. Additionally, the risk of SAE in the Reproductive system and breast disorders with Teri 14 went from 0.5% in Pool 1 to 1.6% in Pool 2.
- The risk of events in the Investigation disorders SOC went from 2.1% and 2.9% for Teri 7 and 14, respectively in Pool 1, to 4.5% and 4.7% for Teri 7 and 14, respectively in Pool 2.

Safety findings in the SUR (Safety Pool 2a) were consistent with those in the original application. The following section presents SAEs by primary SOC in alphabetical order in Pool 1 and 2. Narratives for all SAEs were reviewed. Selected cases are described below.

- SAEs in Blood and lymphatic system disorders SOC

Although the number of events is small, there was an imbalance in the number of SAEs in Pool 1 for this SOC: 2 (0.5%), 3 (0.7%) and 1 (0.2%), cases in the Teri 7, Teri 14 and placebo groups, respectively. These cases are summarized below.

Brief narratives of patients with SAE in Blood and lymphatic system disorders SOC, Pool 1

Patient ID	Age Sex PT Action with drug	Rel day onset/ (Duration days)	Comments
Teri 14			
002001-124-0014-0002	35 F Neutropenia D/C, reintroduced, no recurrence Resolved	21/3	Neutropenia and thrombocytopenia on Day 21 preceded by symptoms of influenza on Day 13. Labs at a local laboratory on Day 21 showed neutrophil count of $0.693 \times 10^9/L$ (reference range 2.0-6.3) and total white count of $2.31 \times 10^9/L$ (reference range 4.0 – 11.0 $\times 10^9/L$). Lymphocyte count was normal, but platelets were decreased at $119 \times 10^9/L$ (reference range 140-400 $\times 10^9$). Drug was temporarily interrupted. Labs repeated 3 days later at the central laboratory were normal. She had started oral contraceptive and tetracycline the month prior, and ibuprofen the same day that she had symptoms of influenza. The event did not re-occur when study medication was reintroduced. <i>Moderate neutropenia and mild thrombocytopenia. Did not recur. Perhaps related to concomitant drug, viral infection or lab error.</i>
002001-124-0014-0014	53 F Neutropenia D/C, reintroduced, no recurrence. Resolved (twice)	85/6 129/3	Neutropenia on Day 85 ($1.3 \times 10^9/L$, nl 1.8 – 7.5). WBC and lymphocyte count were also decreased (WBC $2.6 \times 10^9/L$, nl 3.6-11, and lymphocytes $0.8 \times 10^9/L$, nl 1.0- 3.5). Drug was temporarily interrupted and the patient recovered in 6 days. Second SAE of neutropenia on Day 129. No signs/symptoms of infection. Concomitant medication was acetaminophen. Study drug was continued. Neutrophil count was normal on repeat testing two weeks later but persisted on the low side, until the end of the study. <i>Moderate neutropenia and lymphopenia that improved after drug discontinuation and recurred with rechallenge. Event resolved while on drug but neutrophil and lymphocyte count persisted normal low. This event could be related to teriflunomide. There was no thrombocytopenia or anemia.</i>
006049-616-3007-0005	30 M Neutropenia None Resolved	758/5	Presented neutropenia grade 3 (0.95 Giga/L, [nl 1.96-7.23]), with leukopenia (2.24 Giga/L [nl >3.8]), lymphopenia (0.82 Giga/L [nl >0.91]) at the end of study visit. Normal Hb and platelet count. Recovered after drug discontinuation.
Teri 7			
006049-616-3006-0014	38 F Anaemia NONE	757/42	History of uterine leiomyoma on iron supplementation. Event resolved on Day 798 with Hb to the normal range (120 g/L). Platelet and WBC lines were normal. <i>It does not appear to be</i>

	Resolved		<i>related to teriflunomide.</i>
006049-804-3510-0004	25 M Lymphadenitis NONE Resolved	82/5	Left submandibular lymphadenitis with hospitalization 81 days into Teri 7 treatment. <i>WBC was normal, and neutrophil count was low normal around the time of the event.</i> A dental extraction was performed. He received paracetamol and nimesulide and recovered on Day 86. He continued treatment with teriflunomide. <i>Tooth infection relationship to teriflunomide is unclear.</i>

Source: AE dataset and narratives. Original ISS.

There was also a case of neutropenia on placebo in Pool 1 (patient 002001-124-0014-0004). This was a 48 yo male. His WBC went from $2.5 \times 10^9/L$ (nl 1.8-7.5) at screening to $1.5 \times 10^9/L$ at week 6. The platelet count also decreased. Lymphocyte count was normal. Medication was discontinued but reintroduced. Neutrophil count was intermittently low through the remainder of the study. Concomitant medications included amitriptyline, evening primrose and oral contraceptive. *Amitriptyline has been associated with neutropenia and bone marrow suppression.*

In addition to these cases, there was a SAE of neutrophil count decreased in the Teri 14 group, reported under the Investigations SOC (6049/2401/0005):

- A 50-year-old male (6049/2401/0005) had a serious AE of neutrophil count decrease at 0.90 Giga/L associated with hemoglobin of 40 g/L (normal 127-181 g/L) and platelets at 89 Giga/L (normal 140-400 Giga/L) on Day 364, 11 months after the first intake of teriflunomide. This event did not lead to treatment discontinuation. The three hematopoietic cell lines values normalized by the next scheduled lab test (approximately one month later). The patient continued the study for more than 5 years and all subsequent blood counts were normal. There is no mention of concomitant medications taken. *This was an episode of isolated “pancytopenia” that resolved spontaneously without stopping drug or giving any treatment. This could have been a lab error.*

In Pool 2: No additional events of serious leukopenia or neutropenia were reported in the extension studies.

A total of 5 patients had serious TEAEs of neutropenia/neutrophil count decreased: 1 in placebo and 4 in teriflunomide 14 mg, and none in the teriflunomide 7 mg group. Neutropenia was mild to moderate, sometimes associated with low lymphocyte count or low platelet count. All cases recovered with or without drug discontinuation.

Non-clinical studies of teriflunomide showed that this drug has bone marrow suppression effects. ARAVA is known to be associated with bone marrow suppression. Bone marrow suppression effects appear to be manageable and can be addressed with labeling.

- SAEs in Cardiac disorders SOC

In Pool 1, two patients had SAEs in this SOC. Both were taking placebo (patient ID 006049-040-1602-0005, a 45 yo F who presented angina pectoris and 006049-152-3805-0006, a 51 yo F with

myocardial infarction). In Pool 2a (including the SUR), seven patients had non-fatal cardiac disorders on teriflunomide, including three myocardial infarctions (3 to 5 years into treatment) one resuscitated cardiac arrest, one cardiomyopathy, one cardiac valve disease and one bradycardia with asystole.

Table 16. Serious adverse events in the Cardiac SOC, Pool 2.a

Primary System Organ Class Preferred Term n(%)	teriflunomide	
	7 mg (N=587)	14 mg (N=548)
Cardiac disorders	5 (0.9%)	5 (0.9%)
Acute myocardial infarction	1 (0.2%)	1 (0.2%)
Arteriosclerosis coronary artery	0	1 (0.2%)
Bradycardia	0	1 (0.2%)
Cardiac disorder	0	1 (0.2%)
Cardiac failure acute	0	1 (0.2%)
Myocardial infarction	1 (0.2%)	1 (0.2%)
Tachycardia	0	1 (0.2%)
Cardiac arrest	1 (0.2%)	0
Cardiac valve disease	1 (0.2%)	0
Cardiomyopathy	1 (0.2%)	0

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Source Table 1.5.5.1, 120-day safety Update. (includes one fatal myocardial infarction on Teri 7 and one fatal cardiac disorder/respiratory failure [unknown cause of death] on Teri 14).

Listing of patients with non-fatal SAE in Cardiac disorders SOC, Pool 2

ID	Age, ¹ sex, TRT group (base/extension). PT. Comment
002001-124-0012-0001	52 F, on Teri 7/ Teri 7. Acute myocardial infarction on Day 915. Dx made by ECG. No symptoms. Drug continued. Resolved w sequelae. Drug discontinued on Day 1950 because of patient’s wish. <i>A relationship to study drug can not be ruled out.</i>
006049-124-1204-0009	45 M. Placebo/Teri 7 Cardiac arrest , day 111. Drug interrupted- then continued. Resolved w sequelae. HX of coronary artery disease, smoking and hypercholesterolemia c/o epigastric pain. In ER had Cardiac arrest and was resuscitated. Underwent PCI. <i>Patient had multiple risk factors for coronary artery disease. However, relationship to study drug can not be ruled out. There is no information about laboratory values (CK, troponin, electrolytes) at the time of the event.</i>
006049-124-1209-0022	46 F. Placebo/Teri 7 Cardiac valve disease on Day 879. Drug discontinued. Event did not resolve. Had intermittent dyspnea and chest discomfort during study. On Day 882, ALT 4xULN with normal BR. Drug discontinued. Increased dyspnea leading to hospitalization on Day 904 with non-productive cough and abdominal pain. She also had elevated liver enzymes. Echocardiogram showed severe mitral regurgitation and tricuspid valve insufficiency requiring valvuloplasty. Cardiologist attributed symptoms of congestive heart failure to the patient’s valvular heart disease. Patient admitted to alcohol use. <i>Event does not appear to be related to drug.</i>
002001-124-0017-0009	49 M. Teri 7/ Teri 7 Cardiomyopathy on Day 1014. Drug discontinued/ Event continuing. Hx of smoking, depression, CV risk factors. Cardiomyopathy on Day 757 of Teri 7 treatment, during the extension study. This event led to drug discontinuation. Concomitant therapies included cannabis, ibuprofen, amitriptyline, venlafaxine. Holter monitor: frequent PVC’s including short runs of bigeminy and SV ectopic beats with 50% EF. Drug discontinued on Day 738. Also had decrease vibration and loss of proprioception on days 595 and 929, and increased lipase after drug discontinuation. Event of cardiomyopathy was considered related to study drug by the investigator. <i>I believe that there role of teriflunomide is unlikely but can not be ruled out. Although there is no mention of alcohol use, it could explain cardiomyopathy, ALT/lipase elevation and peripheral neuropathy.</i>

6049-124-1203-0007	55 yo M, with hx of dyslipidemia, was diagnosed with myocardial infarction on Day 981 of Teri 14 treatment. The event was not considered related to study drug by the investigator. Treatment with teriflunomide continues. There is no mention of vital signs in the narrative.
6049-826-2601-006	44 yo F, hx of depression. Concomitant meds: gabapentin, noresthisterone, amitriptyline, aporex, ibuprofen, lisinopril, amlodipine and cetirizine. On day 1220 (5.4 years) into Teri 14 treatment she had myocardial infarction . She had no past medical history of CAD or non ischemic heart disease. She was a smoker and HTN and had a family Hx of MI. She had 1-2 weeks hx of symptoms consistent with unstable angina. ON admission to the hospital she had a clot in the left ventricle and ongoing cardiac arrest . She underwent PCI of the proximal LAD. She was discharged on bisoprolol, Prasugrel and atorvastatin. The event was not considered related to study drug by the investigator. Teriflunomide was continued as planned.
6049-826-2600-0010	46 yo F. Concomitant meds included oxybutynin. On day 1218 (5.4 years) into Teri 14 treatment she experienced bradycardia and brief asystole during anesthetic induction during surgery. She was given CPR and atropine, and recovered within 30 seconds. The surgery continued without further episodes. The investigator thought there could be an interaction between drug and anesthetic agent. She had had a similar episode during an MRI on Day 1016. On day 1359 during a diagnostic investigation she had another episode of severe bradycardia and syncope with a period of 12-13 seconds asystole that was treated accordingly and the patient recovered on the same day. Teriflunomide treatment continued. A fourth episode of bradycardia was reported on Day 1373. She was given solifenacin as corrective treatment. The investigational product was continued. <i>Recurrent episodes of sinus bradycardia and asystole, not thought to be related to study drug. As per additional information submitted on April 6, 2012, the patient had a prior history of syncope. She continues to be treated with teriflunomide.</i>

Source: AE database, original ISS and SUR. ¹ Age at the time of randomization (not the time of the event). Does not include fatal events, which were described under Deaths.

In summary, there was no imbalance in the number of serious cardiac events in the controlled database. There was one unstable angina and one MI on placebo and no ischemic events on teriflunomide. However, there were four myocardial infarctions (one of them fatal); one non-fatal cardiac arrest; one fatal cardiac disorder/respiratory failure/unknown cause of death, and two sudden deaths during the extension monotherapy studies in teriflunomide treated patients, plus one sudden death in TOWER. All patients had some risks factors for coronary artery disease such as smoking, hypertension, dyslipidemia, family history of MI. None of the events was considered to be related to study drug by the investigator. It is difficult to draw conclusions in the absence of a control group. However, the role of teriflunomide in these CV events can not be ruled out.

- SAEs in Ear and labyrinth disorders SOC

In Pool 1, there were only two events, one haematotympanum, on Teri 14 (this patient is discussed under SAEs in Nervous system disorders SOC), and one hypoacusis, on placebo. In Pool 2, one additional case of vertigo was reported on Teri 7. It is hard to assess if they were drug related.

- SAEs in Eye disorders SOC

There were no events in Pool 1. In Pool 2, there were five events in four patients. A summary of cases is below:

- 42 yo female (002001-250-0027-0003) Uveitis, macular edema and retinal vasculitis on Day 800 of Teri 14 therapy, leading to drug dc. Ongoing at the time of last report.
- 38 M (002001-124-0011-0011): chorioretinopathy (central serous retinopathy, L eye) on Day 2197 of Teri 7 therapy. Drug discontinued. Recovered with sequelae.
- 38 F (006049-616-3003-0014): retinal detachment on Day 623 of Teri 14. No action taken with drug. Recovered after 3 days.
- 39 yo female (006049-616-3005-0014): uveitis on Day 1034 of Teri 14 therapy. Drug interrupted. Recovered after 101 days.

It is difficult to assess relationship to study drug in the absence of a comparator group. Non-clinical data with teriflunomide and postmarketing experience with leflunomide did not suggest an effect of teriflunomide in the eye.

- SAE in Gastrointestinal disorders SOC

In Pool 1, there was an excess of SAE of GI disorders in teriflunomide (1.9% each) as compared to placebo (0.2%)

Table 17. Serious adverse events in GI disorders SOC, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Gastrointestinal disorders	1 (0.2%)	8 (1.9%)	8 (1.9%)
Inguinal hernia	0	0	4 (1.0%)
Anal fissure	0	0	1 (0.2%)
Aphthous stomatitis	0	0	1 (0.2%)
Diarrhoea	0	0	1 (0.2%)
Duodenal ulcer	0	0	1 (0.2%)
Intestinal functional disorder	0	0	1 (0.2%)
Abdominal pain lower	0	1 (0.2%)	0
Abdominal wall haematoma	0	1 (0.2%)	0
Colitis	0	1 (0.2%)	0
Colitis ulcerative	0	1 (0.2%)	0
Crohn's disease	0	1 (0.2%)	0
Nausea	0	1 (0.2%)	0
Pancreatitis	1 (0.2%)	0	0
Peritonitis	0	1 (0.2%)	0
Toothache	0	1 (0.2%)	0

Source Table 20, ISS.

The listing of patients with SAE in the GI disorders SOC in Pool 1 is presented below. Comments are included when deemed relevant.

Listing of patients with SAE in GI disorders SOC, Pool 1.

ID	Age (years).Sex . PT. Comments
Teri 14	
006049-246-2202-0007	27F. Diarrhea on Day 606. Drug continued. Resolved after 88 days.

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006049-250-2402-0020	37M. Anal fissure. Day 355. Drug continued. Resolved after 6 days
006049-250-2407-0012	37F. Aphthous stomatitis. Day 34. Drug discontinued. Resolved after 15 days. Patient had experienced previous aphthous stomatitis on Day 13, which recovered without sequelae. On day 34 during the second bout of aphthous stomatitis she received fluconazole, valacicovir and sodium bicarbonate buccal wash. Teri 14 was discontinued on Day 39. On Day 44 a physical examination showed ten lesions, 5-8 mm in size of the oral mucosa (no lip involvement). On Day 48 she recovered without sequaela. <i>The role of teriflunomide can not be ruled out.</i>
006049-643-3205-0008	39M. Duodenal ulcer. Day 159. Drug continued. Resolved after 11 days.. Hx of HTN. On Day 22 developed non SAE of vertigo; Day 30 and 47 complained of back pain. On Day 60 diagnosed with disbacteriosis. Concom meds: enalapril, HCTZ, pancreatin, lactobacillus. On Day 159 presented GI bleeding due to acute duodenal ulcer leading to drug discontinuation. <i>The role of teriflunomide can not be ruled out. Platelet and INR/APTT were normal.</i>
Teri 7	
006049-250-2402-0006	32F. Toothache. Day 273. Drug continued. Resolved after 14 days.
006049-250-2407-0009	26F. Crohn's disease on Day 656. Drug discontinued. Event ongoing. She was previously treated with methylprednisolone and interferon. She experienced the first symptoms of Crohn's Disease on Day 571. She had diarrhea, nausea, gastric ulcer and ileal ulcer. At that time she was diagnosed as gastroileocolitis. Study drug was interrupted for approx 40 days (Day 592 to Day 630) with no change in her symptoms. The patient's condition improved after symptomatic treatment with mesalazine. Symptoms progressed again after reintroduction of study drug (Day 630). The event became serious on Day 656. A diagnosis of Crohn's Disease was confirmed. The event was considered related to study drug by the investigator. Event was ongoing at time of last report. <i>Both MS and Crohn's disease are autoimmune diseases. However, there is no evidence that one increases the risk of the other. The event of Crohn's disease was temporarily related to teriflunomide, improved with drug discontinuation and progressed with drug re-introduction suggesting a causal relationship. (Other drugs reported to be associated with Crohn's like picture are NSAIDs and isotretinoin.)</i>
006049-250-2407-0035	39M. Colitis. Day 574. Drug continued. Event ongoing. He had a medical history of diarrhoea and intestinal obstruction prior to study entry. He was previously treated with interferon beta-1a and methylprednisolone for MS. During the study he had chronic diarrhea (Days 197 to 406 and Day 471 to 537) and weight loss (Day 1 to 43 and Day 502 to 537). Because of worsening of the diarrhea, he had a colonoscopy on Day 540. Biopsy showed lymphocytic inflammation and a diagnosis of colitis was established on Day 574. Budesonide was given as corrective treatment. The event remained ongoing at the last report. The colitis was not considered as related to the IP by the Investigator. Concomitant inflammatory bowel disease, or possible Crohn's disease were considered as an alternative explanation. <i>This case of colitis may be drug related. Chemotherapeutic agents are known to induce colitis.</i>
006049-276-2007-0010	34M. Abdominal pain lower. Day 286. Drug continued. Resolved after 13 days.
006049-528-4602-0004	42F. Nausea on day 93. Drug discontinued. Resolved after 1 year.
006049-528-4605-0001	42F. Abdominal wall haematoma. Day 245. Drug continued. Resolved after 10 days. One day after hysterectomy for uterine myomatosis (006049-528-4605-0001). She had normal platelet count and coagulation parameters. <i>The event does not appear to be related to teriflunomide.</i>
006049-616-3009-0012	49M. Peritonitis. Day 561. Drug Interrupted. Resolved after 9 days.
006049-620-4202-0001	25F. Colitis ulcerative. Day 370, 3 months after drug discontinuation. Patient had been previously treated with betaferon for MS. On Day 252 the patient experienced elevated serum lipase 3x ULN (asymptomatic). <u>Drug was discontinued due to lipase increased, with last dose on Day 276.</u> The patient had cholestyramine washout from Day 276 to Day 282. On Day 311, she recovered from the event of lipase elevated. On Day 370, approx. 3 months after accelerated elimination, the patient experienced colitis with diarrhea. Chronic intestinal inflammatory disease and ulcerative

	colitis were diagnosed by colonoscopy on Day 405. She recovered on Day 450. <i>I believe that lipase increased was possibly drug related, but the episode of colitis three months after complete cholestyramine washout is unlikely to be related to teriflunomide.</i>
Placebo	
006049-616-3008-0001	37F. Pancreatitis on Day 721. Drug discontinued. Event resolved after 37 days. R

Source: AE dataset. Original submission.

In summary, there were three cases of GI inflammatory conditions on teriflunomide (all 3 on Teri 7): one colitis, one Crohn’s disease and one ulcerative colitis. No cases on placebo. The case of ulcerative colitis occurred 3 months after rapid elimination with cholestyramine and it is unlikely to be due to teriflunomide. While the other two cases could be due to chance, it could also be potentially related to inhibition of DNA synthesis in the GI mucosa, although one would expect to see some cases in the Teri 14 group too.

Of interest, there were four cases of inguinal hernia in the Teri 14 group and no cases in the placebo and Teri 7 group. I am not aware of a particular biological explanation for this imbalance.

Given the signal for pancreatic toxicity in non-clinical studies, it is reassuring that there were no cases of pancreatitis in the Teri treatment groups, but one case of pancreatitis in the placebo group.

In Pool 2, there were no additional cases of serious inguinal hernia or inflammatory bowel disease. There were some cases of duodenal ulcer, gastroduodenal hemorrhage, gastric ulcer hemorrhage and hemorrhoidal hemorrhage (one case each). It is difficult to draw conclusions without a comparator group.

Table 18. Serious adverse events in GI disorders SOC, Pool 2

Primary System Organ Class Preferred Term n(%)	teriflunomide	
	7 mg (N=587)	14 mg (N=548)
Gastrointestinal disorders	13 (2.2%)	14 (2.6%)
Inguinal hernia	0	4 (0.7%)
Diarrhoea	0	2 (0.4%)
Duodenal ulcer	0	2 (0.4%)
Abdominal pain	0	1 (0.2%)
Abdominal pain lower	1 (0.2%)	1 (0.2%)
Anal fissure	0	1 (0.2%)
Aphthous stomatitis	0	1 (0.2%)
Diverticulum intestinal	0	1 (0.2%)
Gastroduodenal haemorrhage	0	1 (0.2%)
Ileus	0	1 (0.2%)
Intestinal functional disorder	0	1 (0.2%)
Abdominal pain upper	1 (0.2%)	0
Abdominal wall haematoma	1 (0.2%)	0
Colitis	1 (0.2%)	0
Colitis ulcerative	1 (0.2%)	0
Crohn's disease	1 (0.2%)	0
Gastric ulcer haemorrhage	1 (0.2%)	0
Haemorrhoidal haemorrhage	1 (0.2%)	0
Nausea	1 (0.2%)	0
Oedema mouth	1 (0.2%)	0
Peritonitis	1 (0.2%)	0
Toothache	1 (0.2%)	0
Upper gastrointestinal haemorrhage	1 (0.2%)	0

Patients with SAE of GI bleeding in Pool 2 (excluding the patient in Pool 1) are listed below

ID	Age Sex	PT	Comment	Outcome	Rel day onset	Duration Days
Teri 14						
006049-643-3205-0002	53 M	Duodenal ulcer with bleeding	Received placebo in base study. NO action taken with drug. Drug eventually discontinued on Day 577 due to abnormal pancreatic lesion.	Recovered	541	9
Teri 7						
006049-616-3006-0014	38 F	Gastric ulcer haemorrhage	Received Teri 7 in base study. Drug not discontinued.	R	757	336
006049-616-3007-0004	32 M	Haemorrhoidal haemorrhage	Received Teri 7 in base study. Drug interrupted & resumed. No event recurrence	R	1622	3
002001-124-0013-0027	30 F	Upper GI haemorrhage	Received Teri 7 in base study. Drug interrupted & resumed, no event recurred	R	511	3

As per the patient profiles submitted 10/26/11, platelet count, INR and APTT were normal in most patients, except for the following:

- 006049-616-3007-0004. 32 M developed hepatic steatosis and GI bleeding due to hemorrhoids. He also developed peripheral neuropathy (carpal tunnel syndrome). Platelet count at entry was 176 Giga/L (normal 140 to 400). Throughout the study platelet count was

intermittently low, with lowest value of 119 on week 4 and 118 on week 24, with other values between 130- 150, and occasionally 180 Giga/L. INR and APTT were slightly below normal values throughout the study. Hb and WBC were normal. Treatment was interrupted but resumed and the patient is still in the trial. The patient had preexistent low normal platelet count. The role of teriflunomide in further decreasing the platelet count is unclear.

- SAEs in General disorders and administration site conditions SOC

There were no events in Pool 1. SAEs in Pool 2 consisted of one case of asthenia on Teri 14 and one case each of “adverse drug reaction”, death (reviewed under 7.3.1), and general physical health deterioration in the Teri 7 group.

- SAEs in Hepatobiliary disorders SOC, Pool 1

A summary of SAE in the hepatobiliary disorders SOC in Pool 1 is presented below.

Table 19. Serious adverse events, Hepatobiliary disorders SOC, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Hepatobiliary disorders	2 (0.5%)	9 (2.1%)	2 (0.5%)
Cholecystitis chronic	0	0	1 (0.2%)
Hepatitis toxic	0	0	1 (0.2%)
Cholecystitis	0	1 (0.2%)	0
Cholecystitis acute	0	1 (0.2%)	0
Cholelithiasis	1 (0.2%)	6 (1.4%)	0
Liver injury	1 (0.2%)	1 (0.2%)	0

Source: Table 20, ISS.

As seen in this table, there were more SAE of hepatobiliary disorders in Teri 7 group as compared to placebo and Teri 14. Of the nine events in the Teri 7 group, six were cases of cholelithiasis and 2 cholecystitis.

There was an excess of cholelithiasis/cholecystitis in teriflunomide treated patients, as compared to one on placebo. None of these events of cholelithiasis were thought to be related to study drug. I agree that individually, the cases do not appear to be related to study drug. However, given that 8 cases occurred on teriflunomide and only one on placebo, I believe that cholelithiasis may be related to teriflunomide, although one would expect to see more cases with Teri 14.

In addition to these SAE, some SAE in the hepatobiliary system were coded under the Investigations SOC (see below).

Table 20. Serious adverse events, Investigations SOC, Pool 1 (hepatobiliary)

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Investigations	13 (3.1%)	9 (2.1%)	12 (2.9%)
Alanine aminotransferase increased	8 (1.9%)	6 (1.4%)	6 (1.4%)
Hepatic enzyme increased	3 (0.7%)	0	4 (1.0%)
Neutrophil count decreased	0	0	1 (0.2%)
Transaminases increased	2 (0.5%)	1 (0.2%)	1 (0.2%)
Aspartate aminotransferase increased	0	1 (0.2%)	0
Lipase increased	0	2 (0.5%)	0
Nuclear magnetic resonance imaging abdominal abnormal	1 (0.2%)	0	0

Source: Table 20, ISS.

The following table summarizes patients with events in the hepatobiliary disorders and or/Investigations SOC, hepatobiliary investigations HLGT.

Table 21. Serious adverse events, Hepatobiliary disorders SOC and Investigations SOC/Hepatobiliary HLGT.

	Placebo N=421 n (%)	Teri 7 N=429 n (%)	Teri 14 N=415 n (%)
Total	14 (3.9)	16 (4.2)	14 (4.0)
Hepatobiliary disorders SOC	2 (0.5)	9 (2.1)	3 (0.5)
Investigations SOC/ Hepatobiliary investigations HLGT	12 (3.3)	7 (1.9)	11 (3.1)

Source: ADAE dataset, original ISS.

There was a greater risk of SAE of hepatobiliary disorders in the Teri 7 group, as compared to placebo or Teri 14, driven by cases of cholelithiasis. There was no excess of SAE in the Investigations, Hepatobiliary HLGT on teriflunomide. Altogether there were 14-16 SAE per treatment group in these two SOCs combined.

The listings of patients with SAE in the Hepatobiliary disorders SOC is presented below.

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Listing of patients with SAE in the Hepatobiliary disorders SOC, Pool 1.

Patient ID	Age	Sex	PT	Action with drug	Out come	Rel day onset	Comment
Teri 14							
006049-643-3201-0021	29	M	Cholecystitis chronic	None	R	488	Chronic calculous cholecystitis in baseline US. Prior MS Rx: corticosteroids. On Day 488, exacerbation of chronic cholecystitis. Drug stopped because the patient did not want to continue in the study.
006049-380-2812-0001	32	M	Cytomegalovirus hepatitis ¹	D/C	R	253	
006049-643-3201-0009	35	F	Hepatitis toxic	D/C	R	135	See narrative after the table.
Teri 7							
006049-152-3803-0005	38	F	Liver injury	D/C	R	141	
006049-040-1601-0016	43	F	Cholelithiasis	None	R	351	Previous US showing cholecystolithiasis. Day 351 pain ALT increase. Underwent surgery and continued study.
006049-124-1206-0014	48	F	Cholelithiasis	None	R	121	Previous MS Rx: Rebif and MP. No hx of lithiasis. Underwent cholecystectomy and completed study.
006049-124-1209-0004	43	M	Cholecystitis acute	Temp interrupted	R	60	Hx of cholelithiasis. Acute cholelithiasis (with pain/fever) on Day 60-64, resolved with analgesic and antibiotics. Continued study until the end (2 years).
006049-152-3802-0005	46	M	Cholelithiasis	None	R	428	Prior MS Rx: Avonex. No Hx of previous lithiasis. Underwent cholecystectomy and completed study. ALT <3xULN/nl BR
006049-276-2004-0014	45	F	Cholelithiasis	None	R	503	Prior MS Rx: Rebif and CS. Intermittent mild ALT elevation during study. On Day 503 abd. pain; US showed gallstones. Underwent endoscopic surgery and completed study.
006049-276-2011-0002	23	F	Cholecystitis	Temp interrupted	R	120	No hx of cholelithiasis. Hx of nephrolithiasis. Underwent cholecystectomy and completed study.
006049-616-3003-0024	45	F	Cholelithiasis	None	R w S	534	No Hx of cholelithiasis. Intermittent ALT elevation (non-serious) starting on Day 17. Hepatic colic on Day 483, US showed biliary calculi on Day 534. Underwent cholecystectomy and completed study.
006049-752-3401-0005	41	F	Cholelithiasis	None	R	569	Previous Hx of cholelithiasis. Underwent surgery and completed study.
Placebo							
006049-804-3501-0004	47	F	Hepatitis C ¹	D/C	R w S	212	
006049-246-2202-0002	49	F	Cholelithiasis	None	R	267	No prior Hx of cholelithiasis. Had intermittent attacks starting

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Patient ID	Age	Sex	PT	Action with drug	Out come	Rel day onset	Comment
							on Day 266 with intermittent BR elevation just above the ULN, until surgery on Day 736.

Source: ADAE dataset, original ISS. PT=preferred term. D/C=permanently discontinued. R= recovered. R w S= recovered with sequelae. C= completed core study. ¹ Also listed in the Infections and Infestations disorders SOC.

Of note, most patients with cholelithiasis did not have increased transaminases. Four did, including the patient on placebo, but the increase in ALT was <3x ULN. The patient on placebo had intermittent increase in BR above normal but not >2x ULN; other cases had normal BR.

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Patients with SAE of ALT elevation are as follows:

Listing of patients with SAE in the Investigations SOC. Hepatobiliary investigations HLGT, Pool 1.

Patient ID	Age	Sex	PT	Action with drug	Out come	Rel day onset	Dura tion
Teri 14							
002001-124-0014-0009	45	M	Hepatic enzyme increased	NO CHANGE	R	253	49
002001-124-0014-0032	27	F	Hepatic enzyme increased	D/C	R	183	29
002001-124-0014-0049	40	F	ALT increased ALT increased	NO CHANGE Discont, reintroduced, no recurrence	R	42	23
					R	114	48
002001-124-0015-0009	34	M	Hepatic enzyme increased	D/C	R	154	57
006049-124-1207-0011	53	F	ALT increased	D/C	R	28	127
006049-124-1209-0040	29	F	Hepatic enzyme increased	D/C	R	87	47
006049-152-3803-0001	35	F	Transaminases increased	D/C	R	379	107
006049-203-4101-0006	39	F	ALT increased	D/C	R	57	37
006049-616-3005-0018	41	F	ALT increased	NONE	R	71	15
006049-616-3009-0006	51	F	ALT increased	NONE	R	86	42
006049-826-2609-0003	30	F	ALT increased	NONE	R	505	82
Teri 7							
002001-124-0013-0022	47	F	AST& ALT increased	D/C	Continuing	172	
006049-152-3805-0003	49	F	Transaminases increased	D/C	R	169	50
006049-276-2005-0005	43	F	ALT increased	D/C	R	632	121
006049-528-4604-0009	44	M	ALT increased	D/C	R	85	108
006049-826-2601-0012	40	F	ALT increased	NONE	R	182	163
006049-826-2603-0001	54	F	ALT increased	D/C	R	131	141
006049-826-2609-0006	43	F	ALT increased	NA (after discont)	R	640	7
Placebo							
002001-124-0014-0007	48	F	ALT increased	None	R	127	15
			Hepatic enzyme increased	D/C	R	184	69
002001-124-0014-0041	37	F	ALT increased	None	R	17	34
			ALT increased	None	R	80	20
002001-124-0015-0010	52	M	Hepatic enzyme increased	D/C	R w S	131	226
002001-124-0015-0022	35	F	ALT increased	None	R	127	112
002001-250-0030-0001	31	F	Hepatic enzyme increased	D/C	R	99	51
006049-152-3803-0012	27	M	Transaminases increased	D/C	R	13	113
006049-233-1501-0002	51	F	ALT increased	None	R	56	34

Patient ID	Age	Sex	PT	Action with drug	Out come	Rel day onset	Dura tion
006049-250-2402-0015	43	F	ALT increased	D/C	R	29	25
006049-250-2402-0018	46	M	ALT increased	D/C	Continuing	428	
006049-250-2415-0003	48	F	ALT increased	D/C	Unknown	127	
006049-276-2003-0004	45	F	Transaminases increased	D/C	R	420	60
006049-643-3207-0028	38	F	ALT increased	D/C	R	23	77

Source: ADAE dataset, original ISS. PT=preferred term. D/C=permanently discontinued. R= recovered. R w S= recovered with sequelae. C= completed core study.

A total of 30 patients presented serious AE under the Investigations SOC, Hepatobiliary investigations HLGT (as listed above). A table summarizing these cases is presented below.

Characteristics of patients with SAE in the Hepatobiliary Investigations HLGT, Pool 1

	Placebo	Teri 7	Teri 14
Total (Male/Female)	421 (108/313)	429 (126/303)	415 (116/299)
Total	12	7	11
Male/Female	3 (1%)/ 9(1%)	1 (0.8%)/ 6 (2%)	2(1.8%) / 9 (3%)
Mean age (years)	41.8	45.7	38.6
Mean time to onset (days)	132.9	287.3	163.3

Overall, events were no more frequent in the teriflunomide group as compared to placebo. However, within the teriflunomide treated groups, they appeared to be more common in females than males. Mean age seemed to be a little younger in the Teri 14 group. Mean time to onset was somewhat earlier in the placebo group.

As per the AE datasets, two patients did not recover from ALT elevation (one on Teri 7 and one on placebo). However, review of the narratives indicates that all patients eventually recovered after discontinuation and washout.

Brief narratives of selected SAE cases from Hepatobiliary disorders and Hepatobiliary Investigations in Pool 1 are as follows:

- A 35 yo female (006049-643-3201-0009) experienced **toxic hepatitis** on day 135 of Teri 14 treatment. Laboratory values at screening were normal. ¹¹ She had a medical history of anemia, chronic gastroduodenitis, pyelonephritis. As per the narrative she was given methylprednisolone sodium succinate from Day 78 to Day 79, Day 94 to Day 95, and Day 98 to Day 100 for MS relapse but no concomitant medications were reported at the time of the event.

On Day 135 she experienced discomfort in the right hypochondrium, followed by **fever** (39°C) vomiting, and dark urine. On day 144 she developed **icterus**. On Day 147 she called the investigator

¹¹ Started teriflunomide on [REDACTED] (b) (6) Labs at screening: WBC 4.39 Giga/L (nl 3.8-10.70); neutrophils 2.94 Giga/L (nl 1.96-7.23); Eosinophils 0.08 Giga/L (nl 0-0.57). Hematocrit 0.39 l (nl 0.34- 0.48); platelet count 280 Giga/L (nl 140-400). ALT 33 U/L (nl 6-34); AST 23 U/L (nl 9-34); ALP 66 U/L (nl 31-106); Total BR 8 UMOL/L (nl 0-21); Direct BR 3 UMOL/L (0-7).

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and on Day 148 she saw a gastroenterologist. Labs showed: **ALT 32 x ULN** (1101 U/L), AST 20 x ULN (691 U/L), GGT 4.7 ULN (232 U/L), total bilirubin 1.7x ULN (36 U/L, normal up to 22 U/L), direct BR 2.5 x ULN (20 U/L, normal up to 7 U/L) and alkaline phosphatase 3.1 ULN (326 U/L). Viral serology was negative. She was diagnosed with toxic hepatitis. Metoclopramide, omeprazole and activated charcoal were given as corrective treatment. Teriflunomide was permanently discontinued. Last dose was on Day 151. She was hospitalized on Day 153 and underwent plasmapheresis. Later she had a washout procedure with cholestyramine from Day 303 to 316. On Day 310 the ALT decreased to normal range (17 U/L). On Day 319 she was considered recovered.

Figure 1. Course of liver enzymes in patient with toxic hepatitis (3201-0009)

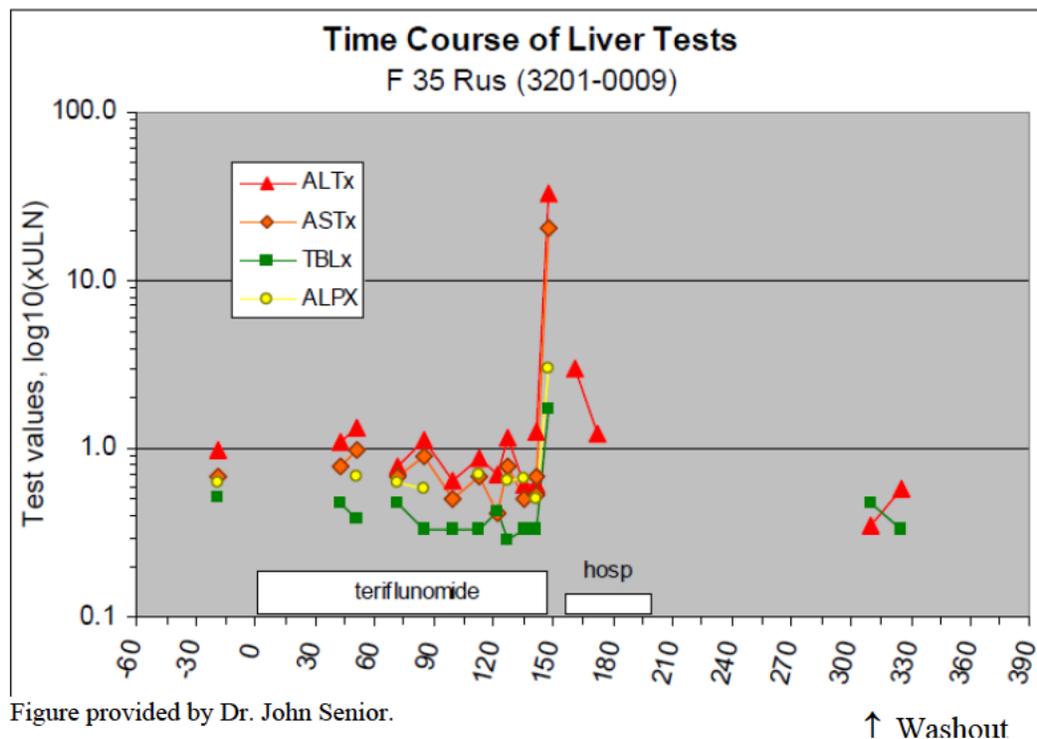


Figure provided by Dr. John Senior.

The narrative is consistent with drug induced liver injury, with ALT x32 ULN and jaundice (total BR was 1.7xULN, direct BR was 2.5 xULN), with no confirmed alternative explanation (infection, obstruction, concomitant meds). The event led to hospitalization for five weeks. The patient recovered after drug discontinuation, plasmapheresis and cholestyramine washout.

As per hospital records submitted in response to an FDA request for information, the patient developed icterus on day 144. Laboratory work on Day 148 showed ALT 1101 U/L (32x ULN BR of 36 U/L (1.7 x ULN)). On that day the absolute eosinophil count was 1.03 Giga/L (nl 0-0.5) or 16.4% of the WBC (normal up to 6.8%). She was admitted to the hospital from Day 153 through Day 188. Hepatitis serologies (HAV IgM, HBsAG, HCVAb and ABcorAB) were negative. There is no information on ALT/BR between Days 148 and Day 154 when BR was normal. The next available

BR is from Day 310 after cholestyramine washout (normal). Albumin and PT/PTT are not available.

As per the patient profile submitted to FDA on 11/28/11, the patient started and discontinued use of some amino acids and vitamin supplements within a month of the onset of the event (cerebrolysin, glycine, hopantenate calcium, trophicard and ascorutin).¹² However, none of these supplements are known hepatotoxins. Moreover, the patient had taken them intermittently prior to entering the trial without apparent liver toxicity.

This appears to be a case of severe drug induced liver injury.¹³ Of note, hepatitis by infectious agents other than Hepatitis A, B and C was not fully ruled out (viral serologies for CMV, EBV, Hep E were not done). Dr. John Senior was consulted regarding the possibility that this is a Hy's law case. Given the available information, he was not able to rule out drug induced liver injury. For details the reader is referred to his review.

On Teri 7

- A 38 yo female (006049-152-3803-0005) developed **liver injury** on Day 141 of teriflunomide 7 mg treatment. The patient had a history of cholecystectomy. She was treated with methylprednisolone (MP) for MS before study entry, and also received MP on Day 114 to 116 for MS relapse. Concomitant therapy included Eugynon (oral contraceptive) for several years. She took one dose of diclofenac on Day 80 and ibuprofen on Day 80 to 82. On Day 141 lab results showed ALT 10x ULN (345 U/L) and AST 6.4xULN. BR 1.2xUL. Drug was discontinued on Day 143 and the patient was withdrawn from the study. Then the patient followed a washout procedure including cholestyramine as per protocol given from Day 147 to Day 157. Maximum ALT was 792 (23xULN), max AST was 419 U/L (12.3xULN) and GGT was 271 (5.5xULN) on Day 160 (after receiving cholestyramine treatment), after which values decreased progressively over a month. On Day 160 she was examined by hepatologist. **She was mildly icteric.** An abdominal US showed fatty liver. On that date she also had positive urobilinogen in urine (16 umol/L; normal is negative). Maximum Alkaline phosphatase was 1.8xULN and total BR was 1.2xULN on Day 168. On Day 189 she recovered from the liver injury with normal ALT/AST. Viral serology was negative. The liver injury was considered related to teriflunomide by the investigator.

This appears to be a case of drug induced liver injury approximately 4 ½ months into teriflunomide 7 mg treatment, with ALT up to 23xULN and BR 1.2xUL. The patient was asymptomatic at the time when first ALT elevation was noted on Day 141. ALT/AST/ GGT/BR persisted elevated until a few days after the accelerated

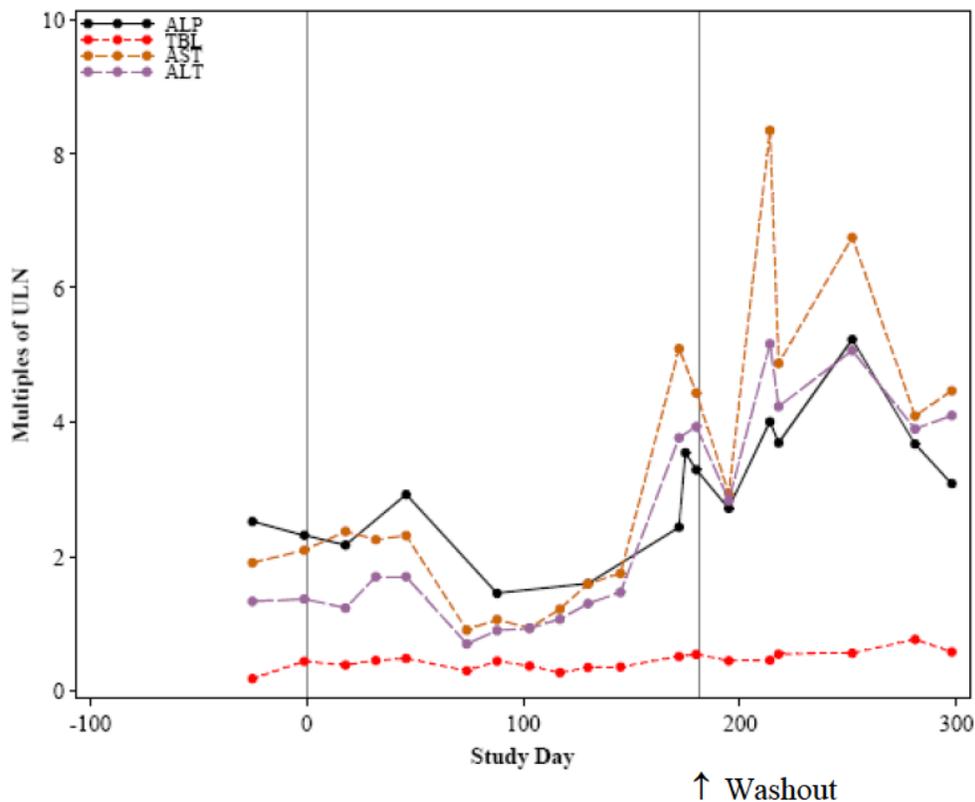
¹² First time ALT elevation was detected was Jan 10, 2006 ALT 38 U/L (nl up to 34). The only concomitant medication she had started was Essentiale, which she discontinued on Jan 19, 2006. On March 28, 2006 ALT was 43, eosinophil 9%. She had started ascurutin on March 17 but stopped on March 26, 2006. Laboratory evaluations and concomitant meds are in Appendix 9.4 of this review.

¹³ As per an updated narrative submitted on January 6, 2012, the patient had a history of chronic cholecystitis with chronic abdominal ultrasound changes. However, the CRF documented a normal abdominal ultrasound at baseline. As per response to a request for clarification on 2/17/12 Sanofi stated that there was no history of previous abnormal US.

elimination procedure with cholestyramine. She was reportedly mildly icteric right after cholestyramine washout. She was also taking an oral contraceptive for several years and took diclofenac/ibuprofen for three days around day 80-82. In my opinion this event may be related to teriflunomide although it may have gotten worse with cholestyramine for which liver function abnormalities are noted in the label.

- A 47 o female (002001-124-0013-0022) experienced **ALT and AST elevation** on Day 171 of teriflunomide 7 mg treatment. The event led to study discontinuation. She had a history of diabetes, Graves's disease, abnormal liver enzymes, and Raynaud's. Concomitant therapies included insulin, pioglitazone, pantoprazole, famotidine, modafinil, tolterodine L-tartrate and levothyroxine. On Day 171 laboratory values showed ALT at 3.8 ULN (113 IU/L), AST at 5.1 ULN (163 IU/L) and GGT at 6.8 ULN (218 IU/L). Total bilirubin levels were 11.3 $\mu\text{mol/L}$ (normal up to 21). Liver oriented serology tests were positive for Epstein Bar virus- IgG. The other serology tests were negative. The patient reported no symptoms associated with liver. Ultrasound was not performed. The patient denied any history of alcoholism. Liver biopsy performed Day 306 showed chronic portal inflammation, grade 0-1; and Fibrosis, stage 1. The events were still ongoing by the day of the last report. Although the patient's history of elevated liver enzymes dates back to 1980's (exact duration is not known), the event of ALT/AST elevation (worsening values) was considered as related to the investigational product by the investigator. Study medication was discontinued on Day 181 and the patient was withdrawn from the study. The patient followed the washout procedure with cholestyramine as per protocol given from Day 181 to Day 182.

Figure 2. Course of liver enzymes in patient 0013-0022, on Teriflunomide 7 mg, Pool 1.



Of note, this patient had elevated AST/ALT and ALK P elevation around 2xULN at baseline. AST increased more than ALT. Bilirubin was within normal levels. Liver

enzymes did not come down right away after cholestyramine washout. Teriflunomide may have worsened an underlying liver disorder.

Several patients presented SAE of transaminase elevations with normal total BR. Of those, some cases appear related to study drug based on the temporal relationship (onset upon starting study drug) and apparent positive dechallenge (improvement after drug discontinuation/cholestyramine washout), although there were some confounding factors. Some of the cases are presented below.

- 44-year-old male 006049-528-4604-0009 showed ALT and AST elevation 84 days into teriflunomide 7 mg treatment. He had a medical history of alcohol abuse. He received MP for MS relapse from Day 71 to Day 75. On Day 84 ALT was **12x ULN**. Concomitant therapies included diclofenac (for 3 years). The abnormal enzyme values remained increased for 3 ½ months and peaked on Day 106. Last dose of drug was on Day 110. He had cholestyramine washout procedure from Day 114 to 124. Liver enzymes decreased and he was considered recovered on Day 192. *Likely related but confounded by concomitant use of MP and diclofenac.*
- A 29-year-old female (006049-124-1209-0040) had elevated liver enzyme on Day 86 of teriflunomide treatment. She had a medical history of cholelithiasis and depression. Concomitant therapies included ethinyl estradiol, gabapentin, and methocarbamol/paracetamol. On day 87 ALT was 2.3 ULN (79 U/L) with normal BR. ALT remained increased. Drug was discontinued due to this event on Day 107. She received cholestyramine from Day 109 to Day 111. The maximal ALT value was **33x ULN** (1122 U/L) on Day 120, after which values fell quickly for about two weeks. Hepatitis serologies were negative. On Day 133, the patient recovered. *Case likely related to teriflunomide but confounded by use of paracetamol.*

Other cases of liver enzyme elevation were considered drug related by the investigator (again based on the temporal relationship and apparent positive dechallenge), and I agree that it is likely that they were in indeed drug related. However, many of these patients had incomplete work up of other potential causes. In particular, liver serologies were not done consistently, and when done, only the most common causes of viral hepatitis were ruled out (A, B, C). Abdominal ultrasound was not done consistently. Some examples are as follows:

- A 43 yo female (006049-276-2005-0005) had increased ALT and AST on Day 631 of teriflunomide 7 mg treatment. She had taken methylprednisolone from Day 598 to Day 602 for the most recent relapse. **ALT was 9.9 ULN** with normal BR. Labs were confirmed. Teriflunomide was discontinued on Day 676. ALT reached a peak value of 15.5 ULN (526 U/L). The patient was asymptomatic. She was not given cholestyramine washout treatment. She recovered from the event approximately 3 months later. *This case appears to be related to teriflunomide treatment. However, there is no mention of hepatitis serology or other possible explanations.*
- A 53 yo female (006049-124-1207-0011) had elevated ALT on Day 27 of teriflunomide 14 mg treatment. Patient received methylprednisolone from Day 7 to Day 9 for MS relapse. On Day 28 she presented **ALTx 5 ULN** (174 U/L) with AST 2xULN (78 U/L) with normal BR and ALK P. Due to this event drug was discontinued on Day 30. Over the next month the value of ALT remained increased with maximum value of 14.3xULN on Day 55 after which values fell progressively for about a month. She underwent washout procedure with cholestyramine from Day 61 to 75. She did not present any signs of symptoms associated with elevated ALT. US was normal. On day 154 she was considered recovered from the event. *This is likely related to study drug. However, no serological tests were performed.*

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- 39-year-old female (006049-203-4101-0006) had 2 episodes of increasing of ALT on Day 28 and 56 of teriflunomide treatment. The second episode led to study discontinuation. Concomitant therapies included citalopram. During first episode drug was not discontinued and she was treated with phospholipids. Two week after recovery, on Day 57, she developed increased ALT, with maximum **ALT value of 8.8xULN** (279 U/L) with AST at 4.4xULN (151 U/L) on Day 64. BR remained normal. ALK phosphatase was mildly elevated. Drug was discontinued on Day 68; cholestyramine was given on Day 70 to 80. The patient was asymptomatic. She recovered on Day 93. *The event appears related to study drug although no US or liver oriented serologies were performed.*

Some cases of ALT increase recovered without need for drug discontinuation, however, these were mostly cases with ALT below 3x ULN. E.g.:

- A 41-year-old female (006049-616-3005-0018) experienced elevation of ALT < 3xULN 70 days into teriflunomide 14 mg treatment. Concomitant therapy included femodene. Patient recovered without corrective treatment and did not discontinue treatment. *Thought to be related. No serologies.*
- A 51 yo female (006049-616-3009-0006) experienced ALT elevation on Day 85 of teriflunomide 14 mg treatment. Concomitant therapies included indapamide, captopril, potassium chloride, and Eugynon. On day 86 she had ALT 3xULN with AST x<2ULN, normal BR and ALK P. At that time she also had eosinophilia (0.65 Giga/L, normal up to 0.5). The ALT values decreased progressively without corrective treatment by Day 127. *The increase in liver enzymes may be related but it is confounded by concomitant medications (Eugynon). No serologies were reported.*

Cases of ALT elevation among patients on Placebo

Most cases of ALT elevation on placebo had alternative explanations such as underlying disease or concomitant use of hepatotoxic drugs. Example:

- 002001-124-0015-0010 – 52 y M experienced increased liver enzymes on Day 131 of placebo treatment. Concomitant meds included baclofen, modafinil, hydrochlorothiazide, oxazepam and sildenafil. On Day 131 **ALT was 2.8xULN**. Other liver enzymes were normal. Drug was discontinued on Day 133. A liver specialist evaluated the patient and concluded that the patient had a fatty liver related to obesity, possibly with *progressive non-alcoholic steatohepatitis (NASH)*.

Many did not have full work up. Examples:

- **002001/124/0014/0007** – 48 yo F on placebo, experienced increased ALT x2 ULN on Day 127 of study, **up to 8.7 x ULN** on Day 192 of study. Normal BR. Drug was discontinued. Concomitant medications at baseline included apo-mefenamic and gabapentin, which had been taken for more than one year. She received IV solumedrol for treatment of MS relapse on Day 115. The event was considered drug related by the investigator.
The increase in ALT could be explained by recent use of methylprednisolone in a patient who was taking two potential hepatotoxic drugs. No serologies were reported. An infectious cause can not be ruled out.
- **002001/250/0030/0001** - 31 yo F, presented SAE of elevation of liver enzymes on Day 99, leading to drug discontinuation. She had a previous history of hepatitis. Baseline meds included ethinyl estradiol/ levonorgestrel. The patient received MP from Day 29 to 33 of study treatment, along with omeprazole and potassium chloride. On Day 99 she had elevation of liver enzymes (**ALT almost 20x ULN, AST 13xULN and BR increased 1.7xULN**). Hepatitis serology was negative for acute hepatitis A, B and C, EBV, CMV and Herpes simplex; with evidence of prior exposure to EBV,

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CMV and Hep B vaccination. On Day 149 patient recovered without treatment and without sequelae. Investigator considered event drug related.

Elevated ALT and BR, negative hepatitis serology but no testing for Hepatitis E. No mention of abdominal US to r/o biliary stones.

- **006049/250/2415/0003** – 48 F, lumbar pain on Day 28 requiring arthrodesis. Elevated ALT on Day 59 and 127 of placebo treatment. Hx of dysuria, high cholesterol and aphthous stomatitis. Concomitant meds: ezetimibe, paracetamol, tramadol, pantoprazole, nimesulide, fentanyl, metopimazine and pregabalin. On Day 59 ALT was 1.6xULN with normal AST/GGT/BR. On Day 127 ALT was **9.9xULN, with AST 12xULN and GGT 12xULN**. Normal BR. Drug was discontinued on Day 134. Retests done over the following week showed ALT and AST levels returning towards normal, but GGT was still above the normal range (4.6 ULN). No additional laboratory data are available after Day 139. The outcome of the ALT and GGT increased were unknown. The ALT was considered related to drug by investigator. No serology or abdominal US.
This is another case of ALT elevation with incomplete workup. In this case the increases in AST and GGT were higher than for ALT. This could be related to alcohol use, although such history is not mentioned.
- **006049/276/2003/0004** – 45 yo F developed SAE of elevated transaminases (**ALT 14 x ULN**) on Day 420. Hx of HTN, seasonal allergy, irritable bowel syndrome, colectomy. Medications at baseline: Loperamide, plantago extract, telmisartan (all taken for more than one year), oral vaccine, amlodipine, certostat (all taken for at least 6 months). After entering the trial: acetylcysteine (Day 154-157 and 327 to 332), aspirin Day 327 to 332, methylprednisolone (Day 371 to 375) and ranitidine (Day 371 to 375). On day 420, in addition to ALT 14x ULN, AST was 5.8x ULN with normal BR. On Day 423 retest showed ALT 7.7x ULN and AST 2.6x ULN. Liver oriented serologies were not performed. Abdominal US was normal. The patient reported nausea from Day 417 to 479. She was also found to have elevated neutrophil count without fever or evidence of infection. Last dose of placebo was received on Day 422. She followed washout procedure from Day 445 to 448. She recovered on Day 479, with normal liver enzymes. Event was considered related to study drug by the investigator.

Another case of significant ALT/AST elevation without liver serology in a patient taking placebo. There is no mention whether the patient used alcohol.

For most events of ALT elevation on placebo, there is an alternative explanation; for those without alternative explanation, workup was incomplete in most cases.

In active treatment Pool 2, in addition to those mentioned in Pool 1, SAEs were reported for 7 patients in the teriflunomide 7 mg group: cholecystitis (3 patients), cholecystitis acute, cytolytic hepatitis (2 patients), and cholelithiasis (this patient discontinued). One SAE was reported in the teriflunomide 14 mg group: hepatic function abnormal.

Selected narratives are provided below:

- **006049/250/2406/0006**, a 48-year-old female and **006049/250/2408/0003**, a 39 yo female, were diagnosed with “hepatic cytolysis” 1595 days and 1091 days into Teri 7. Both were taking concomitant medications known to be hepatotoxic (analgesics and or paracetamol) and the maximum ALT increase was <3x ULN and mild increase in AST. No serology or liver ultrasound was performed. Both patients recovered , one without drug discontinuation, and the other after discontinuing drug.

It appears that the coding of these events as cytolytic hepatitis is inappropriate based on the modest increase in ALT/AST. The transaminase elevation may be related to teriflunomide but confounded by use of multiple medications.

- **002001/124/0011/0007** - 43 yo M, experienced SAE of hepatic function abnormal. On Day 335 of Teri 14 treatment (on Day 80 of the LTS6048 extension study), with increased direct Bili on Day 362 (Day 107 of extension study). Concomitant therapies included lorazepam and baclofen since 3 months prior to entry. During the trial he also took baclofen, atorvastatin, pravastatin and fenofibrate, received MP on Day 330. On Day 335 ALT was 3x ULN, AST 2.5x ULN and GGT 1.6x ULN. Transaminase remained elevated with max value of **ALT 18.3x ULN** on Day 362, when direct Bilirubin was 1.3xULN. Study drug was discontinued on Day 336, followed by discontinuation of baclofen and fenofibrate. He underwent cholestyramine washout. Direct Bili remained elevated for 3 weeks. Patient was asymptomatic.

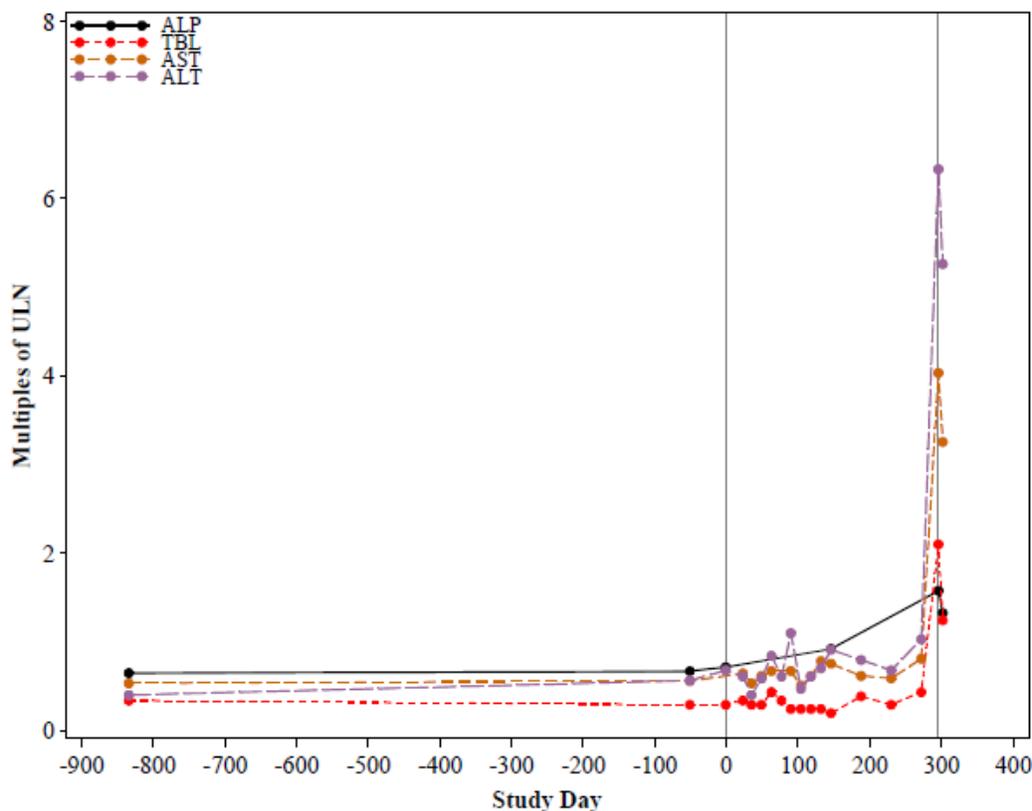
Case confounded by medications that could explain increase in ALT such as fenofibrate, baclofen and methylprednisolone. Negative hepatitis B and C, but no other serologies were done (e.g. CMV, EBV, hepatitis E). (He had eosinophil count 0.6 Giga/L on 10/30/2001 during the base study, it is unclear if he continued to have eosinophilia during the extension)

- **6050/2402/0020**, 37 yo patient 3.4 years into Teri 14 treatment (LTS6050) had an increase in **ALT >20 x ULN** and in total bilirubin (2.0 x ULN), with **jaundice** and asthenia. Serologic testing was positive for **Hepatitis A** due with presence of anti-HAV IgM antibodies. Study treatment was discontinued due to this event. The patient was last known to have improved 3 months after with ALT value of 4.8 x ULN, and normal bilirubin value.

This event was clearly not related to study drug.

- **6050/2602/0001**, 49 yo M from the UK, reported dark colored urine, pale stools and generalized itching on Day 283 (2.9 years) into Teri 7 treatment (in LTS6050). He had transaminase elevation including ALT at **6.3 x ULN and total bilirubin at 2.1 x ULN**. Concomitant medications included oenothera biennis oil, multivitamins, hypromellose, carbamazepine, panadeine, adapalene, propranolol, cetirizine, fusidic acid, sanatogen, protein supplements, carbomer, gabapentin, ibuprofen, and dexamethasone. Abdominal US confirmed multiple small gallstones in the gallbladder and mildly dilated (10 mm) common bile duct, consistent with a bile duct stone (as per the report, "there was just the suggestion of a tiny calculus noted within the extreme lower common duct"). He was diagnosed as **obstructive jaundice and cholelithiasis**. Drug was discontinued on Day 295 of the extension. On Day 296 laboratory showed ALT 6.3 x ULN and total BR 2.1 ULN. On Day 302 ALT was 5.3 x ULN and TB was 1.2 x ULN. He underwent washout procedure from Day 302 to 312. Laparoscopic cholecystectomy was performed on Day 444. On Day 582 he recovered from the event of cholelithiasis, which was considered related to study drug by the investigator.

The course of liver enzymes in patient 6050/2602/0001 is shown below.



The narrative states that “normalization of laboratory values occurred following laparoscopic cholecystectomy.” However, it appears to me that the liver enzymes decreased rapidly after washout, 3 months before the cholecystectomy which was done on Day 444. In my opinion this is a case of transaminase and bilirubin increase related to study drug but confounded by use of concomitant medications and biliary stones.

- **6050/2007/0009** A 34-year-old female patient had asymptomatic increase in transaminases, with ALT up to 24.4 x ULN with normal total BR on Day 595 of the extension study (ie, about 3.7 years after first intake of Teri 14 mg in the main study). Liver enzyme elevation had been identified 4 months prior. On Day 589, ALT was 14.4 x ULN, AST was 7 x ULN. Total BR increased to twice the baseline value but within normal. Serology testing was negative, except for Anti nuclear antibody (ANA) titer of +1/160. Abdominal US was negative. The study medication was permanently discontinued on Day 592. The patient received cholestyramine from Day 595 to Day 606 and recovered on Day 711.

This seems to be drug related. A low positive ANA titer is non-specific. There is no mention of additional workup to rule out an autoimmune process. There is no mention of serology to rule out hepatitis.

An AE of “drug induced liver injury” was reported during the SUR, as follows:

- **6049/616/3009/0007**, 49 yo F on Day 1176 (5.3 years) of Teri 7 treatment complained of epigastric pain and vomiting. Hepatologist diagnosed drug induced liver injury. ALT was 7.9x ULN, AST 3.2 x

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ULN, Alk P was 3.6 x ULN and total bilirubin was within normal range. Liver US showed hepatomegaly and mild cholecystolithiasis. Drug was discontinued on Day 1178. She recovered on Day 1220. No washout data were available.

Of note, several narratives for serious ALT increase in the application state that “liver related serologies were negative or revealed past infection” or that that liver serologies were not done. On December 29, 2011, in response to an FDA request for clarification Sanofi stated the following:

“In clinical protocols, a general guidance is introduced in the appendices describing the recommended handling of increases in transaminases. In case of confirmed elevations > 3xULN, this guidance requests to perform the following serologies: anti-HIV IgM, anti-HBc IgM, anti- HCV IgM, and anti-CMV IgM. In addition, specific serologic markers of recent infection can be done with EBV, herpes viruses and toxoplasma (depending on the clinical context). When “liver serologies were not done” or “liver related serologies were negative” or “revealed past infection.” is mentioned, it refers by default to this list of serologies as described in the clinical protocol appendix, unless specific details are mentioned.”

Therefore, when done, liver serologies appear to have been limited to basic hepatitis A, B and C virus serologies in most cases. Serologies for EBV, herpes viruses and toxoplasma were done in a handful of cases. Hepatitis E is not mentioned in a single case. Abdominal US was not always done. The role of concomitant drugs or alcohol abuse is seldom discussed in the narratives.

There does not appear to be an excess risk of serious hepatic- related adverse events for teriflunomide as compared to placebo in the controlled studies 2001 and 6049 (Pool 1). However, evaluation of cases indicate that most cases on placebo had either a possible cause (e.g hepatitis infection, use of high dose CS) or were not adequately worked up to identify the cause of ALT elevation. Of note, several cases of SAE of ALT elevation on teriflunomide are also missing a full work up or are confounded by the use of concomitant medications or presence of biliary stones. The lack of complete evaluation of the potential causes of liver toxicity decreases the likelihood of detecting differences in the risk of DILI between active drug and placebo

The liver safety profile of teriflunomide in this application is not inconsistent with the known hepatotoxic effects of leflunomide, which carries a box warning for hepatotoxicity, including fatal liver failure. Teriflunomide should carry the same box warning regarding hepatotoxicity.

- Infections and infestations SOC

The risk of overall serious infections and infestations in Pool 1 was similar in the Teri and placebo groups. A listing of SAE in this SOC for Pool 1 is presented below:

Table 22. Serious Adverse Events, Infections and Infestations SOC, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Infections and infestations	9 (2.1%)	6 (1.4%)	9 (2.2%)
Pyelonephritis	0	0	3 (0.7%)
Bacteraemia	0	0	1 (0.2%)
Cytomegalovirus hepatitis	0	0	1 (0.2%)
Gastroenteritis	2 (0.5%)	0	1 (0.2%)
Renal abscess	0	0	1 (0.2%)
Urinary tract infection	1 (0.2%)	0	1 (0.2%)
Urinary tract infection enterococcal	0	0	1 (0.2%)
Appendicitis	0	2 (0.5%)	0
Cellulitis	1 (0.2%)	0	0
Erysipelas	0	1 (0.2%)	0
Hepatitis C	1 (0.2%)	0	0
Herpes zoster	1 (0.2%)	0	0
Infected cyst	0	1 (0.2%)	0
Influenza	1 (0.2%)	0	0
Lung infection	1 (0.2%)	0	0
Pneumonia	0	2 (0.5%)	0
Skin infection	1 (0.2%)	0	0

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Source: Table 20, ISS. N= patients exposed. n (%) = number and percentage of patients with at least one treatment emergent SAE.

In general, there were few serious infectious events and there does not seem to be an imbalance in the overall number of serious infections in Pool 1. The following is an analysis of serious infections by MedDRA High Level Term (HLGT).

Table 23. Serious infections and infestations, Pool 1, by HLT

HLT	Placebo N= 421	Teri 7 N=429	Teri 14 N=415
Any (total)	9	6	9
Abdominal and gastrointestinal infections	3	2	1
Bacterial infections NEC	1	0	0
Cytomegaloviral infections	0	0	1
Enterococcal infections	0	0	1
Hepatitis viral infections	1	0	0
Herpes viral infections	1	0	0
Infections NEC	0	1	0
Influenza viral infections	1	0	0
Lower respiratory tract and lung infections	1	2	0
Sepsis, bacteraemia, viraemia and fungaemia NEC	0	0	1
Streptococcal infections	0	1	0
Urinary tract infections	1	0	5

Source: FDA analysis, AE original NDA dataset.

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As noted in these tables, six patients presented serious events of urinary tract infection in the Teri 14 mg group. These include 3 pyelonephritis, one renal abscess, one urinary tract infection reported as cystitis (in the Urinary tract infections HLT) and one enterococcal urinary tract infection (in the Enterococcal infections HLT) as compared to 1 urinary tract infection on placebo. Other serious infections in Teri 14 were one serious bacteremia (of periodontal origin), one gastroenteritis and one CMV hepatitis (probably a viral reactivation because of the presence of both, IgG and IgM antibodies). There were no opportunistic infections such as tuberculosis or fungal infections in Safety Pool 1. However, three cases of tuberculosis were reported in the ongoing studies (one case of ileal TB in TOWER, and one pulmonary TB on Teri 14 in TENERE and one pulmonary TB in TOPIC on Teri 7).

A listing of patients with SAEs in the Infections and infestations SOC in Pool 1 is as follows. Comments are added when deemed relevant. (In general narratives did not add much to the information provided in the AE datasets.)

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Listing of patients with SAEs in infections and infestations SOC, Pool 1.

Patient ID	Age Sex	PT	Action with drug	Out-come	Rel day onset/ duration (days)	Comments
Teri 14						
006049-124-1212-0003	42 F	Gastroenteritis	Temp interrupted	R	409 (9)	History of irritable bowel syndrome, hospitalized for suspected pancreatitis (lipase elevation with normal amylase) on Day 409. The lipase normalized, and the investigations did not confirm the pancreatitis. All drugs temporarily stopped, and restarted a week later. Review of patient profile indicates that she had started with borderline high amylase (95 U/L, normal 28-1000 U/L) and had intermittent elevated amylase (up to 113 U/L) throughout the study. <i>This is unlikely related to teriflunomide.</i>
006049-152-3803-0015	29 F	Pyelonephritis	None	R	9 (8)	At screening (Day -13), laboratory results showed red blood cell (RBC) in urine was too numerous to count. Seven days later on Day -6, urinalysis showed white blood cell (WBC) 3-7. <i>She may have already had a UTI prior to study entry.</i>
006049-203-4101-0026	50 F	Bacteraemia	Temp interrupted	R	561 (14)	Patient developed fever (39C) on Day 561. An examination by marked leukocytes showed accumulation of leukocytes “in alveolar protuberance in the upper and lower mandibula,” which was suspected to be a periodontal affection. Blood cultures grew streptococcus mitis. She was hospitalized and improved on antibiotic therapy. She was thought to have a bacteremia of odontologic origin.
006049-250-2407-0006	30 F	Pyelonephritis	None	R	664	
006049-276-2003-0003	33 F	Pyelonephritis	Discontinued	R	68 (47)	She recovered after receiving several antibiotics (bactrim, cefotaxime, cefuroxime) within 1.5 months.
006049-380-2812-0001	32 M	CMV hepatitis	Discontinued	R	253 (47)	On day 238 he developed fever. On Day 253 he had increases in ALT, AST and GGT, alkaline phosphatase and total bilirubin (maximum ALT elevation: 13.2 x ULN, maximum total bilirubin elevation: 3.2 x ULN) 9 months into Teri 14 treatment. Amylase was up to 1.6 xULN on Day 256, with normal lipase. He was not taking any concomitant meds. Serology was negative for Hepatitis A, B and C, EVB and Parvovirus B19, and positive for anti-CMV IgG and IgM antibodies. He was diagnosed as CMV hepatitis. Teri was discontinued due to this event. The patient recovered within 5 weeks. As per the patient profile he had normal WBC throughout the study, except for mild neutropenia at visit 11 (at the time that first ALT

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						elevation was detected) lasting for two weeks. Lymphocyte count was normal. <i>Since there is positive IgG and IgM antibodies to CMV, this appears to be a reactivation of prior viral infection.</i>
006049-380-2819-0005	37 M	Urinary tract infection enterococcal	Temp interrupted	R	431 (11)	
006049-616-3004-0009	42 M	Renal and perinephric abscess	Discontinued	R	43 (18)	Hx of calcification of right kidney. Teri had been temporarily interrupted on Day 8 because of MS relapse. On an unspecified day, lab results showed elevated WBC in urinalysis and high CRP level. An abdominal US and CT of the abdomen on Day 46 showed a renal and perinephric abscess and urine culture revealed staph aureous. He was asymptomatic. He received IV antibiotherapy and the abscess was surgically removed. The patient discontinued the study treatment and recovered within 2.5 weeks. WBC/ neutrophil/ lymphocyte count were normal and unchanged from screening (despite the perinephric abscess).
006049-826-2601-0010	43 F	Urinary tract infection	None	R	329 (9)	She was hospitalized, received intravenous (IV) antibiotics therapy (gentamycin, trimethoprim) and fluids and recovered within a week. <i>This was reported as cystitis but it may have been a pyelonephritis, because it required hospitalization and IV treatment. She did have mild neutropenia starting at visit 15 (b)(4), until the end of study (visit 20, (b)(4), but she was treated with multiple medications that may have contributed to neutropenia.</i>
Teri 7						
006049-250-2401-0007	39 F	Appendicitis	interrupted	R	545 (1)	
006049-250-2407-0011	36 F	Erysipelas	None	R	286 (11)	
006049-578-3604-0005	46 F	Pneumonia	None	R	34 (25)	Prior hx of pneumonia and respiratory tract infections. Concomitant meds: carisoprodol & budesonide. Pt hospitalized and treated with antibiotics and recovered. She eventually discontinued because of patient wish on Day 166. <i>It is unclear if this infectious event was related to teriflunomide. She was not neutropenic or lymphopenic at the time of the event.</i>
006049-616-3009-0012	49 M	Appendicitis& peritonitis	interrupted	R	561 (9)	
006049-616-3009-0013	29 F	Pneumonia	interrupted	R	653 (15)	Patient experienced pneumonia a day after she presented status epilepticus. She was treated with antibiotics and acyclovir and

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						recovered from pneumonia. <i>The pneumonia was likely aspiration pneumonia, not related to study treatment.</i>
006049-643-3201-0014	24 F	Infected cyst	None	R	276	
Placebo						
006049-124-1212-0002	22 F	Herpes zoster	interrupted	R	681 (25)	
006049-152-3804-0002	22 M	Gastroenteritis	interrupted	R	331 (4)	
006049-276-2000-0004	49 F	Lung infection	interrupted	R	157 (10)	
006049-528-4605-0007	24 M	Urinary tract infection	None	R	312 (11)	He had MS with spinal cord involvement which led to bladder dysfunction and infections. He had two previous urinary tract infections, around Day 200. On Day 312, he experienced a third urinary tract infection, which led to hospitalization.
006049-804-3501-0004	47 F	Hepatitis C	Discontinued	R	212 (190)	
006049-804-3510-0002	36 F	Influenza	None	R	776 (9)	
006049-826-2607-0001	34 M	Gastroenteritis Gastroenteritis	interrupted interrupted	R R	373(4) 706 (7)	

Source: NDA DAE dataset and narratives. Outcome: R= recovered. C= Completed study.

None of the narratives or CRFs of infectious SAEs include data on WBC at the time of the infection. However, patient profiles submitted on 10/31/11 provided information on laboratory evaluations by date, sometimes close to the date of the event. None of the patients with available data around the time of infection were severely neutropenic or lymphopenic.

Cases 6049/3803/0015, 6049/3004/0009 and 6049/2812/0001 were considered by the investigator not to be related to study drug. I agree. I also think that the episode of gastroenteritis/pancreatitis in subject 6049/1212/0003 was probably not related to teriflunomide. The other serious infections could potentially be related to teriflunomide.

Table 24. Serious adverse events, Infections and Infestations SOC, Pool 2a

Primary System Organ Class Preferred Term n(%)	teriflunomide	
	7 mg (N=587)	14 mg (N=548)
Infections and infestations	25 (4.3%)	22 (4.0%)
Urinary tract infection	3 (0.5%)	4 (0.7%)
Pyelonephritis	1 (0.2%)	3 (0.5%)
Pneumonia	3 (0.5%)	2 (0.4%)
Anal abscess	0	1 (0.2%)
Bacteraemia	0	1 (0.2%)
Cytomegalovirus hepatitis	0	1 (0.2%)
Gastroenteritis	2 (0.3%)	1 (0.2%)
Gastrointestinal infection	0	1 (0.2%)
Hepatitis A	0	1 (0.2%)
Lung abscess	0	1 (0.2%)
Pneumonia streptococcal	0	1 (0.2%)
Renal abscess	0	1 (0.2%)
Respiratory tract infection	0	1 (0.2%)
Urinary tract infection enterococcal	0	1 (0.2%)
Urosepsis	0	1 (0.2%)
Vestibular neuronitis	0	1 (0.2%)
Wound infection	0	1 (0.2%)
Appendicitis	5 (0.9%)	0
Bronchitis	1 (0.2%)	0
Bronchitis viral	1 (0.2%)	0
Bronchopneumonia	1 (0.2%)	0
Cellulitis	1 (0.2%)	0
Diverticulitis	1 (0.2%)	0
Erysipeloid	1 (0.2%)	0
Infected cyst	1 (0.2%)	0
Infected sebaceous cyst	1 (0.2%)	0
Oral herpes	1 (0.2%)	0
Perirectal abscess	1 (0.2%)	0
Pneumonia bacterial	1 (0.2%)	0
Postoperative wound infection	1 (0.2%)	0
Subcutaneous abscess	1 (0.2%)	0
Tooth abscess	1 (0.2%)	0
Tubo-ovarian abscess	1 (0.2%)	0

Source: SUR.

The pattern of serious infections in Pool 2 is similar to Pool 1. Notwithstanding the limitations of the database in terms of size and duration, there was no obvious dose response in the risk of serious infections and infestations between Teri 7 and 14 in Pool 2 or 2a. The most common serious infections were urinary/renal infections (11/ 1135= 1% of all patients on teriflunomide) and respiratory infections (also 1% of patients). It is difficult to draw conclusions in the absence of a comparator group. The case of CMV hepatitis could have been a viral reactivation. There were no apparent serious opportunistic infections except for one case of oral herpes in Pool 2.

- SAE in Injury, poisoning and procedural complications SOC

Patients with serious AE in the Injury, poisoning and procedural complications are shown below.

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Table 25. SAE, Injury, poisoning and procedural complications, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Injury, poisoning and procedural complications	4 (1.0%)	5 (1.2%)	9 (2.2%)
Ankle fracture	0	0	2 (0.5%)
Fall	0	0	2 (0.5%)
Burns third degree	0	0	1 (0.2%)
Concussion	0	1 (0.2%)	1 (0.2%)
Facial bones fracture	1 (0.2%)	0	1 (0.2%)
Foot fracture	1 (0.2%)	1 (0.2%)	1 (0.2%)
Hand fracture	0	0	1 (0.2%)
Ligament injury	0	0	1 (0.2%)
Muscle strain	0	0	1 (0.2%)
Post-traumatic pain	0	0	1 (0.2%)
Skin laceration	0	0	1 (0.2%)
Skull fracture	0	0	1 (0.2%)
Spinal compression fracture	0	0	1 (0.2%)
Tibia fracture	0	0	1 (0.2%)
Contrast media reaction	0	1 (0.2%)	0
Femoral neck fracture	0	1 (0.2%)	0
Lower limb fracture	1 (0.2%)	0	0
Multiple drug overdose	0	1 (0.2%)	0
Traumatic brain injury	1 (0.2%)	0	0

Source: Table 20, ISS.

The risk of SAE in this SOC was twice in the Teri 14 group as compared to placebo, driven by a higher number of fractures (8 vs 3 in the Teri 14 and placebo group) but the numbers are small (2% vs. 1%). Teriflunomide is associated with increased urinary excretion of phosphate. Chronic severe hypophosphatemia is associated with fractures. However, patients with fractures did not have severe hypophosphatemia. There was no increase in incidence of SAE of fractures in the TOWER study or in the evaluation of all serious and non-serious fractures in Pool 1 or TOWER.

In Pool 2, the overall risk of SAE in this SOC was 2.7% on Teri 7 and 2.4% on Teri 14, which is higher than the risk during the core studies (not unexpected, with longer exposure). The pattern of events was similar to that in Pool 1. There was no evidence of dose response.

- SAEs in Investigations SOC

SAEs in the Investigations SOC in Pool 1 presented by 2.1 %, 2.9% and 3.1% of patients in the Teri 7 and Teri 14 and placebo treatment groups, and they were mostly liver-related. A table of SAEs in this SOC is shown in Table 21 of this review. Investigations SAEs other than

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hepatobiliary included one case of neutrophil decreased (discussed under Blood and lymphatic system disorders) and two cases of Lipase increased with Teri 7. These cases are as follows.

- **006049/620/4202/0001**, 25 yo F developed SAE of elevated serum lipase 5xULN (522 U/L) on Day 253 of Teri 7 treatment, leading to study discontinuation on Day 276. She was previously treated with betaferon for MS. Concomitant therapies included diazepam and omeprazole. She underwent washout procedure with cholestyramine from Day 276 to 282 and recovered from the event on Day 311. On Day 370 she experienced colitis with diarrhea; on Day 405 she was diagnosed with ulcerative colitis by colonoscopy. She recovered on Day 450. Both events were considered related to drug by the investigator. *I believe the lipase increased may be related to study drug but the colitis probably not since it occurred after washout.*
- **6049/1802/0005**. 57 yo F developed gastroenteritis on Day 1086 of Teri 7 treatment, and asymptomatic lipase elevation on routine laboratory (at 3.5xULN) on Day 1177 of Teri treatment. Lipase was just above ULN at baseline (1.05xULN) and fluctuated under 2x ULN throughout the study, including the extension period. She had been treated previously with temsirolimus and prednisone for MS. Concomitant meds included ofloxacin and fampridine. She recovered from the events without sequelae without drug discontinuation. Investigator considered the event not related to IP. Treatment is ongoing.

Pool 2.

The overall % of patients with SAE in the Investigations SOC in Pool 2 was 4.6% in Teri 7 and 4.7% in Teri 14. Most of the events were additional SAE of ALT increased and hepatic enzyme increased. There were 2 additional cases of lipase increased in the Teri 7 group.

- **002001/124/0018/0004**, 45 yo F developed elevated lipase on Day 1848 of Teri 7 treatment, On Day 2940 she had an abdominal US that showed cholelithiasis and hepatic steatosis. The same day she reported decreased vibration sensation in four limbs. Approximately 3 months later she presented abdominal pain and was diagnosed with choledocholithiasis and acute cholecystitis. She underwent laparoscopic cholecystectomy. She recovered from cholecystitis and abdominal pain. She has not recovered from peripheral neuropathy. Treatment is ongoing.
- **006049/756/1802/0005**, 57 yo patient referred to above, in Pool 1.

It is difficult to evaluate causality without a control arm. Both patients recovered while still on drug, and one was associated with choledocholithiasis. However, the role of teriflunomide can not be ruled out.

- SAE in Musculoskeletal and connective tissue disorders SOC

In Pool 1 there was no imbalance in SAE in this SOC (1 to 1.2% in each treatment group). In Pool 2, there were very few events and there was no evidence of dose response. Of note, there was one case of rhabdomyolysis (002001-124-0011-0003, 31 year old female) on Teri 7 after a session of spinning on Day 72 of study treatment. CK was 2940 U/L (nl 0-167). No other chemistries are available from that day. Drug was temporarily discontinued and re-started without recurrence of event. On repeat testing five days later, CK was 228 U/L. In a subsequent measurement one week later, CK was normal (132 U/L). The patient recovered without treatment.

- SAE in Neoplasms SOC

Overall, the risk of neoplasms with teriflunomide in safety Pool 1 was no higher than that of placebo. In the placebo group there were one cervix carcinoma, one breast cancer, one meningioma, one thyroid adenoma and one thyroid cancer. In the Teri 7 group there were one uterine leiomyoma and one ovarian germ cell teratoma benign. In the Teri 14 group there were one adrenal adenoma, one cervix carcinoma and one uterine leiomyoma. A table of number of patients with SAE in the Neoplasms SOC in Pool 2 is presented below.

Table 26. Serious Adverse Events, Neoplasms SOC, Pool 2a.

Primary System Organ Class Preferred Term n(%)	teriflunomide	
	7 mg (N=587)	14 mg (N=548)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (2.0%)	8 (1.5%)
Uterine leiomyoma	2 (0.3%)	4 (0.7%)
Adrenal adenoma	0	1 (0.2%)
Cervix carcinoma stage 0	0	1 (0.2%)
Cholesteatoma	0	1 (0.2%)
Renal cancer	0	1 (0.2%)
Basal cell carcinoma	3 (0.5%)	0
Breast cancer	2 (0.3%)	0
Cervix carcinoma	1 (0.2%)	0
Colon cancer	1 (0.2%)	0
Ovarian germ cell teratoma benign	1 (0.2%)	0
Renal cell carcinoma	1 (0.2%)	0
Renal cell carcinoma stage II	1 (0.2%)	0

Source: Table 1.5.5.1., 120-day SUR

Overall in Pool 2a (updated analysis submitted with the 120-day SUR), there were 20 malignancies, including three renal cell carcinomas, 2 ½, 4 and 6 years into teriflunomide treatment. One was symptomatic and two were diagnosed by routine per protocol imaging in asymptomatic patients.

Upon an FDA request, Sanofi conducted a search for all cases of potential renal malignancies in the teriflunomide database other than Pool 2. No additional cases were found in patients treated with teriflunomide. However, one case of asymptomatic renal cell carcinoma was diagnosed during a screening abdominal US in a patient not exposed to teriflunomide (randomized but not treated in study 6045 [adjunct study to IFN beta]).

The cases of renal cell carcinoma in the teriflunomide database are summarized below.

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Patients	Exposure to teriflunomide	Tumour type	Tumour size	TNM
6050-12030017 (47 years-old-male)	2 yrs teriflunomide 14 mg	Adenocarcinoma	1.7x1.5x1.2cm	T1N0M0
6048-250-0024-0002 (39 years-old-male)	6 yrs teriflunomide 7 mg	Adenocarcinoma	- 1.5cm (on surgical specimen) - 1.9x2.4x2.5cm (on CT scan)	pT1N0M0
6048-124-0015-0014 (43 years-old- male)	4 years teriflunomide 7 mg	High grade rhabdoid tumor	5x6x4.5cm (on surgical specimen)	T1N0M0
PDY6045-7005-0005 (48 years-old- male)	Never exposed to teriflunomide	Adenocarcinoma (hypernephroma)	2.6cm (ultrasound) 22 x 21 mm (CT-Scan)	-

Source Table 1. 2/13/12 response to FDA.

In summary, there was no evidence of dose response in terms of serious neoplasm in Pool 2. The size, duration and uncontrolled nature of the database are inadequate to evaluate whether teriflunomide is associated with increased risk of malignancies in the long term. The types of malignancies observed in Pool 2 are common neoplasms such as breast, colon, skin, uterine neoplasms, except for three cases of renal carcinomas in patients exposed to teriflunomide. In a study evaluating the utility of urinary/renal ultrasonography in patients with no upper urinary tract symptoms, the detection rate of incidental renal carcinoma was approximately 0.2% (among subjects 33 to 90 years old [mean 55 years]).¹⁴ The incidence of renal carcinoma in patients treated with teriflunomide who underwent serial US in the teriflunomide program was 0.3% (3/1100 patients). Additionally, one case of renal carcinoma was diagnosed in a patient not exposed to teriflunomide. Therefore, teriflunomide appears unlikely to have had a role in the development or accelerated growth of these cancers.

- SAEs in the Immune System, Endocrine and Metabolism and nutrition disorders SOCs

There were no SAE in these SOCs in Pool 1. In Pool 2 there was one report of sarcoidosis (Immune system disorder, Day 2421), one of thyroiditis (endocrine disorder, Day 1874) and one of diabetes mellitus (metabolism and nutrition disorders, Day 1277), all three on Teri 14.

It is difficult to assess causality in the absence of a comparator group. The case of sarcoidosis was of pulmonary sarcoidosis, and it is described below.

¹⁴ Haliloglu et al. Urinary ultrasonography in screening incidental renal cell carcinoma: is it obligatory? Int Urol Nephrol (2001) 43:687-690.

- **2001/124/0014/0029**, a 43 year old female received placebo in the base study, and Teriflunomide 14 g in extension study, starting in April 2002. Xray at baseline was not done but an Xray from 2001 was normal. She developed chronic cough in Dec 2008, with no fever or shortness of breath. Chest Xray showed confluent fibronodular changes in the upper two thirds of the lung, with volume loss. The radiologist stated that the findings are nonspecific but could represent drug related changes. CT of chest suggested sarcoidosis without adenopathy or infection. A pulmonologist’s note from April 2009 states that the likely diagnosis was sarcoidosis, although he was waiting for PFTs, calcium levels and ACE levels and recommended lung biopsy. Bronchoscopy and punch biopsy of the lung “favors” sarcoidosis. The report of the lung biopsy states: “multiple granulomas which appear to be noncaseating with giant cells. ZN, GMS and PAS stains were negative, but the specimen was quite small to properly assess the possibility of AFB infection. However, in the presence of noncaseating granulomas in the parabrachial tissue, one would favor sarcoidosis.” She was treated with Pulmicort and her cough improved. Prednisone treatment was deemed not necessary.

Although the diagnosis is likely pulmonary sarcoidosis, it is not definitive. As per a response submitted to FDA on 3/6/12, results of calcium levels and Angiotensin Converting Enzyme were normal (ACE level was 49 U/L, normal 9 – 63 U/L for subjects >20 years old), and therefore not supporting a diagnosis of sarcoidosis. Other causes of non-caseating granuloma are lymphoma, small cell carcinoma and infections (e.g. histoplasmosis).

- SAEs in Nervous system disorders SOC

The overall number of SAE in the Nervous system disorders SOC was similar between teriflunomide and placebo in Pool 1. A summary table of such events is as follows.

Table 27. Serious adverse events, Nervous system disorders SOC, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Nervous system disorders	6 (1.4%)	5 (1.2%)	7 (1.7%)
Multiple sclerosis	3 (0.7%)	0	3 (0.7%)
Convulsion	0	0	1 (0.2%)
Loss of consciousness	0	0	1 (0.2%)
Monoparesis	0	0	1 (0.2%)
Syncope	0	0	1 (0.2%)
Cervical myelopathy	0	1 (0.2%)	0
Facial nerve disorder	0	1 (0.2%)	0
Glossopharyngeal neuralgia	1 (0.2%)	0	0
Hypertonia	1 (0.2%)	0	0
Muscle spasticity	1 (0.2%)	0	0
Parkinsonism	0	1 (0.2%)	0
Status epilepticus	0	1 (0.2%)	0
Trigeminal neuralgia	0	1 (0.2%)	0

Source: ISS, Table 20.

There was no evidence of dose response. The event with the most number of reports was multiple sclerosis (3 on placebo, 3 on Teri 14).

Listing of patients with SAE in Nervous system disorders SOC in Pool 1 is presented as follows.

Patient ID	Age Sex	PT	Action with drug	Out come	Rel day onset	Duration (days)
Teri 14						
002001-124-0015-0025*	42F	Loss of consciousness (LOC) Concussion (Fall)	D/C D/C	R w S R w S	182 182	1 70
006049-152-3801-0017	22 M	Convulsion	NONE	R	344	1
006049-276-2007-0012*	46 F	Syncope	NONE	R	326	3
006049-616-3003-0029	51 F	Monoparesis	NONE	R	398	32
006049-643-3205-0014	50 M	Multiple sclerosis	NONE	R	227	154
006049-752-3401-0010	41 M	Multiple sclerosis	NA	R w S	740	39
006049-792-5001-0001	25 F	Multiple sclerosis	D/C	R w S	472	
Teri 7						
002001-124-0019-0006	61 M	Trigeminal neuralgia	NO CHANGE	R	36	126
006049-152-3803-0016	41 F	Parkinsonism	NONE	R	52	32
006049-616-3006-0005	45 F	Concussion	NONE	R	602	22
006049-616-3008-0002	53 M	Cervical myelopathy	NONE	R w S	124	641
006049-616-3009-0013	29 F	Status epilepticus	Interrupt	R w S	653	15
		Status epilepticus	D/C	R w S	695	17
006049-804-3510-0004	25 M	Facial nerve disorder	NONE	R	329	10
Placebo						
006049-152-3802-0006	22 M	Hypertonia	NONE	R	25	8

006049-152-3802-0010	43 M	Muscle spasticity	NONE	R w S	66	17
006049-276-2008-0011	31 F	Meningioma	D/C	Continuing	511	
006049-276-2012-0002	32 F	Multiple sclerosis	NONE	R	260	32
006049-616-3003-0021	30 F	Multiple sclerosis	NONE	R w S	51	35
006049-616-3009-0016	44 M	Glossopharyngeal neuralgia	NONE	R w S	199	16
006049-643-3205-0023	50 F	Multiple sclerosis	NA	R	232	
006049-804-3501-0002	36 M	Traumatic brain injury	NONE	R	174	8

Source: AE datasets. * See comments below.

The following comments apply to selected patients from the above table.

- Patient 002001/124/0015/002 with LOC fell “due to MS” (lost balance at top of the stairs), hit her head and had skull fracture and haematotympanum. She lost consciousness for 2-3 minutes. Concomitant meds modafinil and amytriptiline. The event was not considered related to study drug by the investigator. Patient discontinued because of this AE.
- Patient 006049/276/2007/0012 had a history of hypertension. She had been started on enalapril and HCTZ for HTN on Day 319, which led to hypokalemia and dehydration. These drugs were discontinued on Day 325. On Day 326 she presented hypotensive syncope. She recovered with IV fluids.
- Patient 6049/3801/0017, 22 year old male developed generalized seizures one year into Teri 14 treatment. He a history of tension headache and anxiety disorder. No concomitant meds were reported. On day 334, during an MRI, he had a generalized seizure associated with urinary incontinence, followed by confusion. . The convulsion lasted for 3 hours and stopped without corrective treatment. He had no prior history of seizures. CT scan did not show any acute abnormalities. Routine labs were normal. He was diagnosed with generalized seizure secondary to old demyelinating lesion of MS. He was given carbamazepine as prophylaxis. Patient continued treatment without further seizures.
- Patient 6049/3009/0013, 29 yo female on Teri 7. Concomitant meds: baclofen. She was hospitalized due to status epilepticus on Day 654. CT scan of brain showed no acute changes, chest xray showed pneumonia. Routine labs were normal. She was treated with antiepileptics and antibiotics and recovered from both events. Six weeks later, there was recurrence of status epilepticus that led to study discontinuation.

Except for the case of status epilepticus in Patient 6049/3009/0013, the events in the nervous system disorders SOC in Pool 1 were not considered related to study drug by the investigators.

In general, in this application, there is little information in the narratives beyond the information included in the demographic and AE datasets. In particular, there is no description whether any evaluation was done for patients with syncope/loss of consciousness. There is also no description of AEs of MS relapse that would allow

understanding why they were considered adverse events versus a manifestation of the underlying disease.

On October 21, 2011, the DNP requested the following information: “For adverse event reports of Multiple Sclerosis, provide detailed information about studies conducted to rule out causes of neurologic deterioration other than MS relapse, treatment received and outcome.” On November 15, 2011 the applicant responded that the evaluation of neurologic deterioration was focused on distinguishing MS relapse/progression from peripheral neuropathy. If peripheral neuropathy was suspected, electrophysiological nerve conduction studies had to be performed. If the neuropathy was thought to be drug related, treatment had to be discontinued and rapid elimination procedure had to be performed. There is no mention of work-up needed in cases of MS relapse to rule out CNS infection, neoplasia or vascular events.

Patients with SAE in Nervous system disorders SOC, Pool 2 are presented in the following table.

Table 28. Serious adverse events in Nervous system disorders SOC, Pool 2

Primary System Organ Class Preferred Term n(%)	teriflunomide	
	7 mg (N=587)	14 mg (N=548)
Nervous system disorders	14 (2.4%)	9 (1.6%)
Loss of consciousness	1 (0.2%)	3 (0.5%)
Multiple sclerosis	1 (0.2%)	3 (0.5%)
Convulsion	1 (0.2%)	1 (0.2%)
Monoparesis	0	1 (0.2%)
Syncope	0	1 (0.2%)
Cerebrovascular insufficiency	4 (0.7%)	0
Cervical myelopathy	1 (0.2%)	0
Epilepsy	1 (0.2%)	0
Facial nerve disorder	1 (0.2%)	0
Intracranial aneurysm	1 (0.2%)	0
Parkinsonism	1 (0.2%)	0
Status epilepticus	1 (0.2%)	0
Trigeminal neuralgia	1 (0.2%)	0

Source, Table 1.5.5.2, ISS.

There is no evidence of dose response between Teri 14 and Teri 7 in Pool 2. Of note, there were a total of 3 cases of loss of consciousness (LOC) and one of syncope with Teri 14 and one LOC with Teri 7. Two of the cases were described under Pool 1. The additional cases of LOC are as follows:

- **002001/124/0011/0016:** 31 yo female, presented LOC on Day 1812 of Teri 14 treatment during the extension study (LTS6048). She recovered the same day. The patient had a medical history of depression, epilepsy. Concomitant therapies included gabapentin, oxazepam, clonazepam, almotriptan, diclofenac and cyanocobalamin. On Day 1562 she felt dizzy “as she was getting off.” She lost balance and fell and was unconscious for an unknown length of time. After she awoke she felt disoriented and slow. She recovered the same day. She continued study drug.

This case of LOC was preceded by dizziness and loss of balance.

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- **002001/124/0011/0012:** 43 yo female, presented LOC on Day 1496 of Teri 7 therapy during the extension study (LTS6048). She recovered the same day. Concomitant medication included amitriptyline, naratriptan, rofecoxib, oxybutynin, baclofen, residronate, cerebex, paracetamol and zolmitriptan. The patient suffered loss of consciousness and then she fell down stairs. When she awoke, she was confused, disoriented, and unable to recall the events prior to the fall. She also complained of dizziness, nausea, vomiting, pain in head, neck and back. A CT scan of the head was normal. The patient received methylprednisolone from Day 1496 to Day 1498 for MS relapse. She recovered without sequelae. The LOC and fall were considered as not related to the IP by the Investigator. She continued treatment.

In this case it appears that the LOC preceded the fall. It is unclear if the nausea and vomiting preceded or occurred after the fall. When she woke up she has confused. This could have been a seizure.

Apparently there was no workup done for syncope/loss of consciousness and no information about vital signs in these patients. Both patients were taking multiple concomitant medications. While these events could be drug-related, the patients continued in the trial without repeated events therefore they are likely not related to study drug.

- SAE in Pregnancy, puerperium and perinatal conditions SOC

There was one SAE of spontaneous abortion on placebo and two on Teri 14. Additionally, there was one post-abortion hemorrhage on Teri 14. No events on Teri 7. In Pool 2, there were a total of 4 pregnancies in each treatment group. (See Pregnancy section).

- SAEs in the Psychiatric disorders SOC

There was no imbalance in the number of serious psychiatric disorders in Pool 1: 4 (1.0%), 4 (0.9%) and 2 (0.5%) in the placebo, Teri 7 and Teri 14 groups, respectively. Of note, there was one suicide attempt and one case of depression in the placebo group, two of major depression in the Teri 7 group and one suicide attempt in the Teri 14 group.

Table 29. Serious adverse events in Psychiatric SOC, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Psychiatric disorders	4 (1.0%)	4 (0.9%)	2 (0.5%)
Mood altered	0	0	1 (0.2%)
Suicide attempt	1 (0.2%)	0	1 (0.2%)
Abnormal behaviour	1 (0.2%)	0	0
Conversion disorder	1 (0.2%)	0	0
Depression	1 (0.2%)	0	0
Major depression	0	2 (0.5%)	0
Panic attack	1 (0.2%)	0	0
Psychosomatic disease	0	1 (0.2%)	0
Somatoform disorder	0	1 (0.2%)	0

Source: Table 20, ISS.

Brief narrative of the case of suicide attempt in the Teri 14 group is as follows:

- 002001/250/0021/0002. 42 yo female experienced suicide attempt with lorazepam and citalopram due to increasing depression on Day 118 of Teri 14 treatment. She had a prior history of mood disorder but was not depressed at study entry. She wanted to continue in the trial. The event was considered not related by the investigator. Treatment continued and she eventually discontinued because of hypertension.

A table summarizing SAE in the Psychiatric disorders SOC in Pool 2 is presented below.

Table 30. Serious adverse events, Psychiatric disorders SOC, Pool 2.

Primary System Organ Class Preferred Term n(%)	teriflunomide	
	7 mg (N=587)	14 mg (N=548)
Psychiatric disorders	6 (1.0%)	3 (0.5%)
Suicide attempt	1 (0.2%)	2 (0.4%)
Mood altered	0	1 (0.2%)
Bipolar disorder	1 (0.2%)	0
Depression	1 (0.2%)	0
Major depression	2 (0.3%)	0
Psychosomatic disease	1 (0.2%)	0
Somatoform disorder	1 (0.2%)	0

Source: Table 1.5.5.2, ISS.

There was no evidence of dose response in the Psychiatric disorders SOC in Pool 2. There were two additional suicide attempts in the extension studies (one on Teri 14 and one on Teri 7). Brief narratives of these cases are presented below.

- 45 yo female (006049/208/4801/0001), attempted suicide on Day 1018 of Teri 14 treatment by drug overdose. She had a medical history of depression. She continued to have suicidal ideation and had two other suicidal attempts during the study.

- 38 yo female, (006049/792/5006/0001) attempted suicide on Day 289 of Teri 7 treatment, by drug overdosing with antidepressants. She had received placebo during core DB study and had a history of “mental disorder.”

Depression and suicidality are not uncommon in patients with MS. It is difficult to assess causality in the absence of a control group. Two patients attempted suicide in the controlled period (one on teriflunomide, one on placebo). Two patients completed suicide in the NDA database (one on teriflunomide and one on placebo). There is no evidence that teriflunomide increases the risk of suicide in the controlled database.

- SAE in Renal and urinary disorders SOC

In Pool 1, there was one SAE of renal colic and one of urethral stenosis, both in the Teri 14 group. Narratives are as follows.

- 6049-2005-0015. A 41-year-old male experienced increase of ALT intermittently during Teri 14 therapy, and a renal colic 537 days into teriflunomide therapy. Concomitant therapies included levothyroxine sodium, pregabalin, and ibuprofen. On Day 538, the patient was hospitalized for severe pain in the left kidney area. Laboratory results showed creatinine of 1.4 mg/dL and a renal ultrasound revealed a left kidney grade I ectasia (distension) but without stones. He was diagnosed with renal colic and was treated with tamsulosin, levofloxacin, and transurethral implantation. On Day 540, he was discharged home and the catheter was removed on Day 582. On Day 584, the patient recovered from renal colic without sequelae. *The event was considered as not related to the IP by the Investigator.*
- 6049/3805/0005. A 48-year-old female with history of diabetes mellitus, experienced urethral stenosis, shoulder tendinitis, focal hepatic lesion (coded as haemangioma of liver), and polyneuropathy, respectively 38, 127, 176, and 576 days after the first dose of Teri 14. The patient recovered from the urethral stenosis and tendonitis with corrective treatments. The haemangioma and polyneuropathy were still ongoing by the day of the last report. *It is unclear how the diagnosis of urethral stenosis was made and how she was treated.*

In Pool 2, the extension studies, there were two additional SAE of nephrolithiasis in the Teri 14 group, and one case of bladder prolapse, one acute renal failure and one urinary retention in the Teri 7 group. The cases of nephrolithiasis and the case of acute renal failure are as follows.

- **002001/124/0010/0003**, 44 yo F diagnosed with nephrolithiasis on Day 1379 of Teri 14 treatment. She was hospitalized and percutaneous nephrolithotomy. She also presented SAE of pneumonia on Day 826 of Teri treatment, and fracture of right leg on Day 2190 of Teri 14 treatment. Urinalysis showed intermittent positive blood (trace to large, perhaps related to menstrual period or to lithiasis) over the years, with nitrite also intermittently positive over the years. Drug was not discontinued. Treatment is ongoing. Review of blood inorganic phosphorus levels shows normal phosphate at baseline (1.03 mmol/L, normal 0.87 to 1.45) with intermittent mild hypophosphatemia (0.76 – 0.86) during the study, and low normal phosphate levels at other times. Uric acid also normal at entry (244 umol/L, normal 150-390) with intermittent hypouricemia during the study (lowest value 106 on week 276 of LTS048, roughly day 2184 of Teri treatment).

- **006049/250/2407/0034**, 26 yo M was diagnosed with nephrolithiasis on Day 165 of Teri 14 treatment during extension study. He had received placebo during the core study. There was no baseline US. On day 165 he presented severe lumbar pain. He was hospitalized and diagnosed with nephrolithiasis, requiring lithotripsy. He recovered without sequelae. The investigator considered the event related to study drug but drug was not discontinued. No concomitant meds were reported. Inorganic phosphorus was low normal; uric acid normal throughout the study.
- **006049/152/3803/0003**, 28 yo F diagnosed with acute renal failure on Day 1286 of Teri 7 treatment, during the extension study. Drug was temporarily interrupted. Event lasted 1 day. She had a prior hx of metrorrhagia, depression, cholelithiasis, ectopic pregnancy and dyslipidemia. Concomitant meds included Euginon (oral contraceptive), clonazepam and sertraline. On Day 512 of the extension study she experienced nausea and vomiting leading to hospitalization, laboratory showed serum creatinine 2.5xULN, urea 6.2 xULN and uric acid 3xULN (1297 µmol/L). LABS: on week 72 (close to Day 500) of LTS6050 inorganic phosphorus was 2.36 (nl up to 1.65 mmol/L). At that time creatinine was 248 (nl 31-101 umol/L), creatinine clearance 21.47 ml/min (down from 138 ml/min at entry), urea was 53 (nl up to 8.6 mmol/L) and uric acid was 1297 (nl 125-428 umol/L). Abdominal US showed no renal abnormalities but cholelithiasis. Urine microscopic interpretation was “Positive” since the end of study visit for the base study and all urinalyses in extension. She received hydration and recovered the same day without sequelae. She also presented AE of metrorrhagia on Day 1356 and severe anemia on Day 1446 of Teri 7 treatment, during the extension study. She eventually discontinued because did not want to continue in the study about one year later.

This patient seems to have had an episode of acute renal failure related to dehydration. No lithiasis/obstruction was detected. She had abnormally high uric acid and phosphorus levels, because of the renal failure. The event lasted 1 day. She continued treatment. Approximately 3 years later she had metrorrhagia, followed by severe anemia. No labs are available for that date (lab data goes only to Week 144 of LTS650 [Day 1008]).

Of note, in Pool 1, there were several cases of pyelonephritis with Teri 7 and 14; plus one case of renal colic, one of urethral stenosis and one renal/perinephric abscess on Teri 14. In the extension studies, there were two additional cases of urinary lithiasis on Teri 14.

Teriflunomide is associated with increased excretion of uric acid and phosphorus due to an effect on tubular transport. The applicant believes that there is no clinically relevant consequence of this effect. However, I suspect that the increased risk of infections/obstructions might be related to the uricosuric effect of teriflunomide.¹⁵ In a response to an FDA request for clarification submitted in January 2012, Sanofi stated that the type of stones presented in patients with nephrolithiasis was not evaluated.

¹⁵ Uricosuric drugs lower the concentration of uric acid in the blood but they can increase the concentration of uric acid in the urine. Drinking plenty of fluids—at least 3 quarts a day—may help reduce the risk of uric acid stones developing in the urinary tract. Making the urine alkaline by taking potassium citrate (which increases the solubility of uric acid in the urine) can further help reduce the risk of uric acid stones forming in the urinary tract. However, if the urine becomes too alkaline, crystals or stones of another and more dangerous kind—calcium oxalate—may form.

- SAE in Reproductive system and breast disorders SOC

There were no imbalances in this SOC. Events in Pool 1 are summarized below.

Table 31. SAEs, Reproductive system and breast disorders SOC, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Reproductive system and breast disorders	2 (0.5%)	6 (1.4%)	2 (0.5%)
Menorrhagia	0	0	1 (0.2%)
Uterine haemorrhage	1 (0.2%)	1 (0.2%)	1 (0.2%)
Uterine polyp	0	0	1 (0.2%)
Benign prostatic hyperplasia	0	1 (0.2%)	0
Endometriosis	0	2 (0.5%)	0
Fallopian tube cyst	0	1 (0.2%)	0
Metrorrhagia	0	1 (0.2%)	0
Ovarian cyst	1 (0.2%)	0	0

Source: Table 20, ISS.

Pool 2.

The overall risk of SAE in this SOC was slightly higher in Pool 2 as compared to Pool 1 (it was 1.5% and 1.6% in the Teri 7 and Teri 14 groups respectively). There were a total of 5 SAE of reproductive system bleeding (3 on Teri 7 and 2 on Teri 14), including the cases in Pool 1.

Cases of reproductive system bleeding in Pool 2 are listed below.

ID	Age	Sex	Rx during core	PT	Action	Out come	Rel day on Teri	Duration
Teri 14						R		
006049-276-2012-0003	44	F	14 mg	Menorrhagia	NONE	R	540	7
006049-616-3003-0005	32	F	14 mg	Menorrhagia	NONE	R	1059	2
Teri 7								
006049-643-3205-0012	46	F	7 mg	Menorrhagia	NONE	R	1158	140
006049-152-3803-0003	28	F	7 mg	Metrorrhagia	NONE	R	1357	99
006049-528-4605-0001	42	F	7 mg	Metrorrhagia	NONE	R	169	77

As per patient profiles submitted 10/26/11, all these patients had normal platelet count, INR and APTT.

- SAEs in Respiratory, thoracic and mediastinal disorders SOC

In Pool 1, one patient reported a SAE of traumatic hemothorax/pneumothorax after car accident (006049-804-3510-0001), and one reported pulmonary embolism (006049-124-1203-0015), both cases in the Teri 14 group. In Pool 2, there was one report of PE and two reports of respiratory failure (one on Teri 7, one on Teri 14), and one of asthma (on Teri 7). The cases of PE (in patients

who also had thrombophlebitis) will be described in the Vascular disorders SOC. The following narratives refer to the other SAE in the respiratory SOC.

- **002001/250/0030/0004** - 51 female developed **respiratory failure** on Day 728 of Teri 14 during the extension study, along with pneumonia and tachycardia. She had received placebo during core study. There is little information in the narrative about this event. She recovered from this event. This patient eventually died, 3 years later due to cardiorespiratory arrest (discussed under deaths).
- **006049/250/2402/0016** - 53 female developed **mixed ventilatory deficiency** coded as **respiratory failure**, on Day 533 of Teri 7 treatment during extension study, leading to drug discontinuation. Concomitant therapies included Lasix, levothyroxine, esomeprazole, ergocalciferol, meteospasmyl, sumatriptan, clonazepam, ezetimibe, escitalopram, levocetirizine, peribedil, alprazolam, budesonide, almotriptan, metoclopramide and duloxetine. She was previously treated with IFN beta1a, glatiramer and solumedrol for MS. During the study she presented several episodes of upper respiratory tract infections for which she received antibiotics, analgesics and corticosteroids. Teleradiography performed on Day 450 of Teri treatment showed normal respiratory dynamics, and congestive thickening of the pulmonary interstitium with no focal parenchymatous lesion. On Day 575 she was admitted to the hospital for worsening of bronchitis with bouts of dry coughing. On physical examination she had bilateral wheezing and rales on expiration with a focus of rhonchus in the base of the left lung. Heart rate was 96 bpm with no murmur or signs of right cardiac insufficiency. BP was 117/95. Blood gases showed hypoxia and hypocapnea. Chest Xray showed bilateral increased markings to the base of the lungs. CT scan of chest showed no pulmonary embolism or infection focus. She recovered after 5 days. On Day 579 of Teri 7 treatment she consulted a pneumology and allergology specialist for annoying cough, which seemed to be increased since the beginning of the study. PFT showed mixed ventilatory deficiency with a strong restrictive component: Vital capacity 13%, FEVs 76%. She was treated with terbutaline, ipatropium and beclometasone, which reduced the symptoms but did not eliminate them. On Day 683 after Teri treatment had been interrupted, a clear improvement of the respiratory function was noted with VC +10% and FEVs+12%. However, dry cough resumed when drug was re-started. Teri was permanently discontinued due to the respiratory AE on Day 775 of treatment. She underwent rapid elimination procedure. Respiratory function is reported to have improved one day after drug discontinuation. The event was considered related to study drug by the investigator.

This case of “respiratory failure” could be related to teriflunomide. Chest XRay showed bilateral increasing markings at the base of the lungs; PFTs showed mixed ventilatory deficiency. Dry cough improved during drug interruption and resumed when drug reintroduced.

- **002001/124/0015/0008**. 43 yo M with history of smoking (1 pack/day), glaucoma, headache and drug hypersensitivity. He experienced **bronchitis and exacerbation of bronchial asthma** on Day 1385 of Teri 7, during extension period. The patient was exposed to Teri for a total of 1638 days (251 days in the core study 2001 and 1385 in LTS6048). On Day 430 of Teri treatment he was diagnosed with hypertension and treated with telmisartan and atorvastatin (screening BP was 148/80 mmHg). After approx 3 months stopped telmisartan and started candesartan, then changed to blopress plus (angiotensin II receptor antagonist and diuretic). The highest BP on record for this patient was 165/95 on Day 1186. All BP reported after Day 1261 were below 140/90. On Day 443 he experienced non-serious upper respiratory infection wheezing that lasted 76 days, treated with clarithromycin (Days 458-464). On Days 703 to 803 he was treated with salbutamol and seretide inhalers for upper resp. infection.

On Day 1385 (3.8 years into study treatment) he developed dry cough, shortness of breath and wheezing. He was hospitalized. He had no fever; pulse rate was 100 bpm, respiratory rate 14, blood pressure 102/71 mmHg, O₂ saturation 89% on room air, peak flow 170. Chest X-ray was negative. Blood analyses and ECG were normal. Chest CT and Bronchoalveolar lavage (BAL) were not done. The patient spent 4 days in the hospital and was administered intravenous solumedrol. He was quite wheezy with chest tightness for the first couple of days. He continued to improve with intensive nebulization and intravenous medication. He was diagnosed with acute bronchitis and acute exacerbation of bronchial asthma (*although he did not have a prior history of asthma*). He was considered recovered 3 weeks later.

He was discharged on Day 1408) with clarithromycin, prednisone, salbutamol and budesonide, for asthma/bronchitis. On Day 1446 he experienced another “asthma attack.” On Day 1450 was given fluticasone (Flovent) prednisone, tiotropium for asthma attack. He recovered within 14 days. Since then, the patient was on fluticasone, tiotropium and salbutamol. Events were considered not related to study drug by the investigator. Study treatment continued as per protocol. The patient decided to discontinue drug on Day 1638 of Teri treatment. On Day 1656 the patient experienced another episode of asthma. The patient discontinued the study on Day 1687. The event of asthma was ongoing at the end of study visit.

This appears to be a case of new onset of hypertension and “asthma” during treatment with teriflunomide. It is unclear how the diagnosis of asthma was made. There is no one single pulmonary function test with FEV1 and DLCO values. This could be a case of interstitial lung disease/pneumonitis. In response to an FDA request for information, Sanofi stated that the investigator did not deem it necessary to follow up this patient.

In summary, in Pool 2, there is at least one case in which interstitial lung disease is a possibility and one case of respiratory symptoms diagnosed as “exacerbation of bronchial asthma” in a patient who had no objective evidence for a diagnosis of asthma. Interstitial lung disease (or interstitial pneumonitis) has been reported in association with leflunomide (Arava®). The cases in this application have not been adequately evaluated to rule out interstitial lung disease.

- SAE in Skin and subcutaneous tissue disorders SOC

In Pool 1, there was one SAE of decubitus ulcer on placebo, one eczema with Teri 7 and one skin necrosis with Teri 14. The case of skin necrosis is as follows.

- **6049/2409/0002** - A 45-year-old female experienced skin necrosis (verbatim: cutaneous necrosis [4th left toe, partial]) on Day 184 of teriflunomide 14 mg. She had a previous medical history of peripheral ischemia. She was previously treated with betamethasone for MS. Concomitant therapies included naproxen, paracetamol and femodene, which had been started >3 months prior to entry. The patient permanently discontinued study treatment and recovered in 70 days. As per the narrative, she received the first dose of drug in May 2005. In February 2005, prior to entering the study she had a partial purple coloration of the left 3 toes without any necrosis. Doppler ultrasonography was normal. “Dermatologists suspected a possible iatrogenic vascularitis which was not confirmed by the normal result of the arteriography.” (It is unclear when the ultrasound was done). Drug was discontinued on Day 232 of treatment due to this event. The patient then followed a washout procedure including

cholestyramine as per protocol given from Day 233 to Day 246. She received mupirocin, pristnamycin, povidone-iodine, paracetamol, preparation for treatment of “wounds and ulcers” and crilanomer as corrective treatments. On Day 253, the patient recovered with sequelae. Later, on Day 258, the patient experienced mild cutaneous involvement of the first left toe (red aspect), which resolved on Day 378. As per CRF, at the screening visit a “left toe blue” was already recorded.

The investigator attributed the skin necrosis as probably related to study drug. If the patient had evidence of toe ischemia at the screening visit, the event is probably not related to teriflunomide. There are no cases of peripheral ischemia in the teriflunomide database, although there are a few cases of venous thromboses.

SAE in the Skin and SC tissue disorders during extension studies in Pool 2 included one case of lichen planus on Teri 7 and one of decubitus ulcer on Teri 14. Additional, in the SUR there was one SAE report of pustular psoriasis, as follows.

6049/616/3004/0004, 51 yo F with history of megaloblastic anemia, was diagnosed with psoriasis pustulosa on Day 954 (2.6 years) into Teri 14 treatment. She had been previously treated with corticosteroids for MS and received placebo during TEMSO. On Day 954 she developed a pustular rash on palms and soles. Histopathology revealed psoriasis pustulosa. The patient had no previous history of psoriasis, had not family history of psoriasis and had no concomitant viral or bacterial infection. She recovered with local treatment on Day 1056. Study drug treatment is ongoing.

I agree that an event of pustular psoriasis would be unlikely related to teriflunomide.

- SAE in Vascular disorders SOC

Number of patients with SAE in the Vascular disorders SOC in Pool 1 are shown below.

Table 32. Serious adverse events, Vascular disorders SOC, Pool 1.

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Vascular disorders	0	2 (0.5%)	4 (1.0%)
Circulatory collapse	0	0	1 (0.2%)
Hypertension	0	0	1 (0.2%)
Orthostatic hypotension	0	0	1 (0.2%)
Thrombophlebitis	0	0	1 (0.2%)
Varicose vein	0	1 (0.2%)	0
Venous thrombosis	0	1 (0.2%)	0

Source: Table 20, ISS.

Narratives of selected cases are presented below

On Teri 7

- **006049/250/2402/0014**. 32 yo female, experienced malaise due to contrast agent injection on Day 249, venous thrombosis on Day 379 of Teri 7 treatment. She had a medical history of carpal tunnel syndrome, depression and psoriasis. She was previously treated with glatiramer acetate and

methylprednisolone for MS. Concomitant therapies included escitalopram, carbamazepine, ibuprofen, eletriptan hydrobromide, fluindione, tetrazepam, and baclofen. On Day 379, the patient presented to an ER with thoracic oppression, left arm pain, facial edema, and scapular edema. No diagnosis was given. At a second emergency room visit on Day 393, edema was again noted, and an angio CT scan of the thorax was requested. A diagnosis of venous **thrombosis of the left brachiocephalic trunk** was made, possibly related to the change of the port-a-cath in the prior month (which she had for receiving treatment with IV steroids). She was treated with aspirin and the IP was temporarily interrupted. She recovered on Day 613. The events were not considered as related to the IP by the Investigator.

The brachiocephalic trunk is an uncommon site of venous thrombosis. The patient had a port-a-cath. It is unclear which kind of work up this patient had, if any, to evaluate risk factors.

On Teri 14

- **006049/124/1203/0015**. 27-year-old female patient experienced **pulmonary embolism (PE)** and thrombophlebitis left leg 249 days into teriflunomide 14 mg treatment. She was previously treated with Avonex and Betaseron for MS. Concomitant therapies included oral contraceptive and herbal preparation. On Day 247, she developed a pain in her left shoulder, under left breast and left neck and was diagnosed with PE by a pneumologist. Treated with nadroparin and warfarin. Study drug and oral contraceptive were d/c. The events of PE and thrombophlebitis were not considered as related to the IP product by the Investigator.

It is difficult to attribute thrombophlebitis and PE to teriflunomide in the presence of an oral contraceptive. However, a contributory role of teriflunomide to this event can not be ruled out.

- **002001/250/0021/0002**. 42-year-old female patient with medical history of affective disorder developed **hypertension** on Day 222 of Teri 14 treatment. Concomitant meds included oral contraceptive. She had a previous episode of HTN on Day 203 to 219, from which she recovered without specific treatment. On Day 223 she was diagnosed with HTN. At that time her BP was 190/120 mmHg, leading to drug discontinuation. During the follow up visit, 27 days after last Teri 14 dose (Day 250), BP was still 190/120 mmHg. Three days after the completion of washout (Day 261) the patient's BP was 160/100 mmHg. In addition to HTN, she had increased ALT elevation up to 2.8 xULN on Day 29 and attempted suicide on Day 118 neither of which led to drug discontinuation.

The investigator did not think hypertension was related to study treatment, however, leflunomide is known to be associated with increase in BP and BP monitoring is recommended before start and periodically thereafter in the leflunomide label. I believe this case is related to teriflunomide.

- **006049/152/3802/0014**. 42 yo F experienced **orthostatic hypotension** on Day 62 of Teri 14, 2 days after being hospitalized for MS relapse when attempting to stand up from wheelchair. No corrective treatments were given.

This event of orthostatic hypotension does not appear to be related to teriflunomide.

- **006049/246/2202/0006**, 44 yo F experienced **circulatory collapse** on Day 141 of Teri 14 treatment. After unsuccessful attempt for intrauterine device (IUD) placement the patient developed fever and pain in her abdomen and lower back the next day (Day 140). On Day 141 she collapsed while sitting, and was admitted to the hospital for monitoring. She recovered following intervention. On Day 337 she had elevated transaminases that resulted in discontinuation of the study drug.

This episode of circulatory collapse was attributed to an acute infection and pain although there is no information about blood pressure or ECG evaluation at the time of the event. It is unclear if she lost consciousness.

In Pool 2, eight additional patients had SAE in this SOC, including four cases of “venous stenosis” (2 in each group) and two varicose vein, one hypertension and one phlebitis (all on Teri 7).

Table 33. Serious adverse events in Vascular disorders SOC, Pool 2.

Primary System Organ Class Preferred Term n(%)	teriflunomide	
	7 mg (N=587)	14 mg (N=548)
Vascular disorders	8 (1.4%)	6 (1.1%)
Venous stenosis	2 (0.3%)	2 (0.4%)
Circulatory collapse	0	1 (0.2%)
Hypertension	1 (0.2%)	1 (0.2%)
Orthostatic hypotension	0	1 (0.2%)
Thrombophlebitis	0	1 (0.2%)
Deep vein thrombosis	1 (0.2%)	0
Phlebitis	1 (0.2%)	0
Varicose vein	2 (0.3%)	0
Venous thrombosis	1 (0.2%)	0

Source: Table 1.5.5.2, original ISS.

The adverse events of “venous stenosis” were not actually symptomatic AEs, but a condition that was diagnosed during the trial: chronic cerebrospinal venous insufficiency (CCSVI). Some neurologists believe that CCSVI is associated with the development of MS. The condition is treated with an experimental surgical procedure (jugular vein stenting). All four patients discontinued teriflunomide treatment and had the surgical procedure. Outcome is unknown.

The cases of DVT and phlebitis are as follows:

- **002001/124/0013/0004** – 22 yo F experienced left leg **deep venous thrombosis** on Day 384 of Teri 7 treatment, during extension study. Hx of hypothyroidism and smoking. Concomitant therapies included levothyroxine and Cliest (ethinylestradiol and norgestimate). On Day 384 during a study visit she complained of left leg pains. Two days later she noted calf swelling. She went to ER and was diagnosed with left leg DVT and **pulmonary embolism**, which led to drug discontinuation. She received warfarin and dalteparin. She was monitored as outpatient. On Day 546 she recovered from both events without sequelae. Events of DVT and PE were considered related to drug by the investigator.

It is difficult to attribute thrombophlebitis and DVT to teriflunomide in the presence of an oral contraceptive that could by itself explain the event. However, a contributory role of teriflunomide to this event can not be ruled out.

- **6049/124/1205/0010** 45 yo F experienced **thrombophlebitis** (coded as phlebitis) on Day 900 of Teri 14 treatment, during extension study. She had a medical history of depression, hepatic steatosis. Concomitant meds included ibuprofen, cod-liver oil, citalopram, unspecified herbal, multivitamins with minerals, fish oil. On Day 145 of the extension study, the patient experienced thrombophlebitis of right leg with swelling of the entire right leg which led to study discontinuation. Laboratory results showed factor V Leiden mutation (506 heterozygote), platelets were 212 Giga/L, and prothrombine was 11.3 seconds on Day 147. Doppler showed extensive thrombophlebitis of the right lower limb including the common deep superficial femoral vein with a suspicion of extension to the right iliac

vein. She received enoxaparin sodium and warfarin sodium as corrective treatment. On Day 508, the patient recovered from the event without sequelae. The event was considered as related to the IP by the Investigator. After study discontinuation the patient followed the washout procedure.

An additional case of pulmonary embolism was reported as an IND safety report on 7/2/12, as follows:

- Patient 0001, Investigator 2606, Study LTS6050 (3004). 61F on an unspecified time after starting the investigational product during the extension study, the patient, with breast lump and meningioma and concomitantly treated with propranolol and prochlorperazine, complained of feeling very unwell with palpitations, vertigo, and a feeling of shaking inside. She looked pale, unwell and tachycardic. BP was 164/98 mmHg with a heart rate of 98 bpm. Chest x-ray done at admission showed normal results for the heart, lungs and mediastinum. She had D-Dimer of 8512 mcg/L (0-500), fibrinogen of 8.2g/L, erythrocyte sedimentation rate at 64 mm/hr, prothrombin time of 11.1 second, APTT of 27.5 second, WBC of 9.1 Giga/l, platelets of 211 Giga/l and C-reactive protein of 50.4 mg/l. The patient complained of shortness of breath. CT pulmonary angiogram showed multiple large bilateral pulmonary emboli, consistent with acute pulmonary emboli. The patient had never previously presented a similar event, had no history of deep venous thrombosis, denied any recent long travel or surgery and was not obese. There were no risk factors for venous thrombosis. The patient was commenced on low molecular weight heparin. Echocardiogram showed trivial mitral regurgitation. ECG was normal. Treatment with warfarin and dalteparine was initiated. The patient was still on the investigational product, as planned. At time of report, the patient had not recovered yet. According to the investigator, there was a reasonable possibility that this serious event was associated with the investigational product.

Overall, there were four cases of venous thromboses in the monotherapy studies (one on Teri 14, three on Teri 7), two of which were associated with pulmonary embolism (one from each dose group). There was one additional IND report of pulmonary embolism in study LTS6050, on teriflunomide (dose unknown). All patients had some risk factor for increased risk of thrombosis (oral contraceptive in the case of patients with PE; factor V Leiden mutation in one of the cases of thrombophlebitis, a port-a-cath in the case of the thrombosis of brachiocephalic trunk, except the patient recently reported with pulmonary embolism. Additionally, one patient taking teriflunomide in one of the ongoing studies developed thrombosis of the right subclavian vein. This patient was taking an oral contraceptive.

Loss of mobility and venous and lymphatic stasis may increase the risk of venous thromboembolism in patients with advanced MS.¹⁶ However, a contributory role of teriflunomide to these events can not be ruled out.

7.3.2.2 SAE in Adjunctive therapy studies

Patients receiving Teri as adjunctive therapy to IFN- β (PDY6045+LTS6047):

¹⁶ Arpaia G, et al. Risk of deep venous thrombosis (DVT) in bedridden or wheelchair-bound multiple sclerosis patients: a prospective study. *Thromb Res.* 2010 Apr;125(4):315-7. Epub 2009 Jul 29.

Overall, 7 patients experienced a total of 10 SAEs.¹⁷

- In the placebo + IFN- β group one patient experienced ankle fracture and one experienced ALT increase (up to 9 xULN, on Day 221, with normal BR, which decreased to 2xULN without drug discontinuation).
 - One patient on Teri 14 + IFN- β group experienced lobar pneumonia, cystitis and cholecystitis.
 - Four patients in the Teri 7 + IFN- β group experienced the following events: one DVT (during hospitalization for MS relapse, after drug discontinuation); one musculoskeletal stiffness (in a patient with history of shoulder arthroplasty); one pseudoarthrosis (after fall and contusion of left wrist) and one ALT elevation (3.6 x ULN, which led to study drug discontinuation. ALT normalized after discontinuation of study drug (patient # 006045-724-7007-0001, see narrative below).
- **006045/724/7007/0001**, 36 F, on Teri 7 mg and IFN, On Day 210 of study was found to have ALT 3.6 xULN. BR and ALKP normal. It was considered serious. Drug discontinued on Day 214. Retest on day 222 ALT 3.8xULN. On day 232 abdominal US showed suspected liver angioma, incidental finding not related to study drug. Pt underwent washout procedure from Day 232 to 242. Event resolved Day 252. Event considered by investigator to be related to drug. No serology mentioned. Entry meds include tiroprium and doxilamine. Concomitant meds during the trial included zafirlukast (started on Day 169 and stopped Day 214) and citalopram, taken from Day 183 to 200). Methylprednisolone was give Day 89 to 91 and Day 183 to 185.

This case of liver toxicity is confounded by use of zafirlukast which has a WARNING for hepatotoxicity. IT is unclear why patient started zafirlukast, a drug used for prevention of asthma. Narrative does not provide information.

Patients receiving Teri as adjunctive therapy to glatiramer acetate (PDY6046+LTS6047):

Twelve patients experienced a total of 17 treatment-emergent SAEs as follows:¹⁸

- Six patients in the placebo + GA group experienced: one paravertebral abscess; one facial bone fracture after road accident; one muscle spasticity; one vertigo; one herpes zoster and one cerebral ischemia (30 days after study discontinuation during rapid elimination procedure; the patient also had increased hepatic enzymes (ALT 15x ULN) 10 weeks after cholestyramine, therefore unlikely to be related to teriflunomide).
- Five patients in the Teri 14 + GA group experienced the following SAEs: one recurrence of epileptic seizure (Day 23 of study treatment; he was on oxcarbazepine treatment, the dose of oxcarbazepine was increased and patient completed the study); one patient had ALT increase 2xULN that led to study discontinuation; one patient had mastoiditis, otitis, hypertension and ALT increase; one had suicidal ideation and suicide attempt; one suspicious interstitial lung disease (patient# LTS6047-PDY6046, 3001/1019, see narrative below);

¹⁷ Additionally, three patients presented SAE either before starting study drug (one chronic pancreatitis, one renal cell carcinoma) or several months after last dose (invasive breast ductal adenocarcinoma was diagnosed 9 months after last dose of study drug).

¹⁸ Additionally, two patients presented SAE before receiving drug (one femoral fracture and one depression).

- One patient on Teri 14 + GA had tendon rupture. *Of note, tendon rupture was reported as an AE in 1% to < 3% of the rheumatoid arthritis patients in the leflunomide treatment group in controlled clinical trials, according to the ARAVA label.*
- LTS6047-PDY6046, 3001/1019. 38 yo female was hospitalized for suspected ILD 71 days after first dose of Teri 7 and glatiramer acetate. History of osteoporosis. Concomitant therapy: amitriptyline. Severe smoker. On day 71 of treatment she experienced difficulty breathing. Chest Xray showed reticular-nodular alterations in bottom fields of both lungs. Interstitial pneumonia was suspected. Teriflunomide was permanently discontinued on Day 72. Dyspnea persisted. She was hospitalized on Day 73 and treated with prednisolone, clarithromycin, theophylline and tiotropium. The event improved and she was discharged on Day 83. She was withdrawn from the study on Day 85. She received washout with cholestyramine on Days 188 to 198. She improved with symptomatic treatment and eventually recovered several months after drug discontinuation and cholestyramine washout, with residual difficulties in breathing. The event was considered as related to study drug by the investigator.

This case is consistent with interstitial lung disease. There was no BAL or lung biopsy to confirm the diagnosis. No PFT values are available from this patient.

Leflunomide is suspected to be associated with interstitial lung disease. The teriflunomide database has some events consistent with interstitial lung disease. PFTs have been incorporated into TOWER study (ongoing, blinded). Evaluation of PFTs from the interim analysis of TOWER does not suggest any safety signal but can not rule out an effect either.

7.3.2.3 Serious AE in other studies

The safety profile of teriflunomide in Clinical pharmacology studies and ongoing phase 3 studies was consistent with that in Safety Pools 1 and 2. Selected cases of interest are discussed below. Other SAE are described in Appendix 4 of this review.

- **Pulmonary tuberculosis.** Patient #006, Investigator 348004 (MFR report 2011SA047846) in **TENERE** study. This was a 38 year-old female from Hungary, treated with Teri 14 for 1.3 years. She was asymptomatic. She was hospitalized for suspicious **tuberculosis (TB)** based on a hollow pulmonary lesion in the left upper lobe detected by screening chest X-Ray. In the previous 2 years she lost 4 kg (8 Lbs). A CT scan showed the apical lesion of approximately 1 cm and lesions of residual nature in both pulmonary apices and a nodular calcification within the liver.

The investigator considered that this SAE was not associated to teriflunomide; However, teriflunomide is an immunosuppressant. Leflunomide has been associated with serious and opportunistic infections, including reactivation of TB and the role of teriflunomide in this event can not be ruled out. This does not appear to be a primary infection, as the CT scan showed “lesions of residual nature” in both apices. This seems to be a case of tuberculosis reactivation.

- **Pulmonary tuberculosis. 8510/0005 in TOPIC study** – (Ukraine). This 34-year-old female patient had a medical history of ear and sinus operation. Randomized to Teri 7. Concomitant therapies azithromycin, diclofenac sodium, gatifloxacin, fenspiride hydrochloride, serrapeptase, acetylcysteine,

methylprednisolone and tocopherol. On Day 296, the patient experienced acute respiratory disease with dyspnea, fever and hemoptysis. Bronchoscopy on Day 299 showed destructive **tuberculosis of right lung**. Due to the pulmonary tuberculosis, the IP was permanently discontinued with the last dose taken on Day 302. Specific TB therapy started on Day 358 (combitub, ethambutol, isoniazid, pyrazinamide and rifampicin). At last follow up he was stable but not fully recovered.

Patient was on Teri 7. Laboratory values (WBC, neutrophil, lymphocyte counts) are not provided. The event is likely related to teriflunomide use.

- **Ileal tuberculosis. 010531/792//0002/0003. TOWER study.** This 38-year-old female patient from Turkey had no relevant medical history. On Day 74 of Teri 14, the patient experienced gastroenteritis. For 2 months prior to this event, the patient complained of watery, yellow colored diarrhea with small amounts 10-15 times daily, associated with abdominal pain and fever 38C. Electrocardiogram (ECG) and routine blood tests were normal. Due to the event, drug was permanently discontinued with last dose taken on Day 98. She received metronidazole (Flagyl), metaclopramide and ciprofloxacin. On Day 96, colonoscopy was normal. Terminal ileum biopsy showed necrotizing granulomatous inflammation. Tuberculosis was suspected. Results of thorax and abdominal CT scans were normal. Tissue PCR was negative. On Day 98, pantoprazole and saccharomices boulardii were started. This adverse event became serious on Day 103, leading to hospitalization. The patient was diagnosed with **ileal tuberculosis** (coded as tuberculosis gastrointestinal). The patient received metronidazole, etambutol, isoniazid and rifampicine as additional treatment. The event was considered as *not related to the IP* by the Investigator. At the last report, the patient had not recovered. No washout treatment was administered.

This is a case of ileal tuberculosis. GI symptoms apparently started 2 weeks into teriflunomide treatment but a diagnosis of “gastroenteritis” was made on Day 74. At that time routine laboratory results were reportedly normal (no results in narrative/CRF). I agree the event appears unlikely related to teriflunomide given the onset 2 weeks into the study, however, the role of teriflunomide can not be ruled out.

- A report of **osteomyelitis by prevotella species** (an anaerobe agent) was submitted to FDA on 12/22/11 (MFR # 2010SA007331). The case had occurred in the TOWER study (Patient 003, on Teri 14 mg) back in 2009, however, the report had been recently reassessed by the investigator as serious and possibly related and by the sponsor as unexpected, which made it reportable as a 15-day IND report. This was a 43 yo woman with foot surgery (unspecified site) prior to study entry, who 7 months into Teri 14 treatment developed pain in the right great toe. She was hospitalized for one day for surgery of infected non-union distal phalanx of right great toe. The case was initially reported as post operative infection to right great toe. Xrays were suggestive of a neuropathic Charcot type joint. She underwent open reduction and pin insertion, along with drainage. The infection was initially identified as staph aureous, however, the culture report from (b) (4) indicates growth of prevotella species.

Osteomyelitis by anaerobes is extremely rare. Prevotella is associated with soft tissue infections of the mouth. Prevotella osteomyelitis seems to be an opportunistic infection associated with use of teriflunomide in this case.

- **Enterococcal endocarditis** (Teri 7). Investigator 792012, patient 003. Turkey). IND report

MFR# 2011SA081991. 55 yo M had a history of tuberculosis more than 20 years prior to study entry, acute bronchitis and thyroidectomy. Concomitant diseases included hypertension and benign prostatic hypertrophy. No risk factors for endocarditis were noted. Concomitant meds were fenyamidol, escitalopram and indapamide. Approximately 1.8 years into study drug he complained of fatigue and fever. He was hospitalized for 1 week and treated with cefuroxim and ceftriaxone but he persisted febrile. Blood count “was considered **mildly pancytopenic** due to immunosuppressive use”. No infectious focus was detected but Xray showed suspicious infiltration on basal parts of the lungs. He was given empirical treatment with piperacillin and tazobaktam and temperature returned to normal. He was discharged on oral antibiotics. The final diagnosis was “infection of the respiratory system”. Approximately a month later he returned to the hospital with high fever, inability to walk and weight loss. Blood cultures grew enterococcus, initially thought to be a contaminant, but a repeated culture again grew enterococcus fecalis. Stool and urine cultures were negative. He developed an arrhythmia (not specified) treated with metoprolol. During hospitalization blood tests showed decreased electrolytes with sodium to 130 mmol/l (nl 136-145) and potassium to 2.8 mmol/l (N:3.5-5.1) requiring potassium replacement. Liver function tests remained in normal range. White blood cell count and neutrophils were in normal range, hemoglobin, hematocrit, red blood cell count and platelet count remained under normal values. He also developed swelling of right foot, and diagnosed as “soft tissue infection”. Blood pressure remained elevated; metoprolol was changed to valsartan. Approximately one month after re-admission, a transesophageal echocardiogram showed echogenicity of the mitral valve consistent with vegetation on the atrial surface of posterior leaflet. The events of respiratory infection, high fever of unknown origin and infective endocarditis were associated with study medication.

*This is a case of infective **enterococcal endocarditis** in a previously healthy individual. The patient is described as being “mildly pancytopenic”, however, values were not provided. The event is likely related to teriflunomide.*

The infectious AE described above from non ISS studies, are consistent with an immunosuppressive effect of teriflunomide.

- **Subclavian Vein thrombosis. 5401/0004** from TOPIC study (Canada). This 36-year-old female patient with no significant medical history. No history of DVT. She was taking Marvelon 21 as birth control for 10 years. She was not a smoker. On day 285 (nine months into therapy) she presented acute thrombus of the right subclavian vein confirmed by venous Doppler and thoracic MRI. On Day 169, she had reported heavy menstruations/increased intermittent menstrual flow, considered as a nonserious adverse event. At that time she had a prolonged INR (up to 48, not unit provided). Six weeks prior to the event of **subclavian vein thrombosis** she was diagnosed with right shoulder impingement, for which she had received physical therapy. On Day 545, the patient recovered from the subclavian vein thrombosis without sequelae and the event was considered as related to the IP by the Investigator. Other risk factors for thrombosis included obesity and use of oral contraceptive. Drug was not discontinued, treatment is ongoing. Workup for hypercoagulability (tests not described) did not find a cause for the clot, and the event was diagnosed as idiopathic.

Treatment was unblinded, she was on Teri 14. There was also a case of venous thrombosis of the brachiocephalic trunk on Teri 7 in a patient who had a port-a-cath in this application. A role of teriflunomide in these events can not be ruled out.

- IND Safety Report: Patient 004, Investigator 703006, TOWER, A 42-year-old female patient was diagnosed with **focal nodular hyperplasia** of liver 4½ months into teriflunomide 14 mg treatment. She was asymptomatic. An abdominal US was done as part of the end of study visit, because she had dropped from the study for personal reasons. A liver MRI showed a 41 x 24 x 38 mm lesion in the 6th segment of the liver, consistent with focal nodular hyperplasia (FNH), coded as hepatic dysplasia. A baseline ultrasound had shown a normal liver with no focal changes. According to the investigator, there was a reasonable possibility that the adverse event was associated with the study medication. US imaging repeated 8 months later show that the lesion was stable. An accessory spleen and a small (2 mm) liver cyst was also observed dorsally in the 6th segment (likely incidental findings). Several tumor markers were evaluated (Ca 15-3; Ca 1909; CA 72-4; CA 125: CEA, CYFRA, NSE) and all were negative.

Focal nodular hyperplasia is not known to occur with leflunomide. This case is interesting because of the documented normal liver ultrasound before starting treatment, and the presence of a 4 cm lesion 4 ½ months into treatment.

- IND safety report (MFR# 2012SA041325): Patient 003, Investigator 348002, study EFC10891 (TENERE). Hemorrhagic stroke. A 48 yo male with history of diabetes mellitus, hypertension, hypercholesterolemia and family history of stroke developed severe headache and speech disorder and syncope 2.5 years into blinded therapy. Family measured 240 mmHg systolic blood pressure. In the ER, BP was 180/110 mmHg, with a HR of 100 bpm. CT scan showed hemorrhagic stroke. Laboratory evaluations showed K level of 3.3 mmol/L and evidence of **renal failure** with creatinine of 291 mcmol/L (normal 80-115), estimated GFR of 21 ml/min (nl >60), urea 18.9 (nl 2.5–7.5) and uric acid (586 Mcmol/L (nl 214-488)). He was diagnosed with **hypertensive encephalopathy and hemorrhagic stroke**, treated with antihypertensive medication, hydration and potassium replacement. He was discharged five days later with improvement in neurologic and renal function, although there was still some renal insufficiency (creatinine 51, GFR 60 ml/min) and mild anemia (HTC was 34%; nl for that lab 39-50%).

This is a case of hypertensive encephalopathy with measured BP of 240 mmHg systolic BP, with hemorrhagic stroke and acute renal failure in a patient with predisposing cardiovascular risks (diabetes, hypercholesterolemia, prior HTN).

7.3.3 Dropouts due to adverse events

7.3.3.1 Dropouts in the ISS (Pools 1 and 2)

In Pool 1, comparable numbers of subjects in each treatment group completed the study treatment period (see Table below). Placebo-treated subjects discontinued because of lack of efficacy more frequently than teriflunomide-treated subjects. Teriflunomide-treated subjects discontinued because of adverse events more frequently than placebo-treated subjects (9.3%, 11.1% and 7.8% of patients in the Teri 7, Teri 14, and placebo treatment groups, respectively)

Table 34. Patient disposition, Pool 1 Safety Population

	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Completed study treatment period	314 (74.6%)	335 (78.1%)	307 (74.0%)
Did not complete the study treatment period	107 (25.4%)	94 (21.9%)	108 (26.0%)
Reason for treatment discontinuation			
Adverse event	33 (7.8%)	40 (9.3%)	46 (11.1%)
Lack of efficacy	35 (8.3%)	18 (4.2%)	21 (5.1%)
Poor compliance to protocol	3 (0.7%)	2 (0.5%)	5 (1.2%)
Lost to follow-up	3 (0.7%)	0	3 (0.7%)
Other	33 (7.8%)	34 (7.9%)	33 (8.0%)

Note: Percentages are calculated using the number of safety patients as denominator.
 Source: Table 6, original ISS (page 76)

The difference was driven mostly by events in the Skin and subcutaneous tissue disorders and the GI disorders SOC. The most common AE leading to discontinuation were in the Investigations SOC (mostly hepatobiliary investigations) but there were no differences between active treatment and placebo. A summary table of number of patients who discontinued due to AE by SOC is presented as follows.

Table 35. Adverse events leading to discontinuation, Safety Pool 1

Primary System Organ Class	Placebo (N=421) n (%)	7 mg (N=429) n (%)	14 mg (N=415) n (%)
Any class	32 (7.6)	39 (9.1)	49 (11.8)
Infections and infestations	4 (1.0)	1 (0.2)	5 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.0)	0	1 (0.2)
Psychiatric disorders	3 (0.7)	1 (0.2)	2 (0.5)
Nervous system disorders	2 (0.5)	2 (0.5)	2 (0.5)
Vascular disorders	0	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.2)
Gastrointestinal disorders	1 (0.2)	6 (1.4)	5 (1.2)
Hepatobiliary disorders	2 (0.5)	1 (0.2)	1 (0.2)
Skin and subcutaneous tissue disorders	0	4 (0.9)	13 (3.1)
Musculoskeletal and connective tissue disorders	0	2 (0.5)	2 (0.5)
Pregnancy, puerperium and perinatal conditions	1 (0.2)	1 (0.2)	4 (1.0)
Reproductive system and breast disorders	0	1 (0.2)	0
General disorders and administration site conditions	0	1 (0.2)	0
Investigations	15 (3.6)	18 (4.2)	13 (3.1)
Injury, poisoning and procedural complications	0	1 (0.2)	0

SOC: System organ class, MedDRA version: 13.1. n (%) = number and percentage of patients with at least one treatment emergent event leading to drug discontinuation. Note: Table sorted by SOC internationally agreed order
 Source: Table 22, original ISS.

Of note, there is a discrepancy between the numbers of patients who discontinued due to AE as per Table 6 and Table 22 of the ISS. In response to a FDA request for clarification, on June 8, 2012 Sanofi indicated that the tables are based on two separate CRF data sources. Table 6 is based on the End of Treatment page, while Table 22 is based on the action taken field on the Adverse Event page. Although in most cases they are the same, it led to discrepancies in a small number of cases. Additionally, studies included in this integrated analysis had long-term extensions and some additional data on actual core study events not included in the locked core study database continued to be collected and included in the pooled data.

In Pool 2, the two doses of teriflunomide had a similar profile of reasons for discontinuation (see Table below).

Table 36. Patient disposition, Pool 2, Safety Population

	teriflunomide	
	7 mg (N=587)	14 mg (N=548)
Completed study treatment period	29 (4.9%)	17 (3.1%)
Ongoing with treatment	327 (55.7%)	306 (55.8%)
Did not complete the study treatment period	231 (39.4%)	225 (41.1%)
Reason for treatment discontinuation		
Adverse event	94 (16.0%)	83 (15.1%)
Lack of efficacy	44 (7.5%)	39 (7.1%)
Poor compliance to protocol	3 (0.5%)	6 (1.1%)
Lost to follow-up	1 (0.2%)	6 (1.1%)
Other	89 (15.2%)	91 (16.6%)

Note: Percentages are calculated using the number of safety patients as denominator.
 Source: Table 7, original ISS.

As per the above table, in Pool 2, 16% and 15.1% of patients discontinued from the studies because of AEs in the Teri 7 and Teri 14 groups, respectively. The main contributor was again the Investigations SOC (Hepatobiliary investigations HLGT). Patients who discontinued because of AE in Pool 2 are summarized as follows.

Table 37. Adverse events leading to discontinuation, Safety Pool 2

Primary System Organ Class Preferred Term n(%)	Teri 7 (N= 587) n (%)	Teri 14 (N=548) n (%)
Any class	93 (15.8)	83 (15.1)
Infections and infestations	3 (0.5%)	7 (1.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.7)	2 (0.4)
Blood and lymphatic system disorders	0	3 (0.5)
Immune system disorders	0	1 (0.2)
Psychiatric disorders	2(0.3)	2 (0.4)
Nervous system disorders	10 (1.7)	2 (0.4)
Eye disorders	0	2 (0.4)
Cardiac disorders	2 (0.3)	1 (0.2)
Vascular disorders	3 (0.5)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	3 (0.5)	1 (0.2)
Gastrointestinal disorders	9 (1.5)	9 (1.6)

Hepatobiliary disorders	3 (0.5)	2 (0.4)
Skin and subcutaneous tissue disorders	7 (1.2)	13 (2.4)
Musculoskeletal and connective tissue disorders	2 (0.3)	3 (0.5)
Pregnancy, puerperium and perinatal conditions	4 (0.7)	4 (0.7)
Reproductive system and breast disorders	1 (0.2)	0
General disorders and administration site conditions	3 (0.5)	1 (0.2)
Investigations	39 (6.6)	32 (5.8)
Injury, poisoning and procedural complications	1 (0.2)	0

Source: Appendix 1.5.6.2 ISS. ORIGINAL SUBMISSION.

Again there are minor discrepancies between the Disposition table and the AE leading to discontinuations tables because of the use of two different datasources.

There was no evidence of a dose response in terms of discontinuations due to AE between Teri 7 and 14 mg/day, except perhaps for skin and subcutaneous tissue disorders (twice the risk in Teri 14 as compared to 7).

There were few additional AE leading to discontinuation during the extension studies, except for events in the Investigations SOC. The main contributory was hepatobiliary investigations.

Dropouts in ISS studies (Pools 1 and 2) in alphabetic order, by SOC are described below.

- Dropouts to AE in Blood and lymphatic disorders SOC and Investigations SOC (hematologic investigations), Pools 1 and 2.

No patient discontinued due to AE in the Blood and lymphatic system SOC in Pool 1 or 2. However, some patients discontinued with events in the Investigations SOC, Hematologic investigations. Two discontinued from Pool 1 because of non-serious events of low neutrophil count (**6049/2003/0008** and **2001/0014/0032**, one from each Teri group; they recovered; Hb and platelets were within normal) and three from Pool 2 (one anemia, one leukopenia and one neutropenia, all in Teri 14). Cases are as follows:

In Pool 2

- **6049/260/0001:** 42 yo F showed mild ALT increase 42 days and d and leukopenia with **neutropenia** 156 days after first dose of teriflunomide 14 mg. Concomitant meds paracetamol, cod-liver oil, eugynon, oenothera biennis laxatives and ibuprofen. WBC at nadir was 2.64 Gig/L with ANC 1.22 Giga/L on day 288. Drug stopped on Day 296. She underwent washout procedure from Day 302 to 312. She recovered on Day 463. No infections reported.

- **6049/3401/0003** 21 yo female presented three episodes of **neutropenia** 56, 800 and 1134 days into teriflunomide 14 treatment. ANC count was around 0.9 Giga/L in all these dates. The patient also experienced non-serious ALT elevation in TEMSO. Drug was discontinued because of neutropenia on Day 1141 and she recovered on Day 1148.

There is no information in the narrative about ANC values outside these dates, or values on platelets, hematocrit to evaluate if other bone marrow cell lines were also affected. There is no information on ALT values either.

- **6049-1241204-0010**, 42 yo F had low neutrophils 21 days after first Teri 7 dose. She had been on placebo in TEMSO. She had been previously treated with Tegretol. Concomitant meds included amitriptyline, domperidone, multivitamins, and gabapentin. She had low ANC (1.5 Giga/L) during TEMSO, but on Day 22 of Teri 7 treatment her ANC dropped to 0.9 Giga/L. On Day 26 it was 0.86 Giga/L. Drug was discontinued because of neutropenia. Last dose taken on Day 32. She received cholestyramine from days 52 to 67. ANC increased to 2.01 Giga/L on Day 204.

- Dropouts due to AE in GI disorders SOC in Pools 1 and 2

Pool 1. A higher percentage of patients discontinued because of AEs from the Teri 7 (1.4%) and Teri 14 (1.2%) as compared to placebo (0.2%). A summary table is presented below.

Table 38. AE leading to discontinuation, GI disorders, Pool 1

Primary System Organ Class	teriflunomide		
	Placebo	7 mg	14 mg
Preferred Term n(%)	(N=421)	(N=429)	(N=415)
Gastrointestinal disorders	1 (0.2%)	6 (1.4%)	5 (1.2%)
Aphthous stomatitis	0	0	1 (0.2%)
Diarrhoea	0	1 (0.2%)	1 (0.2%)
Dyspepsia	0	0	1 (0.2%)
Gastrointestinal haemorrhage	0	0	1 (0.2%)
Pancreatitis chronic	0	0	1 (0.2%)
Abdominal pain	0	1 (0.2%)	0
Abdominal pain upper	0	2 (0.5%)	0
Crohn's disease	0	1 (0.2%)	0
Nausea	0	1 (0.2%)	0
Pancreatitis	1 (0.2%)	0	0

Source: Table 22 ISS

Several of these cases were serious and have been discussed in the SAE section of this review. Of note, there were two cases of non-serious pancreatitis that led to discontinuation, one in the placebo group (006049-616-3008-0001, 37 yo F on Day 721, with lipase 43xULN and amylase 21xULN, and normal transaminases) and one in the Teri 14 group. Both cases were confounded by choledocolithiasis. The narrative of the patient on teriflunomide is as follows.

- **006049-643-3201-0002**. 42 yo F experienced exacerbation of chronic cholestypancreatitis (coded as pancreatitis chronic) on Day 87 of Teri 14 treatment. Concomitant medication included

methylprednisolone (MP). On Day 99, laboratory results showed elevated ALT at 4.1 ULN (140 U/L) and elevated GGT at 6.2 ULN (306 U/L). The chronic pancreatitis and cholecystitis were treated with thioctic acid, hymecromone, and hepabene. ALT returned to the normal range approximately on Day 108, and the GGT normalized by Day 156. She also developed non-serious polyneuropathy of upper and lower extremities on Day 104 of Teri 14 treatment. She recovered from neuropathy without corrective treatment on Day 130. The narrative states that the patient discontinued drug on Day 161 due to exacerbation of chronic cholecystitis. She had already recovered from chronic pancreatitis on Day 130 of study treatment.

Event may have been related to teriflunomide but is confounded by chronic cholecystitis. She also had polyneuropathy that seems to have resolved prior to drug discontinuation.

Three additional cases led to drug discontinuation from the Teri 7 group (abdominal pain, abdominal pain upper, diarrhea) and four from the Teri 14 group (abdominal pain, abdominal tenderness, flatulence, hyperchlordyria, ileus). Leflunomide is known to be associated with various GI symptoms. No additional cases of pancreatitis occurred in Pool 2.

- Dropouts in the General disorders and administration site conditions in Pools 1 and 2.

A case of pyrexia led to study drug discontinuation from Teri 7 in Pool 1. One case of fatigue and one of gait disturbance led to drug discontinuation from Teri 7 in Pool 2. The case of fatigue is presented below.

- **6049/276/2003/0002**, 41 yo F, 825 days after first dose of teriflunomide 7 mg, 53 days into the extension study. Concomitant meds included antifungol and magnesium. On Day 54, the patient experienced **fatigue**. She presented metrorrhagia, abdominal distension, mycosis vaginalis, and vomiting. Due to the event, the IP was permanently discontinued with the last dose taken on Day 144. No corrective treatments were given. The event was ongoing at the last report. The fatigue was considered as not related to the IP by the Investigator.

There was minimal information in this patients' narrative. Additional information was submitted for this patient at the FDA request, on April 6, 2012. LFTs and renal function were within normal.

- Dropouts due to AE in the Hepatobiliary disorders SOC in Pools 1 and 2

There was no excess of AE leading to discontinuation in teriflunomide groups. There was one case of hepatitis toxic in the Teri 14 group and one of liver injury in the Teri 7 group, both discussed in the SAE section. There was also one case of liver injury and one hypertransaminasemia leading to discontinuation from the placebo group which were non-serious. AE leading to discontinuation in Pools 1 and 2 are summarized below.

Table 39. AE leading to discontinuation, Hepatobiliary disorders SOC, Pool 1

Primary System Organ Class Preferred Term n(%)	teriflunomide		
	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)
Hepatobiliary disorders	2 (0.5%)	1 (0.2%)	1 (0.2%)
Hepatitis toxic	0	0	1 (0.2%)
Hypertransaminasaemia	1 (0.2%)	0	0
Liver injury	1 (0.2%)	1 (0.2%)	0

Source: Table 22 ISS.

Table 40. AE leading to discontinuation, Hepatobiliary disorders SOC, Pool 2

Primary System Organ Class Preferred Term n(%)	teriflunomide	
	7 mg (N=587)	14 mg (N=548)
Hepatobiliary disorders	3 (0.5%)	2 (0.4%)
Hepatic function abnormal	0	1 (0.2%)
Hepatitis toxic	0	1 (0.2%)
Cholelithiasis	1 (0.2%)	0
Cytolytic hepatitis	1 (0.2%)	0
Liver injury	1 (0.2%)	0

Source: Table 1.5.6.2 Original ISS.

There were three cases leading to drug discontinuation in this SOC in the extension studies: one cytolytic hepatitis and one cholelithiasis in the Teri 7 group and one Hepatic function abnormal in the Teri 14 group. These cases were discussed in the SAE section of this review.

- Dropouts in the Infections and infestations disorders SOC in Pools 1 and 2

Pool 1. There was no difference in the number of overall events leading to discontinuation in this SOC. There is a suggestion of a dose response between Teri 7 and 14, but the risk on placebo is in between. All cases are summarized in the following table.

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Table 41. AE leading to discontinuation, Infections and infestations AE, Pool 1

Primary System Organ Class	Placebo	teriflunomide	
		7 mg	14 mg
Preferred Term n(%)	(N=421)	(N=429)	(N=415)
Infections and infestations	4 (1.0%)	1 (0.2%)	5 (1.2%)
Anogenital warts	0	0	1 (0.2%)
Cytomegalovirus hepatitis	0	0	1 (0.2%)
Pyelonephritis	0	0	1 (0.2%)
Renal abscess	0	0	1 (0.2%)
Upper respiratory tract infection	1 (0.2%)	0	1 (0.2%)
Bronchitis	0	1 (0.2%)	0
Cellulitis	1 (0.2%)	0	0
Hepatitis C	1 (0.2%)	0	0
Urinary tract infection	1 (0.2%)	0	0

Source: Table 22, ISS.

In Pool 2, there were few additional cases of serious infections in the extension database. Again there is a suggestion for a dose response between Teri 7 and 14 but the number of events is small.

Table 42. AE leading to discontinuation, Infections and infestations AE, Pool 2a.

Primary System Organ Class	teriflunomide	
	7 mg	14 mg
Preferred Term n(%)	(N=587)	(N=548)
Infections and infestations	3 (0.5%)	7 (1.3%)
Anogenital warts	0	1 (0.2%)
Cytomegalovirus hepatitis	0	1 (0.2%)
Hepatitis A	0	1 (0.2%)
Pyelonephritis	0	1 (0.2%)
Renal abscess	0	1 (0.2%)
Respiratory tract infection	0	1 (0.2%)
Upper respiratory tract infection	0	1 (0.2%)
Bronchitis	2 (0.3%)	0
Cellulitis	1 (0.2%)	0

Source: Table 1.5.6.1 SUR.

Most cases of infection leading to drug discontinuation were serious and therefore discussed in Section 7.3.2 of this review.

- Dropouts due to AE in the Investigations SOC in Pools 1 and 2

Discontinuations due to investigations in Pool 1 and Pool 2 are presented in the following tables.

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Table 43. AE leading to discontinuation in Investigations SOC, Pool 1

Primary System Organ Class	teriflunomide		
	Placebo	7 mg	14 mg
Preferred Term n(%)	(N=421)	(N=429)	(N=415)
Investigations	15 (3.6%)	18 (4.2%)	13 (3.1%)
Alanine aminotransferase increased	8 (1.9%)	11 (2.6%)	8 (1.9%)
Hepatic enzyme increased	3 (0.7%)	1 (0.2%)	3 (0.7%)
Transaminases increased	4 (1.0%)	3 (0.7%)	2 (0.5%)
Neutrophil count decreased	0	1 (0.2%)	1 (0.2%)
Aspartate aminotransferase increased	0	1 (0.2%)	0
Gamma-glutamyltransferase increased	0	1 (0.2%)	0
Lipase increased	0	1 (0.2%)	0

Source: Table 22. ISS.

Table 44. AE leading to discontinuation in Investigations SOC, Pool 2

Primary System Organ Class	teriflunomide	
	7 mg	14 mg
Preferred Term n(%)	(N=587)	(N=548)
Investigations	39 (6.6%)	32 (5.8%)
Alanine aminotransferase increased	19 (3.2%)	19 (3.5%)
Hepatic enzyme increased	7 (1.2%)	10 (1.8%)
Transaminases increased	4 (0.7%)	2 (0.4%)
Aspartate aminotransferase increased	1 (0.2%)	1 (0.2%)
Bilirubin conjugated increased	0	1 (0.2%)
Lipase increased	2 (0.3%)	1 (0.2%)
Neutrophil count decreased	4 (0.7%)	1 (0.2%)
Gamma-glutamyltransferase increased	1 (0.2%)	0
HIV test positive	1 (0.2%)	0
Heart rate irregular	1 (0.2%)	0

Source: Table 1.5.6.2. original ISS.

Again, no imbalance in the risk of discontinuation due to Investigations AE, which were mostly driven by hepatobiliary related investigations.

Per protocol, patients with ALT elevation >3x ULN twice were to discontinue drug treatment. There were approximately 80 cases with hepatobiliary investigations leading to discontinuation in this application. Of those, SAE were evaluated in the SAE section of this review. Clinically relevant cases that were non-serious but led to drug discontinuation should be captured in the analyses of patients with ALT>3xULN and BR>2xULN (Section 7.3.4.1 of this review).

Other AE in the Investigations SOC

One case of heart rate irregular (002001/124/0017/0009, a 49 yo M, on Teri 7 mg on Day 678 of treatment) and one HIV test positive (006049-643-3201-0015, a 22 yo F was found to be HIV positive 974 days into Teri 7 treatment) lead to drug discontinuation in Pool 2. Neither case was thought to be related to study drug. The heart rate irregular is reported as recovered but there is very little information about this patient.

- Dropouts in Musculoskeletal and connective tissue disorders in Pools 1 and 2

In Pool 1, there were two cases of pain in extremity (one in each teriflunomide group), one of rheumatoid arthritis (on Teri 14) and one of spinal osteoarthritis (on Teri 7). Additionally, a case of connective tissue disorder was reported in the extension studies, on Teri 14 mg.

The cases of RA and connective tissue disorder are described below:

- **006049/152/3801/0006**, 45 yo male developed rheumatoid arthritis leading to drug discontinuation on Day 35 of Teri 14 treatment. He had a history of diabetes, affective disorder and atrial septal defect. Concomitant meds included glibenclamide, clonazepam and sertraline. On Day 35 he was diagnosed with RA treated with nimesulide.

As per review of additional information submitted on 4/12/12, this patient did not have RA. He had a seronegative oligoarthritis with spondylopathy and enthesitis involvement. He was treated with methotrexate and eventually with sulfasalazine, discontinued drug and underwent elimination procedure. Lab parameters were unremarkable. There was no mention of lung involvement. He did not recover after drug discontinuation/washout. This seronegative arthritis that started 2 weeks into study treatment appears unrelated to study drug.

- **002001/124/0015/0020**, 52 yo F diagnosed with connective tissue disorder on Day 260. She received placebo in base study and Teri 14 during the extension. She also reported decreased vibratory sense on the day of the first dose of Teri 14 that persisted throughout the study. The diagnosis of CTD was done on Day 260 but she was discontinued from the study due to this event on Day 1030. Treatment of CTD included NSAIDs, hydroxychloroquine, prednisone, azathioprine and methotrexate. Event was not considered related by the investigator. As per the AE datasets, on Day 1030 she also reported a respiratory infection.

There was limited information about this case or why there was a diagnosis of connective tissue disorder. As per information submitted on April 12, 201, approximately 3-4 months into treatment she presented Raynaud's and typical SLE rash with photosensitivity, arthralgias and malar rash, diagnosed as moderate SLE. She was later evaluated by rheumatologists and treated with hydroxychloroquine, naproxen, indocin and acetaminophen. She was also diagnosed with diabetes mellitus treated with metformin. Lab evaluation showed positive anti-Ro (marker for Sjogren's syndrome) and anti Jo-1 (marker of polymyositis), with negative double stranded DNA, consistent with a mixed connective tissue disease. Subsequently she was treated with prednisone and short term azathioprine. Study drug was discontinued approximately 2 years after initiation of first symptoms of connective tissue. At a follow up visit 3 months after drug discontinuation her SLE symptoms were worse, but her MS appeared to be under control. The SLE was considered not related to study drug by the investigator.

- Dropouts due to AE in the Nervous system disorders SOC in Pools 1 and 2

In Pool 1, 0.5% of patients had events that led to study discontinuation in each treatment group (see table below).

Table 45. AE leading to discontinuation in Nervous system disorders SOC, Pool 1

Primary System Organ Class	teriflunomide		
	Placebo	7 mg	14 mg
Preferred Term n(%)	(N=421)	(N=429)	(N=415)
Nervous system disorders	2 (0.5%)	2 (0.5%)	2 (0.5%)
Multiple sclerosis	0	0	1 (0.2%)
Polyneuropathy	0	1 (0.2%)	1 (0.2%)
Headache	1 (0.2%)	0	0
Paraesthesia	1 (0.2%)	0	0
Status epilepticus	0	1 (0.2%)	0

Source: Table 22 of ISS.

As noted above, AE leading to early discontinuation in this SOC included two cases of polyneuropathy (one in each Teri group) and one case of paresthesia on placebo.

Narratives of the two cases of polyneuropathy are presented as follows:

- 006049/643/3210/0004**, 43 yo F, on day 173 of Teri 7 presented polyneuropathy of moderate intensity. Non-serious. She was previously treated with cerebrolysin, nicotinic acid, pentoxifylline, piracetam, vitamin B1 and B6, chlorprothixene, mexidol, milgamma, vasobral, ascorbic acid, mildronate, and thiogamma for MS. Concomitant therapies included trimetazidine, bipredonium, thioctic acid, and glatiramer acetate. On Day 174, drug was permanently discontinued because of this event. On Day 181, a nerve conduction study was compatible with a slight/moderate polyneuropathy dominated by axonal degeneration, involving sural and peroneal nerves, bilaterally. She was given cholestyramine washout from Day 182 to 192. Patient did not recover from polyneuropathy. As per labs included in patient profile, the patient also presented neutropenia (ANC 1.48 at week 18 and ANC 1.28 at week 24, ANC 1.85, 9 months after washout) although the event was not reported as an AE.

Polyneuropathy and neutropenia developed approximately 6 months into Teri 14 treatment. They are consistent with teriflunomide-induced effect although there are several confounding medications for which the starting treatment day is unclear. Patient had not recovered at time of last follow up.
- 006049/643/3210/0003**, 42 yo F. She started Teri 14 on (b) (6). Concomitant meds included ascorbic acid, pyridoxine iron and vitamin supplements. A false positive reaction for Lues (syphilis) was recorded on Jul 9, 2008. On day 337 of Teri 14 (b) (6) patient presented peripheral polyneuropathy of lower extremity, categorized as mild, non-serious. Event of polyneuropathy lasted 212 days. A NCS confirmed decreased conduction velocity of right sural nerve. The event was considered drug related and led to permanent drug discontinuation on Day 343. She underwent washout with cholestyramine from Day 346 to 356. Patient recovered from the neuropathy. On Jan 9, 2009 an AE of late latent syphilis was recorded, treated with dexamethasone and benzylpenicillin. The patient also had liver steatosis which was present at baseline and was ongoing at time of last FU.

The CRF and narrative in this case were not consistent. On an unknown date, the patient was diagnosed with latent syphilis and treated as such. Sanofi was asked to clarify whether this patient had syphilis reactivation or not. After Sanofi’s discussion with the investigator, it is still unclear if the patient had syphilis reactivation or not.

Other events leading to study drug discontinuation in Pool 1 were one case of headache on placebo, one case of multiple sclerosis in the Teri 14 group (006049-792-5001-0001, discussed under SAEs) and one of status epilepticus in the Teri 7 group, described below.

- **006049/616/3009/0013.** This 29-year-old female patient experienced **pneumonia** 652 days and two events of **status epilepticus** (653 days and 695 days into treatment with Teri 7. The patient was 31 years old at the time of the first event and recovered from status epilepticus with corrective treatments. The event epilepsy was ongoing at the time of last report. Concomitant therapy included baclofen for many years. The patient was diagnosed with epilepsy on Day 668. The status epilepticus was considered as related to the IP by the investigator. Drug was discontinued. No washout treatment was administered. On Day 711, the patient recovered from the event.

New onset seizures, status epilepticus, almost 2 years into teriflunomide 7 mg treatment. The role of teriflunomide in the new onset of seizures and epilepsy can not be ruled out.

Adverse events leading to permanent drug discontinuation in the Nervous system disorders SOC in Pool 2 (as per the SUR) are presented below.

Table 46. AE leading to discontinuation, Nervous System disorders SOC, Pool 2a

Primary system organ class Preferred Term	Teri 7 mg N= 587 n (%)	Teri 14 N= 548 n (%)
Nervous system disorders	10 (1.7)	2 (0.4)
Multiple sclerosis	1 (0.2)	1 (0.2)
Polyneuropathy	2 (0.3)	1 (0.2)
Coordination abnormal	1 (0.2)	0
Epilepsy	1 (0.2)	0
Headache	1 (0.2)	0
Intracranial aneurysm	1 (0.2)	0
Neuropathy peripheral	1 (0.2)	0
Posterior reversible encephalopathy syndrome	1 (0.2)	0
Status epilepticus	1 (0.2)	0

Source: SUR

Cases of polyneuropathy and peripheral neuropathy leading to permanent discontinuation during the extension study are as follows:

- **6049/643/3206/0007**, 54 yo M, on Day 1600 of Teri 7 therapy presented peripheral neuropathy. Non-serious, did not recover. He had a medical history of hypertension and urticaria. He was previously treated with nicotinic acid, pentoxifylline, pyracetam, phezam, prednisolone, vinpocetine, analgin, dimedrol, and reopolyglukin for MS. Concomitant therapies included bendazol, dipyridamole, and

enalapril. On Day 842 of LTS6050 (Day 1600 since first dose) peripheral neuropathy was reported as AE, confirmed by NCS that showed axonopathy of upper and lower extremities. Drug was permanently discontinued the same day. No corrective treatment was given. Event was considered related by the investigator. Patient followed cholestyramine washout from Day 834 to Day 853 of LTS6050. Event had not resolved at time of last follow up.

*Polyneuropathy diagnosed approximately 4 years into Teri 7 mg treatment.
Consistent with drug induced event. Not resolved after washout.*

Other cases leading to drug discontinuation in Pool 2 are summarized below:

- **002001-124-0018-0005** 22M. Multiple sclerosis. *The narrative does not provide a description that justifies report as an AE versus lack of efficacy.*
- **006049-203-4101-0032** 36 yo F, received placebo during the base study. Three days into teriflunomide 7 mg treatment an MRI showed an aneurysm of the medial cerebral artery on the right, at the site of transition of M 1-2 and lesions of demyelination. At the time she had “tension cephalgia.” She was hospitalized for surgery, and study drug was discontinued on Day 14. *The event is not related to study therapy.*
- **006049-616-3009-0003** 36 yo F. Seizure. Patient received placebo in the base study and Teri 7 in LTS6050. On Day 909 (2.5 years into treatment) the patient had two partial seizures with secondary generalization, leading to hospitalization. MRI was unchanged. Drug was discontinued on the same day. Event was considered related to study drug. She underwent washout procedure. *The narrative does not mention what kind of work up the patient had.
Seizures are not uncommon in patients with MS. This occurred in the extension study. In the absence of a control arm it is difficult to attribute it to study drug, however, the role of teriflunomide can not be ruled out.*
- **6049/124/1203/0003** 35 F experienced headache 2 weeks into extension study. She was on placebo during the base study. Event led to drug discontinuation on Day 82. She recovered on Day 84, before washout. Event was considered related to drug. *The narrative does not mention MRI or CT scan or vital signs.*
- **6049/124/1201/0002**, 42 yo F developed Posterior Reversible Encephalopathy (PRES). She had a history of depression, hypothyroidism, neurogenic bladder and was diagnosed with MS 4 years before study entry. Concomitant therapy included ibuprofen, metronidazole oxybutynin, fluoxetine, levothyroxine, almotriptan, buspirone, naproxen, mometasone, medroxyprogesterone, doxazosin, pramipexole solifenacin, clonazepam, arthrotec and paracetamol. She received Teri 7 in the DB and extension study. Four years into treatment she presented ALT 4x ULN with normal BR, thought to be related to paracetamol. Serologies or abdominal ultrasound were not done. ALT resolved after paracetamol discontinuation. One month later, on Day 1496 she fell “due to loss of consciousness” and was diagnosed with PRES. She presented seizures, vomiting and diarrhea, confusion, increased weakness and visual disturbances. Brain MRI and MRA on Day 1497 showed new lesions bilaterally in the occipital, parietal and left frontal lobes with a small area of focus of restricted diffusion consistent with PRES. At that time she was also found to have elevated CK (“on the 700’s”) thought to be related to being down on the ground for an extended period of time. Regarding BP the report states “Her blood pressure on admission was not elevated and intermittently may have been up to 140,

with a baseline closer to 110 or 120 systolic, but was not consistently elevated.” EEG on admission showed epileptic activity without clinical seizures. Between the seizures there were periodic lateralized epileptiform discharges from the same location (left occipital area). Drug was discontinued, she was treated with Dilantin and had cholestyramine washout. The CSF results showed no significant abnormalities including cell count, protein and glucose level measurement, as well as a culture. ESR was elevated 76-116 mm/h during admission. A vasculitis screen including IgG and ANA and ANCA, was negative. Over the subsequent week, the patient’s symptoms began to slowly resolve including improved neurologic testing with regards to motor and visual function and cognitive status. MRI scan on Day 1505 demonstrated resolution of the signal changes compatible with PRES and stable chronic MS lesions.

The investigator considered the event of PRES related to study drug. The diagnosis is consistent with PRES, however, PRES is usually associated with increased BP. There is no documentation of increased BP in this case. As per information submitted on April 12, 2012 at the FDA request, CSF JC virus testing and cultures were negative.

- Dropouts due to AE in Neoplasms SOC in Pools 1 and 2

In Pool 1, overall, there were few events. There was a higher percentage of events in the placebo group (1.0%) than in either teriflunomide groups (0.2% in Teri 14). In Pool 2, there was no evidence of a dose-response between teriflunomide doses. Two patients discontinued from Teri 7 because of breast cancer, one because of colon cancer and one because of renal cell carcinoma. One patient discontinued from Teri 14 because of breast neoplasm and one due to adrenal adenoma. By the time of the 120-day safety report, an additional patient discontinued Teri 14 due to renal cell carcinoma.

- Dropouts due to AE in Psychiatric disorders SOC in Pools 1 and 2

In Pool 1 the percentage of psychiatric events leading to drug discontinuation was higher in the placebo group (0.7%) as compared to Teri 7 (0.2%) and Teri 14 (0.5%) groups. On Teri 7 there was one AE of anxiety leading to study discontinuation; on Teri 14 there was one delusional disorder and one event of insomnia; on placebo there was one suicide attempt, one event of depression and one of abnormal behaviour. In Pool 2 there was an additional case of confusional state on Teri 7 and no additional cases on Teri 14.

The case of Confusional state is described below:

- **6049/840/1037/0001**, 43 yo F from the US. Medical history included anxiety and depression. She received placebo during base study. On day 2 of Teri 7 treatment, she experienced confusion, leading to study drug discontinuation on Day 5. She recovered on Day 14.

The narrative does not include any information as to what kind of work up she had, whether there was a seizure or any changes in vital signs. As per information submitted on April 12, 2012 at the FDA request, this was a non-serious, self reported AE after it had already resolved. She also had epistaxis that lasted for 5 days. Concomitant therapies included vitamin B complex,

alprazolam, duloxetine, tramadol and marijuana. Drug was discontinued on day 5 but there was no further follow up. There is no mention of BP values.

- Dropouts in Skin and subcutaneous tissue disorders SOC in Pools 1 and 2

In Pool 1, there was an excess of events leading to drug discontinuation in the teriflunomide treatment groups in this SOC. The difference was driven by events of alopecia. Except for one case of serious skin ulcer (reviewed under SAE) and one case of eczema, events were considered non-serious. Events leading to discontinuation in Pool 1 are summarized below.

Table 47. AE leading to discontinuation, Skin and subcutaneous tissue disorders SOC, Pool 1

Primary System Organ Class	teriflunomide		
	Placebo	7 mg	14 mg
Preferred Term n(%)	(N=421)	(N=429)	(N=415)
Skin and subcutaneous tissue disorders	0	4 (0.9%)	13 (3.1%)
Alopecia	0	2 (0.5%)	6 (1.4%)
Eczema	0	1 (0.2%)	1 (0.2%)
Erythema multiforme	0	0	1 (0.2%)
Onychoclasia	0	0	1 (0.2%)
Pruritus	0	0	1 (0.2%)
Skin necrosis	0	0	1 (0.2%)
Skin ulcer	0	0	1 (0.2%)
Urticaria	0	0	1 (0.2%)
Rash generalised	0	1 (0.2%)	0

Source: Table 22, ISS.

A total of 8 patients dropped out because of alopecia in Pool 1 (six on Teri 14, 2 on Teri 7 and none on placebo). They were all female, ages 20 to 52 years. Mean time to onset was 77 days (range 11 to 114 days). All are reported to have recovered, but the duration of the event is missing in 4 cases. Time to recovery was roughly 2 to 6 months after drug discontinuation for those with available data.

Of note, there were several skin reactions leading to discontinuation other than alopecia, all in teriflunomide-treated patients. Cases are summarized below

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.Skin reactions leading to drug discontinuation in Pool 1.

ID	age sex	AE code	Outcome	Rel Onset	Duration	Comment
Teri 14						
002001-250-0030-0003	51F	Urticaria	Continuing	28	-	No prior hx. No concomitant meds. Drug discontinued, no washout. Event ongoing at last fu. Other events at the time were GGT >2.5 ULN and eosinophil count 0.6 Giga/L (normal up to 0.5). <i>Possibly related to study drug.</i>
006049-124-1203-0009	34F	Eczema	Resolved	210	67	No prior hx of allergies or eczema. Concomitant therapy included Diane (oral contraceptive). Treated with triamcinolone. Drug discontinued. Recovered after 2 months. <i>Possibly related to study drug.</i>
006049-643-3204-0013	48F	Pruritus	Resolved	139	106	No prior hx of allergy. Concom meds included Kliogest (oral contraceptive). Drug discontinued due to this event on Day 169. Washout with charcoal Day 174-184. Recovered on Day 244. <i>Possibly related to study drug.</i>
Teri 7						
002001-124-0010-0002	55F	Rash generalized	Resolved	29	99	Prior hx of rash while receiving minocycline, estrogens and carbamazepine. Generalized rash and pruritis. AlkP 1.8xULN other labs normal including eos. Started on minocyclin and sulfa drug one month prior to randomization. Treated with discontinuation and Topical triamcinolone acetone. <i>Possibly related to study drug. Case is confounded by recent treatment with minocyclin/sulfa.</i>
006049-643-3205-0003	35M	Eczema	Unknown	535 Worsen 562	-	No hx of allergies. He was taking multiple meds/herbals but no new meds were added. On Day 535 she had dermatitis with extensive lesions of macular rash on distal parts of extremities. Rash worsened on Day 562. Dermatologist diagnosed eczema, treated with bethametasonone and local treatment. The eczema on arms improved but was extensive on feet. Patient was lost to fu. <i>Possibly related to study drug.</i>

Source: AE dataset and narratives.

In pool 2 there were no additional cases of discontinuations due to alopecia. There was one additional case of pruritus generalized and two cases of rash in the Teri 7 group.

In summary, there were a few skin reactions consistent with an allergic reaction but they were non-serious, of mild to moderate intensity and resolved with drug discontinuation and local treatment. Only one of them was associated with increased eosinophil count. At least two cases were confounded by use of concomitant meds known to induce skin reaction (minocyclin/sulfa and modafinil).

Leflunomide carries a contraindication for patients with hypersensitivity to the drug, and a WARNING for occurrence of skin reactions such as Stevens-Johnson syndrome (SJS) and Toxic epidermic necrolysis (TEN). There were events of erythema multiforme, urticaria, pruritus and generalized rash in this application, but no cases of SJS or TEN. Still, teriflunomide should carry the same labeling as leflunomide regarding serious skin reactions.

Dropouts due to AE in SOCs not discussed in this section (such as Eye disorders, Cardiac disorders, Immune system, Vascular disorders and Respiratory, thoracic and mediastinal disorders SOCs) in Pool 1 and Pool 2 were serious and have been described in the SAE section of this review.

7.3.3.2 Dropouts and discontinuations in Adjunctive therapy studies

- Among patients receiving teriflunomide as adjunctive therapy to IFN- β (PDY6045+LTS6047), 8 patients had AE that led to study drug discontinuation
 - 2 (4.9%) in the placebo + IFN- β (one neurodermatitis and one ALT increased)
 - 3 (8.1%) in the Teri 7 mg + IFN- β group (one diarrhea, one alopecia, one ALT increased)
 - 3 (7.9%) in the Teri 14 mg + IFN- β group (one insomnia, one fatigue, one ALT increased)

The cases of ALT increase leading to discontinuation are summarized as follows:

ID	Age sex	Treatment group	Outcome	Rel day Onset	Duration	Comments
006045-380-5001-0003	51M	Placebo + IFN	ongoing	15	continued	Hx of hepatic steatosis. ALT 1.5xULN at baseline. On Day 15 ALT 2.5 xULN; on retest ALT 3.1 xULN on day 31 leading to discontinuation on Day 37. Normal BR and ALkP. Cholestyramine washout Day 39-57. ALT still elevated at last FU. No concomitant meds reported. No serology reported. <i>Event non-serious, appears related to study drug..</i>
006045-724-7007-0001	36F	7mg teri + IFN	R	210	54	Described in SAE section.
006045-276-4012-0008	29M	14mg teri + IFN	unknown	126	continued	Non-serious. Elevated ALT (ALT 2.4xULN on Day 43 and 6.2xULN on Day 125. Concomitant therapies ibuprofen, sildenafil for at least one year prior to entry. Study drug was discontinued on Day 133. Patient underwent washout procedure with

						cholestyramine on Day 134 but had vomiting. She had activated charcoal from Day 135 to 145. She recovered from first episode but outcome of second episode is unknown (ongoing at time of last follow up but no values after washout). No mention of serologies or abdominal US. <i>Event appears related to study drug, however, infectious etiology was not adequately ruled out.</i>
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- Among patients receiving teriflunomide as adjunctive therapy to glatiramer (PDY6046+LTS6047), 10 patients discontinued due to AE
 - 2 (5%) on placebo (headache and herpes zoster)
 - 3 (7.1%) in Teri 7 + GA (interstitial pneumonia [discussed under SAE], dyspnea after copaxone injection and facial rash)
 - 5 (12.2%) in Teri 14 + GA (fibromyalgia, diarrhea, 2 alopecia, and one seborrheic dermatitis)

In general AE profile in adjuvant studies is consistent with that of Pool 1.

7.3.3.3 AE leading to discontinuation in Clinical pharmacology and ongoing studies

The safety profile of teriflunomide in Clinical pharmacology studies and ongoing phase 3 studies was consistent with that in Safety Pools 1 and 2. AE leading to discontinuation in these studies are presented in Appendix 5 of this review.

7.3.3.4 Discontinuations likely due to adverse events but not categorized as such

Narratives for subjects who prematurely discontinued treatment were reviewed. The table below summarizes Pool 1 subjects who, according to the assessment of Dr. Mentari, likely discontinued because of an adverse event, but were not categorized as such by the Sponsor. These subjects had ongoing adverse events at the time of discontinuation, and no other reason for discontinuation was documented.

Table 48. Subjects with Adverse Events and No Other Documented Reason for Discontinuation, Pool 1

Study Subject Number	Treatment	Reason Per Sponsor	Comment
EFC6049 1207-0004	Teriflunomide 7 mg	Subject did not wish to continue	Comment listed: “subj feels she is having symptoms that never occurred while on infb. she would like to restart Avonex.” No specific adverse event was listed at the time of discontinuation.
EFC6049 1208-0004	Teriflunomide 14 mg	Protocol violation due to noncompliance	Subject had an adverse event of worsening depression at the time of discontinuation.

Study Subject Number	Treatment	Reason Per Sponsor	Comment
EFC6049 1209-0013	Teriflunomide 14 mg	Lost to follow-up	Severe flu symptoms at the time of discontinuation.
EFC6049 2008-0014	Teriflunomide 14 mg	Subject did not wish to continue	An adverse event of a psychiatric disorder, verbatim term “organic phsyoxis,” categorized as severe, started 2 days prior to discontinuation and was ongoing at discontinuation.
EFC6049 2408-0004	Teriflunomide 14 mg	Patient did not wish to continue the study	Pt. had 4 ongoing AEs, each rated as severe, at time of discontinuation. AEs were abdominal pain, gingival hypersensitivity, myalgia, and abdominal meteorism (flatulence).
EFC6049	Placebo	Subject did not wish to continue	Narrative said “Discontinuation reason: Subject did not wish to continue (the patient did not wish to continue due to adverse event and lack of efficacy)” No specific adverse event was listed at the time of discontinuation.

There was one Pool 2 subject who, according to the assessment of Dr, Mentari, likely discontinued because of an adverse event, but were not categorized as such by the Sponsor (see table below).

Table . Pool 2 Discontinuations: Subjects with Adverse Events and No Other Documented Reason for Discontinuation

Study Subject Number	Treatment	Reason Per Sponsor	Comment
LTS6050 1210-0008	Teriflunomide 14 mg	Subject did not wish to continue	Narrative commented that dyspepsia contributed to discontinuation. Subject had right upper quadrant tenderness and elevated liver enzymes ongoing at discontinuation.

7.3.4 Significant Adverse Events (Adverse Events of Special Interest [AESI])

As noted earlier in this review, the DNP and the Applicant agreed on a list of AESI. The definition (search terms) for AESI is presented in the following table:

Table 49. Search terms for Adverse Events of Special Interest (AESI)

AESI	SMQ(s) (MedDRA 13.1) if applicable	Scope if applicable	Description
Nausea			PT: Nausea
Diarrhea			HLT: Diarrhoea
Hepatic disorders	20000006	Narrow	Drug related hepatic disorders - comprehensive search_Narrow
Interstitial lung disease (pulmonary disorders)	20000042	Narrow	Interstitial lung disease_Narrow
Peripheral neuropathy	20000034	Narrow	Peripheral neuropathy_Narrow
Malignancy	20000091 20000092 20000094	Narrow	Malignant or unspecified tumours_Narrow Malignancy related conditions_Narrow Tumour markers_Narrow
Hypertension/Blood pressure increase	20000147	Narrow	Hypertension_Narrow
Hematopoietic cytopenias (Bone marrow disorders)	20000027	Narrow	Haematopoietic cytopenias_Narrow
Infections and Infestations			SOC: Infections and Infestations
Anaphylactic reaction (Hypersensitivity)	20000021	Broad+Narrow	Anaphylactic reaction_Broad+Narrow
Pancreatic disorders	20000022	Narrow	Acute pancreatitis_Narrow + PTs Blood amylase increased (10005328) Lipase increased (10024574) Pancreatic enzyme abnormality (10033619) Lipase abnormal (10054821) Blood amylase abnormal (10054822) Pancreatic enzymes abnormal (10061899) Pancreatic enzymes increased (10061900) Hyperlipasaemia (10067725)
Cardiac arrhythmias	20000049	Narrow	Cardiac arrhythmias_Narrow
Convulsions	20000079	Narrow	Convulsions_Narrow
Hemorrhages	20000038	Narrow	Haemorrhages_Narrow
Embolic and thrombotic	20000081	Narrow	Embolic and thrombotic events_Narrow

HLT= High level term; PT= preferred term. SMQ= Standardized MedDRA Query; SOC= system organ class. Additionally, the search included Alopecia as AESI. The search for alopecia included 16 different PTs (not included in this table). Source: Table 5 of ISS

The search strategy was acceptable, in general. However, it is based on Narrow SMQs (instead of broad SMQs) and may have missed some events. Some of the SMQs have more than one Narrow SMQ (e.g. events related to cardiac arrhythmia). An alternative search approach will be discussed under each AESI, if needed.

The incidence rate of TE AEs of special interest (AESI), as per Sanofi’s analysis in Safety Pool 1 is presented as follows:

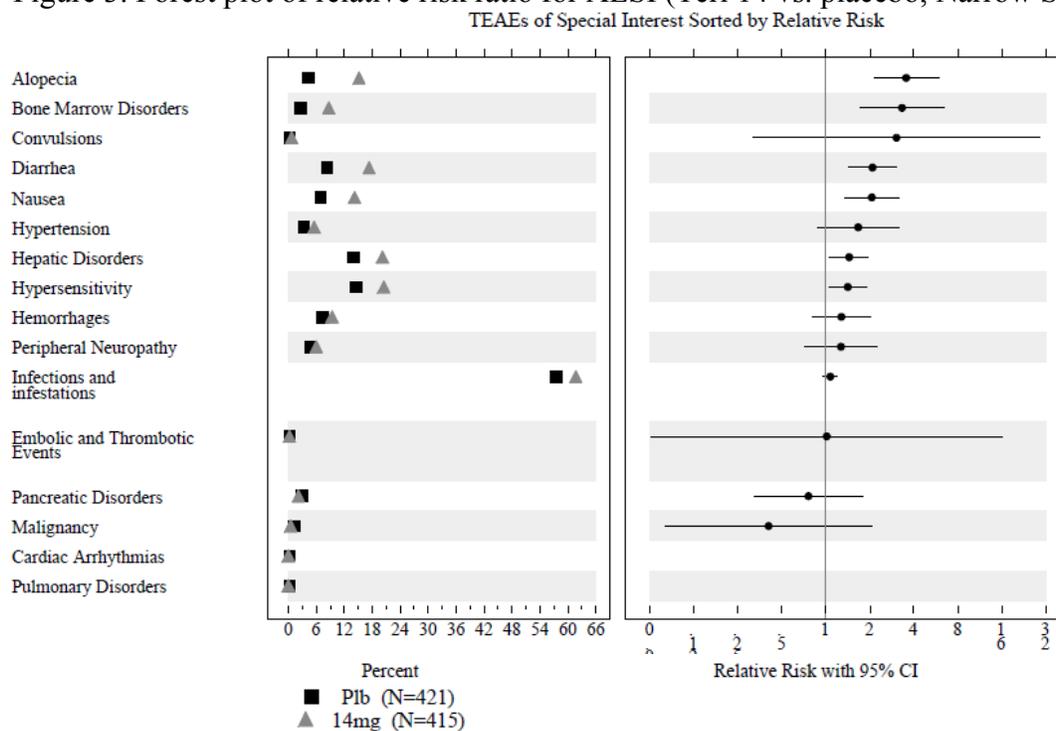
Table 50. Adverse events of special interest (Narrow SMQ terms), Safety Pool 1.

AESI n (%)	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)	Relative risk 14 mg vs placebo	Relative risk 7 mg vs placebo
Nausea	29 (6.9%)	40 (9.3%)	59 (14.2%)	2.06 (1.35 to 3.15)	1.35 (0.86 to 2.14)
Diarrhea	35 (8.3%)	61 (14.2%)	72 (17.3%)	2.09 (1.43 to 3.05)	1.71 (1.15 to 2.53)
Hepatic Disorders	59 (14.0%)	88 (20.5%)	84 (20.2%)	1.44 (1.07 to 1.96)	1.46 (1.08 to 1.98)
Pulmonary Disorders	1 (0.2%)	0	0	0.00 (NC)	0.00 (NC)
Peripheral Neuropathy	20 (4.8%)	16 (3.7%)	25 (6.0%)	1.27 (0.72 to 2.25)	0.79 (0.41 to 1.49)
Malignancy	5 (1.2%)	1 (0.2%)	2 (0.5%)	0.41 (0.08 to 2.08)	0.20 (0.02 to 1.67)
Hypertension	14 (3.3%)	23 (5.4%)	23 (5.5%)	1.67 (0.87 to 3.19)	1.61 (0.84 to 3.09)
Bone Marrow Disorders	11 (2.6%)	44 (10.3%)	36 (8.7%)	3.32 (1.71 to 6.43)	3.93 (2.06 to 7.50)
Infections and infestations	242 (57.5%)	256 (59.7%)	256 (61.7%)	1.07 (0.96 to 1.20)	1.04 (0.93 to 1.16)
Hypersensitivity	61 (14.5%)	82 (19.1%)	85 (20.5%)	1.41 (1.05 to 1.91)	1.32 (0.97 to 1.79)
Pancreatic Disorders	12 (2.9%)	14 (3.3%)	9 (2.2%)	0.76 (0.32 to 1.79)	1.14 (0.54 to 2.45)
Alopecia	18 (4.3%)	49 (11.4%)	63 (15.2%)	3.55 (2.14 to 5.89)	2.67 (1.58 to 4.51)
Cardiac Arrhythmias	1 (0.2%)	1 (0.2%)	0	0.00 (NC)	0.98 (0.06 to 15.64)
Convulsions	1 (0.2%)	2 (0.5%)	3 (0.7%)	3.04 (0.32 to 29.14)	1.96 (0.18 to 21.56)
Hemorrhages	31 (7.4%)	29 (6.8%)	39 (9.4%)	1.28 (0.81 to 2.00)	0.92 (0.56 to 1.50)
Embolic and Thrombotic Events	1 (0.2%)	2 (0.5%)	1 (0.2%)	1.01 (0.06 to 16.16)	1.96 (0.18 to 21.56)

n (%) = number and percentage of patients with at least one treatment emergent Adverse Event of Special Interest.

Source: Table 24, ISS. These events are represented in the figure below.

Figure 3. Forest plot of relative risk ratio for AESI (Teri 14 vs. placebo, Narrow SMQs). Pool 1.



Source: Figure in original ISS.

As seen in this table and figure, for most AESI, the risk was greater in the Teri 14 group than in the placebo group. The point estimate for alopecia, bone marrow disorders, nausea and diarrhea showed a relative risk of >2, with a 95% CI above 1, supporting a true increase in risk. Hepatic disorders and hypersensitivity have a point estimate above 1 but below 2 with a 95% CI above 1, suggesting a true increase in risk.

The point estimate for convulsions was 3.04 but with a 95% CI that included 1, not statistically significant. The relative risk of pulmonary disorders, malignancy, infections, pancreatic disorders, cardiac arrhythmias and embolic/thrombotic events in the Teri 14 group was no higher than placebo. However, a point estimate of 1 or less, or a point estimate above 1 with a wide CI do not rule out an association.

AESI in TOWER interim analysis are presented below.

Table 51. Adverse events of special interest in TOWER (original submission)

AESI n (%) TOWER	Placebo (N=363)	7 mg (N=379)	14 mg (N=350)
Hepatic Disorders	33 (9.1%)	45 (11.9%)	39 (11.1%)
Pulmonary Disorders	0	0	0
Peripheral Neuropathy	10 (2.8%)	14 (3.7%)	10 (2.9%)
Malignancy	0	1 (0.3)	0
Hypertension	2 (0.6%)	14 (3.7%)	12 (3.4%)
Bone Marrow Disorders	15 (4.1%)	36 (9.5%)	43 (12.3%)
Infections and infestations*	145 (39.9)	157 (41.4)	128 (36.6)
Hypersensitivity	38 (10.5%)	38 (10%)	40 (11.4%)
Pancreatic Disorders	0	3 (0.8%)	3 (0.9%)
Alopecia	17 (4.7%)	40 (10.6%)	42 (12.0%)
Cardiac Arrhythmias	3 (0.8%)	4 (1.1%)	6 (1.7%)
Convulsions	0	0	0
Hemorrhages	17 (4.7%)	21 (5.5%)	17 (4.9%)
Embolic and Thrombotic Events	0	0	1 (0.3%)
<i>PSYCHIATRIC</i>	22 (6.1%)	25 (6.6%)	17 (4.9%)

Source: Section 14.2.7.5 of TOWER CSR. *Infections and infestations were not included among AESI in TOWER but they included in this table for completeness (from Table 24 of report, Patients with TAE in Safety population). Psychiatric disorders added as AESI in TOWER. The interim report did not include statistical analyses as presented for Pool 1.

The findings of increased risk of hypertension, alopecia and bone marrow disorders in TOWER are consistent with Pool 1. There is a suggestion for increased risk of pancreatic disorders and arrhythmias. Statistical analyses of relative risk were not submitted for AESI in TOWER.

The following section of this review evaluates individual AESI.

7.3.4.1. AESI related to Hepatotoxicity

Analyses of AE related to hepatotoxicity in Pool 1 are presented in the following table.

Table 52. Patients with hepatic disorder AESI by primary SOC, and PT, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Any class	59 (14.0%)	88 (20.5%)	84 (20.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.0%)	3 (0.7%)	6 (1.4%)
Haemangioma of liver	4 (1.0%)	3 (0.7%)	6 (1.4%)
Focal nodular hyperplasia	0	1 (0.2%)	1 (0.2%)
Hepatobiliary disorders	13 (3.1%)	15 (3.5%)	5 (1.2%)
Hepatic steatosis	7 (1.7%)	3 (0.7%)	3 (0.7%)
Hepatitis toxic	0	0	1 (0.2%)
Hepatotoxicity	1 (0.2%)	0	1 (0.2%)
Hepatic cyst	2 (0.5%)	2 (0.5%)	0
Hepatic pain	0	2 (0.5%)	0
Hepatomegaly	2 (0.5%)	5 (1.2%)	0
Hyperbilirubinaemia	1 (0.2%)	1 (0.2%)	0
Hypertransaminasaemia	1 (0.2%)	0	0
Liver disorder	0	1 (0.2%)	0
Liver injury	1 (0.2%)	1 (0.2%)	0
Investigations	44 (10.5%)	75 (17.5%)	74 (17.8%)
Alanine aminotransferase increased	30 (7.1%)	54 (12.6%)	58 (14.0%)
Aspartate aminotransferase increased	5 (1.2%)	13 (3.0%)	13 (3.1%)
Gamma-glutamyltransferase increased	6 (1.4%)	18 (4.2%)	12 (2.9%)
Hepatic enzyme increased	7 (1.7%)	5 (1.2%)	6 (1.4%)
Transaminases increased	6 (1.4%)	6 (1.4%)	4 (1.0%)
Blood bilirubin increased	3 (0.7%)	4 (0.9%)	1 (0.2%)
Prothrombin time prolonged	1 (0.2%)	2 (0.5%)	1 (0.2%)
Alanine aminotransferase abnormal	1 (0.2%)	0	0
Aspartate aminotransferase abnormal	1 (0.2%)	0	0
Bilirubin conjugated increased	1 (0.2%)	0	0
Blood bilirubin unconjugated increased	1 (0.2%)	1 (0.2%)	0
Gamma-glutamyltransferase abnormal	0	1 (0.2%)	0
Liver function test abnormal	0	1 (0.2%)	0
Prothrombin time abnormal	0	1 (0.2%)	0

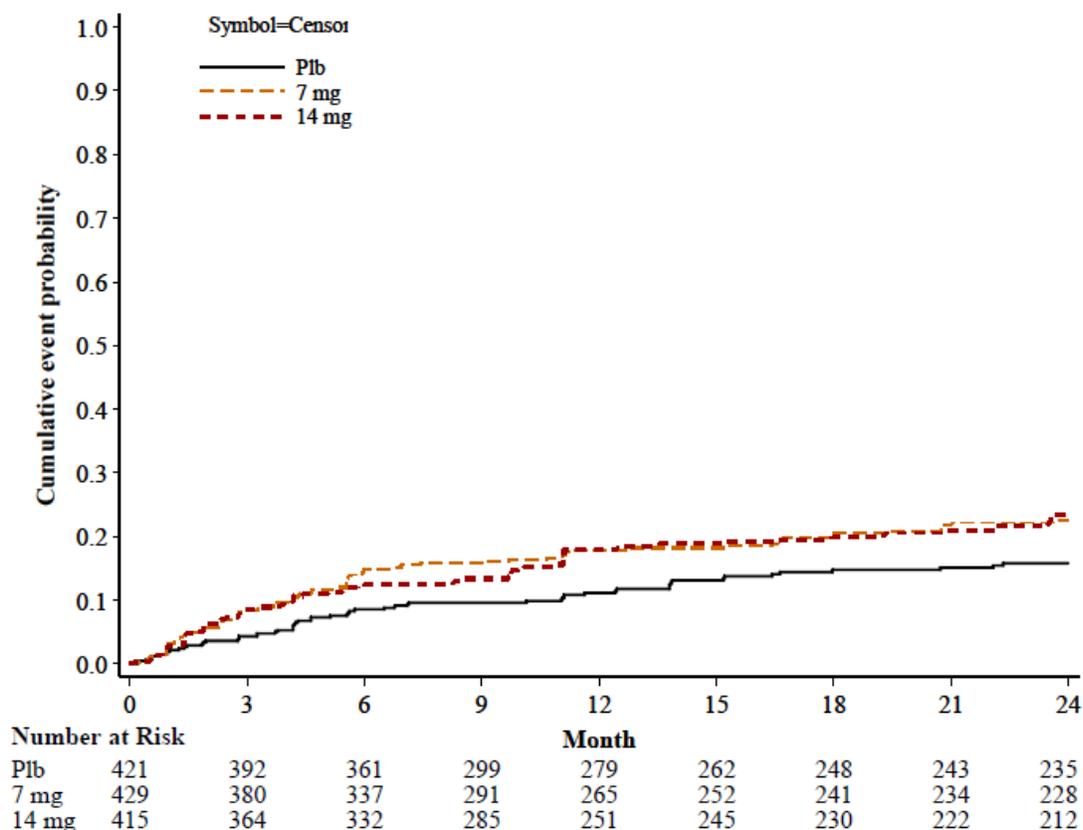
Source: Table 26, ISS.

This table shows that the risk of abnormal hepatobiliary investigations was greater in the teriflunomide treatment groups as compared to placebo (approx. 17-18% on teriflunomide, and 10.5 % on placebo).

A Kaplan Meier analysis of hepatic disorders AE over time in Pool 1 indicates that the curves start to separate from placebo within one

month and the risk persists (almost twice as placebo) throughout the 24-month period. There is no dose response between Teri 7 and 14 mg/day.

Figure 4. Kaplan-Meier plot for time to onset of hepatic AESI, Pool 1



Hepatic related SAE and AE leading to drug discontinuation were described in section 7.3 of this review.

Of note, there were two cases of focal nodular hyperplasia (FNH) (one in each teriflunomide treatment group and none on placebo). An additional case of FNH was recently reported from TOWER within 4 ½ months of being treated with Teri 14 mg as noted in Section 7.3.2.3, above. FNH is not an AE described with leflunomide and this could be an incidental finding. The numbers are small but this is a potential toxicity to follow in the postmarketing setting.

The median time to onset of hepatic disorders was 141 days in placebo, 129 days in Teri 7 and 127 days in Teri 14. The median duration of the events was 27 days in placebo, 50 days in Teri 7 and 43 days in Teri 14. There was a suggestion for increase in risk of hepatic disorders in females as compared to males in patients taking teriflunomide. (Source table 1.5.7.4.15 of ISS, data not shown).

7.3.4.1.1. Analyses of liver-related laboratories in Pools 1 and 2

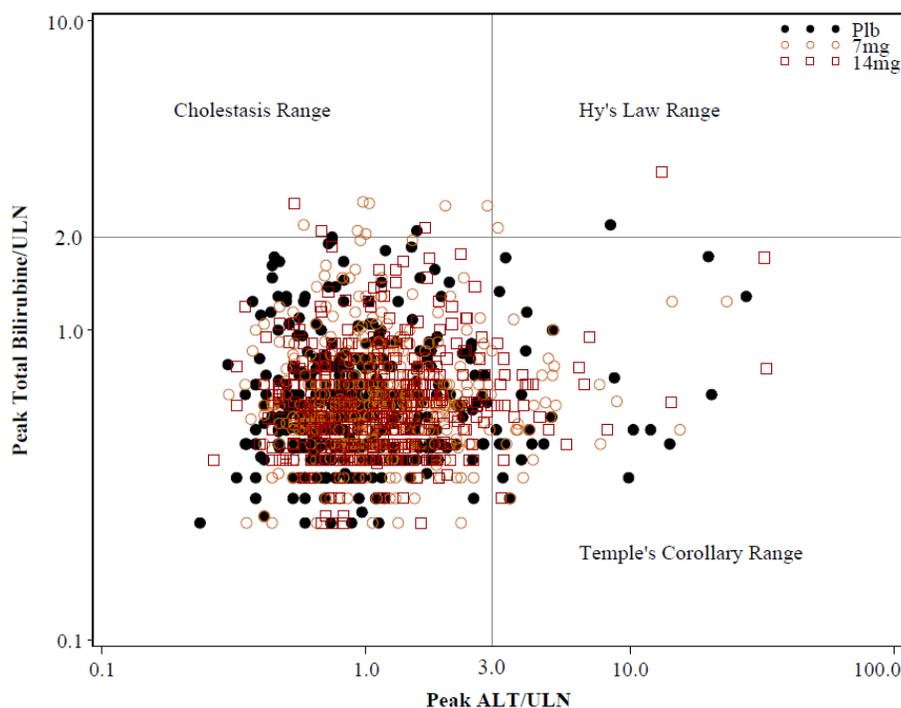
There were no clinically relevant changes from baseline in mean and median ALT, AST, ALK P, total BR and GGT in teriflunomide studies. Outlier analyses and evaluation of liver enzyme elevation using the NCI CTCAE criteria did not show an increased risk of developing ALT or AST >3x ULN, or total BR >1.5xULN. The risk of increased GGT >5x ULN was higher in teriflunomide treated patients (2.1% and 1.2% in the Teri 7 and 14 groups respectively) as compared to placebo (0.5%), suggesting a cholestatic component for liver toxicity. There was no difference in the incidence of elevated alkaline phosphatase.

Liver related laboratories are presented in detail in section 7.4.3.2 of this review.

- eDISH analyses

Sanofi submitted plots for peak values of ALT versus peak values of total bilirubin. The plot was divided into 4 quadrants by a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin. Individual case summaries and assessment of potential drug-induced liver toxicity was provided for each subject who appeared in the upper right-hand quadrant (Hy's Law range). Subsequently, Dr. Senior's requested the datasets to support these analyses. The analyses were reproduced by FDA reviewers using the eDISH program.

Figure 5. Plot of distribution of peak values of ALT versus peak values of total bilirubin, Pool 1



Three patients had ALT>3xULN and total BR >2xULN in Pool 1:

- **6049/3501/0004**, a 47-year-old female patient in the placebo group had increase in ALT, AST, GGT and total bilirubin in relation to hepatitis C infection (discussed under SAE Infections).
- **6049/2812/0001**, a 32-year-old male patient treated with Teri 14 mg for 9 months had increases in ALT, AST and GGT, alkaline phosphatase and total bilirubin with fever (maximum ALT elevation: 13.2 x ULN, maximum total bilirubin elevation: 3.2 x ULN). The events were related to a cytomegalovirus (CMV) hepatitis infection confirmed by positive testing for anti-CMV IgG and IgM antibodies. Study medication was discontinued due to this event. The patient recovered within 5 weeks. (discussed under SAE, Infections)
- **6049/3505/0005**, a 54-year-old male patient treated with Teri 7 mg had asymptomatic, intermittent increase in ALT (> 3 x ULN), AST, GGT and alkaline phosphatase starting on Day 127 of treatment, with an increase in Total BR on Day 295. At that time ALT was 1.5 x ULN. Serologies were not reported. Concurred gallbladder disease was suspected. Abdominal US before entering the study was normal. Abdominal US on Day 337 showed liver enlargement. Normalization of laboratory values occurred while on treatment. Patient entered the study extension.

Additionally, a 21-year-old, male (**6049/3802/0019**), with past medical history of Henoch-Schönlein purpura and total bilirubin 1.5 x ULN at baseline had increased values of ALT at 2.2 xULN, and total bilirubin at 2.0 x ULN 1 month after starting Teri 7. The retest done 7 days later showed ALT at 1.7 x ULN and total bilirubin at 2.5 x ULN. The maximum value of ALT was 2.9 x ULN about 3 months after the initiation of study treatment. He recovered on Day 170, while still on treatment. Drug was discontinued on Day 294 because the patient decided to discontinue from the study. He received cholestyramine washout from Day 296 to 305.

As noted in the eDISH plot, five patients had ALT>20 ULN without increase in BR >2xULN in Safety Pool 1. These five cases have been discussed under the SAE section but are presented again:

- **6049/3207/0003** and **6049/3803/0012** on placebo experienced asymptomatic increase in transaminases. Viral serology was negative in both cases. Methylprednisolone administered for one-week 1 month before the event was a

¹⁹ Upon discussion with Dr. John Senior, FDA hepatologist, additional information regarding potential liver toxicity cases was requested on 12/19/2011. Specifically, Sanofi was asked to provide datasets in a format that can be analyzed by eDISH by FDA reviewers. This information was submitted on 1/6/12. The FDA analysis confirmed 3 cases with ALT>3xULN + BR>2xULN and 5 cases with ALT>20xULN.

possible alternative explanation in patient 0012. For the other case, no reason was found.

- **6049/3803/0005** on Teri 7, with a prior history of cholelithiasis and cholecystectomy with asymptomatic increase in transaminases on Day 141. Viral serology was negative. Treatment with teriflunomide was discontinued. Transaminases increased reaching a maximum during the rapid elimination procedure on Day 160 (ALT 23.3 xULN). Peak ALK P and Total bilirubin were 1.2 xULN. The patient recovered 1.5 months after the event.
- **6049/1209/0040** on Teri 14, with a known history of cholelithiasis had asymptomatic ALT increase about 3 months after first intake of study medication. Concomitant drugs included paracetamol. ALT reached 33 x ULN after discontinuation and the completion of rapid elimination procedure.
- **6049/3201/0009** on Teri 14 developed fever of 39°C, bile vomiting and jaundice about 4.6 months after first intake of study medication. Elevation of total bilirubin (1.7 x ULN) and alkaline phosphatase (3.1 x ULN) were detected along with an increase in transaminases (ALT at 32.4 x ULN). She was taking some vitamins and supplements, none of which are specifically known to cause liver toxicity and some of which she had already taken in the past without liver toxicity. Viral serology was negative for hepatitis A, B and C. The case was diagnosed as toxic hepatitis. Drug was discontinued on Day 151. She was hospitalized on Day 153 when she received plasmapheresis and charcoal. She later received cholestyramine on Day 303-316. On Day 310 the ALT decreased to normal range. Review of available laboratory data showed intermittent eosinophilia. Eosinophil values during hospitalization are not available. *This appears to be a case of severe drug induced liver toxicity (See review by Dr. John Senior). Concomitant meds and laboratory data are included in Appendix 6 of this review.*

In Pool 2, two additional patients were in the so called “Hy’s law range,” as follows.

- **6050/2602/0001**, 49 yo M from the UK, with a history of cholelithiasis was diagnosed with obstructive jaundice 2.9 years into Teri 7 treatment (in LTS6050). Last dose of Teri was on Day 295 of the study. On Day 296 ALT was 6.3 x ULN and total bilirubin was 2.1 x ULN. Concomitant medications included gabapentin, ibuprofen, and dexamethasone. Abdominal US showed a suggestion of a tiny stone in the common bile duct. On Day 302 ALT was 5.3 x ULN and TB was 1.2 x ULN. He underwent washout procedure from Day 302 to 312. Laparoscopic cholecystectomy was performed on Day 444.
There appear to be a mixed hepatocellular and cholestatic pattern of liver toxicity in this case. There were gallstones but the patient recovered from ALT elevation at least 3 months before the surgery.
- **6050/2402/0020**, 37 yo patient 3.4 years into Teri 14 treatment (LTS6050) had an increase in ALT >20 x ULN and in total bilirubin (2.0 x ULN), with jaundice and asthenia. Serologic

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testing was positive for Hepatitis A with presence of anti-HAV IgM antibodies. Study treatment was discontinued due to this event. The patient was last known to have improved 3 months after with ALT value of 4.8 x ULN, and normal bilirubin value.

Additionally, during the extension studies, two patients in the Teri 14 group had significant ALT elevation with normal total BR as follows.

- **002001-124-0013-0017**, 42 yo female from Canada, on Teri 14 mg, presented increased BR direct along with ALT and AST elevation on Day 394 of treatment (Day 142 of extension), leading to permanent discontinuation. Event was severe but non-serious (regulatory term). It lasted 13 days. She was 43 years old at the time of the events and recovered from all the events without corrective treatment. The patient was an alcohol consumer. She was previously treated with methylprednisolone for MS. Concomitant therapies included multivitamins, glucosamine, ubidecarenone, ginkgo biloba, ranitidine, amitriptyline and amantadine. The patient had been receiving robaxisal compuesto and paracetamol daily for back pain since Day 121. On Day 141 of the extension, laboratory results showed **ALT at 9.3x ULN** (279 IU/L), and direct bilirubin at 1.6 ULN (7.8 µmol/L). On Day 143, ALT was 6.4x ULN (193 IU/L), AST was 3.2x ULN (102 IU/L), total BR was 18.8 (within normal) but direct bilirubin was 2x ULN (10.2 µmol/L). Drug was permanently discontinued along with robaxisal and paracetamol. The patient followed cholestyramine washout from Day 145 to Day 147. On Day 155, the patient recovered from the events.

ALT elevation > 9 x ULN with Dir BR 2 x ULN approximately 1 year into teriflunomide 14 mg treatment. It could be drug related but case is confounded by a history of alcohol consumption and use of paracetamol.

- **6050/2007/009**, 34 yo F had asymptomatic increase in transaminases, with ALT up to 24.4 x ULN and normal total bilirubin on Day 595 of the extension study (ie, about 3.7 years into Teri 14 treatment). No concomitant meds were reported. Serology testing was negative except for low positive ANA (1/160). The study medication was permanently discontinued on Day 592. The patient received cholestyramine from Day 595 to Day 606 and recovered on Day 711.

The event appears drug related. There was no increase in BR.

- Hepatic AESI in TOWER

Hepatic AESI in the TOWER interim report were consistent with findings in Pool 1. One patient had ALT>20xULN. This patient was on placebo and discussed under serious adverse events. ALT analyses in the TOWER study are presented in 7.4.2.1 of this review.

Three patients had ALT/BR in the Hy's law range in TOWER, two were on placebo (patient #276 002 005 [post high dose corticosteroid treatment] and #840 0015 0007 [found to have Hepatitis C, reported as non serious]); and one on Teriflunomide (patient #250 0001 0003 on Teri 7, had Gilbert's syndrome and maximum TBR did not coincide with maximum ALT elevation).

- Hepatic related AESI in TENERE (submitted as part of SUR)

The frequency of hepatic disorder AEs was higher in the Rebif® treatment group (39.6 %), as compared to either Teri 7 (13.6%) or Teri 14 (12.7%). The difference was driven by ALT increase, presented by 10.9%, 10% and 30.6% of patients in the Teri 7, Teri 14 and Rebif, respectively (See table below).

Table 53. Number of patients with hepatic disorders AEs in TENERE

Preferred Term n(%)	teriflunomide		Rebif (N=101)
	7 mg (N=110)	14 mg (N=110)	
Any class	15 (13.6%)	14 (12.7%)	40 (39.6%)
Alanine aminotransferase increased	12 (10.9%)*	11 (10.0%)*	31 (30.7%)
Transaminases increased	1 (0.9%)	2 (1.8%)	2 (2.0%)
Hepatomegaly	0	1 (0.9%)	1 (1.0%)
Aspartate aminotransferase increased	0	0	3 (3.0%)
Gamma-glutamyltransferase increased	0	0	2 (2.0%)
Haemangioma of liver	0	0	3 (3.0%)
Hepatic cyst	0	0	1 (1.0%)
Hepatic enzyme increased	1 (0.9%)	0	2 (2.0%)
Hepatic steatosis	1 (0.9%)	0	3 (3.0%)
Ultrasound liver abnormal	0	0	1 (1.0%)

Source: Table 17, TEAE: Treatment emergent adverse event. *nominal p value <0.05 as compared to Rebif

Evaluation of ALT elevations in TENERE showed a higher risk of ALT elevation >3xULN in the Rebif group (11.9%) as compared to Teri 7 (4.5%) and Teri 14 (7.3%). However, the risk of any increase in total BR was greater in teriflunomide groups (6.3% on Teri 7, 9% on Teri 14) than on Rebif (3%). There were no cases of ALT >3xULN and total BR >2x ULN, but the database is small (approximately 100 patients per group).

The findings with Rebif are consistent with those in the clinical trials for the interferons that all carry warnings of hepatic injury (see Appendix 7 of this review).

- **Hepatic events with ARAVA®**

As discussed earlier, teriflunomide is the active metabolite of leflunomide. Leflunomide is known to induce liver injury. In 2003, the FDA added a bolded WARNING for hepatotoxicity associated with ARAVA. Subsequently, on June 13, 2010, FDA issued a Drug Safety communication related to severe hepatic injury with ARAVA and updated the bolded WARNING to a boxed WARNING.²⁰ This decision was based on a review by the Office of Surveillance and Epidemiology, of postmarketing events from August 2002 to May 2009, with 49 cases of severe liver injury including 14 deaths, 5 cases of liver failure leading to liver transplantation and 9 life-threatening liver-related events. The greatest risk for liver injury was seen in patients taking other drugs known to cause liver injury and in patients with pre-existing liver disease. The estimated duration of leflunomide treatment before the occurrence of severe liver injury ranged from 9 days to 6 years, with the majority of patients developing severe liver injury within the first 6 to 12 months of treatment. The extent of patient exposure at the time of the review is not provided in the safety communication.

²⁰ <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm218679.htm>

FDA continues to follow liver events with ARAVA® very closely. As per the Hepatic AE report submitted by Sanofi to the Division of Pulmonary, Allergy and Rheumatology Products for ARAVA (NDA20905), on January 12, 2012, the cumulative reporting frequency of **acute liver failure, hepatic necrosis, fulminant hepatitis and fatal hepatic-related events is approximately 3.8 per 100,000 PYRs** (82 reports in 2.17 million PYRs of exposure, at the cut-off date of September 2011). A listing/summary of cumulative cases in the submission includes 33 deaths. Most cases are confounded by concomitant medications and comorbidities, including ETOH use, multiorgan failure/sepsis and Stevens-Johnson syndrome or contain insufficient information for adequate evaluation. The report is consistent with the known hepatotoxicity profile of leflunomide. A detailed review of the leflunomide cases exceeds the scope of this NDA review.

CONCLUSIONS REGARDING TERIFLUNOMIDE LIVER SAFETY

Review of the narratives and patient profiles of patients with liver related and hepatobiliary investigations AE as well as liver related laboratory evaluations in teriflunomide studies indicates that teriflunomide causes an increase in transaminases. ALT increased was reported as an adverse event in 14% of patients treated with Teri 14, as compared to 7.1% of patients treated with placebo. Most of these cases did not have a complete workup to rule out causes other than drug toxicity. However, except for a few cases, ALT elevation occurred without increase in total BR.

Eight patients presented ALT >3xULN and BR >2xULN in the teriflunomide database including 3 patients on placebo, two in each teriflunomide treatment group and one on Teri 7. All cases seem to have an explanation other than drug toxicity. In addition to these cases, one patient presented ALT elevation and jaundice in Pool 1. The DNP consulted Dr. John Senior, hepatologist at the FDA, for evaluation of this possible case of **severe Drug Induced Liver Injury (DILI)** (6049/3201/0009). This patient developed toxic hepatitis with ALT levels >30x ULN. She was very sick with jaundice and required hospitalization for 5 weeks. The maximum documented total BR level was 1.7 x ULN before hospitalization, however, BR values during hospitalization are missing. She underwent plasmapheresis and washout with activated charcoal and cholestyramine. Based on the available information Dr. Senior could not rule out DILI.

Extensive experience with leflunomide has identified that the drug has the potential to cause severe liver injury and death. As per the most recent ARAVA Hepatic Safety report with cut-off of September 2011, the rate of serious liver injury (acute liver failure, hepatic necrosis, fulminant hepatitis and fatal hepatic-related events) remains around **4 per 100,000 PYR**. There is no evidence that the risk of severe liver injury with teriflunomide will be lower than with leflunomide. We do have one possible case of severe DILI in this database of approximately 3100 patients (including 1500 exposed for 6 months or more).

Multiple sclerosis is a devastating disease. All available therapies are associated with potentially serious and fatal adverse events (see Table 2 and Appendix 7 of this review for AE comparisons). Despite the risk for liver injury, I believe that if the efficacy of teriflunomide is robust, it could be approved with adequate WARNINGS (similar to the current ARAVA® label) and an appropriately written MedGuide. (b) (4)

7.3.4.2 Pulmonary disorders

The search approach used in this category (Narrow SMQ for Interstitial Lung Disease (ILD)) captured one case of pneumonitis in a patient receiving placebo in Pool 1.

- **0649/3805/0001.** A 54 yo F was diagnosed with pneumonitis from Day 558 to Day 581 of treatment with placebo. She recovered without drug discontinuation. *There is no information about how the diagnosis was made.*

In Pool 2, two subjects had AE in the ILD SMQ. These cases are summarized below.

- **6050/1802/0008.** A 37-year-old female in the Teri 14 group with recent severe cold and long-term history of tobacco was diagnosed with bronchiolitis and interstitial lung disease on Day 1 of the extension study. This patient was previously receiving placebo during the main study. The study treatment was temporarily interrupted. The event was ongoing at the interim cut-off date. A follow up report was submitted on June 26, 2012; event was still unresolved. *Considering the chronology of events, this case of ILD on Day 1 is unlikely related to the study drug.*
- **6050/3203/0012.** A 50-year-old female with a history of cardiomyopathy, autoimmune thyroiditis, drug hypersensitivity to sulfanilamide, experienced a non-serious event of mild pulmonary fibrosis (reported as diffuse pneumosclerotic changes bilateral), diagnosed on CT scan on Day 397 of Teri 14 treatment. There was no clinical manifestation of the event. The event did not lead to study treatment discontinuation and no corrective treatment for the event was listed. The event was ongoing at last contact, 9 months after the event's onset, and no additional imaging testing for the evaluation of the event was performed. *Apparently PFTs were not done in this patient. The possibility of drug-related pulmonary toxicity was not adequately evaluated and can not be ruled out.*

Additionally, two cases which could be consistent with pulmonary toxicity were reported in the extension studies as follows

- **6050/2402/0016.** A 53 female developed a serious AE of mixed ventilatory deficiency coded as respiratory failure, on Day 533 of Teri 7 treatment during extension study, leading to drug discontinuation. Chest XRay showed bilateral increasing markings at the base of the lungs; PFTs showed mixed ventilatory deficiency. Dry cough improved during drug interruption and resumed when drug reintroduced. *Although the possibility of pneumonitis or ILD was not considered at the time, this case of "respiratory failure" could be related to teriflunomide, (full narrative is in section 7.3.2 of this review)*
- **002001-124-0015-0008** 43 yo M with history of smoking (1 pack/day), glaucoma, headache and drug hypersensitivity. During the study he presented HTN treated with ACE inhibitors and several

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episodes of upper respiratory infection with wheezing treated with salbutamol and seretide inhalers. Approximately 3.8 years into Teri treatment he developed dry cough, dyspnea and wheezing treated with IV solumedrol, diagnosed with bronchitis and bronchial asthma.

It is unclear how the diagnosis of asthma was made. There is no information about imaging and there are no pulmonary function tests with FEV1 and DLCO values. This could be a case of ACE inhibitor-induced cough but could also be interstitial lung disease/pneumonitis that was not fully characterized.

In the adjunctive therapy studies:

- **LTS6047-PDY6046, 3001/1019.** 38 yo female was hospitalized for suspected ILD 71 days after first dose of Teri 7 and glatiramer acetate, leading to drug discontinuation. Concomitant therapy: amitriptyline. Heavy smoker. On day 71 of treatment she experienced difficulty breathing. Chest Xray showed reticular-nodular alterations in bottom fields of both lungs. Interstitial pneumonia was suspected. She recovered with sequelae of residual dyspnea. The event was considered as related to study drug by the investigator.

This case is consistent with interstitial lung disease. She improved with symptomatic treatment and eventually recovered several months after drug discontinuation and cholestyramine washout. There was no BAL or lung biopsy to confirm the diagnosis. No PFT values are available from this patient.

From Ongoing studies:

In TOWER, there were two SAE of asthma on placebo and one in the Teri 14 group in the Respiratory disorders SOC. There were no events in this SOC in TENERE. There was 1 SAE of dyspnea in TOPIC (still blinded).

- Pulmonary function tests in TOWER

Because of the potential lung toxicity with leflunomide, PFTs have been incorporated into the TOWER study, which is still ongoing and blinded. The DNP requested submission of preliminary standard analyses of PFTs in this study. Sanofi responded on March 29, 2012. These analyses do not show worsening lung function with teriflunomide but do not allow definitive conclusions regarding lung toxicity of teriflunomide as they were done in a small subset of patients with 5-6 patients available by week 84. For details about the submitted analyses the reader is referred to section 7.4.5 of this review.

CONCLUSIONS REGARDING LUNG TOXICITY: Interstitial lung disease has been reported with teriflunomide in patients with rheumatoid arthritis. Postmarketing surveillance for all patients prescribed with leflunomide in Japan showed that 80 of 5911 patients developed interstitial pneumonia; of these, 27 died, with ILD being judged to be the primary cause of death in at least 18 cases.^{21, 22} In an epidemiologic study, preexistent lung disease, cigarette smoking, low body

²¹ Sakai et al. Leflunomide-related lung injury in patients with rheumatoid arthritis: imaging features. *Mod Rheumatol* 2005; 15: 173–179.

²² Chikura et al. Clinical expression of leflunomide-induced pneumonitis. *Rheumatology (Oxford)*. 2009 Sep, 48(9); 1065-8.

weight (<40 kg) and the use of a loading dose were identified as risk factors for ILD.²³ There is at least one published report of leflunomide induced pneumonitis in a patient with RA and dramatic response to cholestyramine washout.²⁴

The teriflunomide database has several events suspicious of ILD/pneumonitis, but the work up is incomplete in most cases. A preliminary analysis of PFTs in the ongoing TOWER study does not suggest a safety signal for ILD but does not rule out the possibility either.

Teriflunomide should carry the same WARNINGS and PRECAUTIONS as ARAVA®.

7.3.4.3 Peripheral neuropathy

Sanofi conducted a search for peripheral neuropathy using the Narrow MedDRA SMQ. Patients with potential peripheral neuropathy as per Sanofi’s analysis is presented below.

Table 54. Patients with AESI of peripheral neuropathy Narrow SMQ, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Any class	20 (4.8%)	16 (3.7%)	25 (6.0%)
Nervous system disorders	20 (4.8%)	16 (3.7%)	25 (6.0%)
Sensory disturbance	13 (3.1%)	9 (2.1%)	14 (3.4%)
Neuralgia	0	4 (0.9%)	5 (1.2%)
Neuropathy peripheral	2 (0.5%)	2 (0.5%)	3 (0.7%)
Polyneuropathy	0	1 (0.2%)	3 (0.7%)
Sensory loss	2 (0.5%)	0	1 (0.2%)
Decreased vibratory sense	5 (1.2%)	3 (0.7%)	0
Loss of proprioception	1 (0.2%)	0	0

Source: Table 41 ISS.

Overall, the percentage of patients with PTs in the peripheral neuropathy Narrow SMQ was slightly higher in the Teri 14 group (6.0%) as compared to placebo (4.8%). Within this SMQ, the PTs neuralgia and polyneuropathy were present only on teriflunomide treated patients.

Cases with PT of neuralgia, polyneuropathy and peripheral neuropathy in Pool 1

A total of 9 patients developed neuralgia (8 consistent with neuropathic pain and one unspecified neuralgia) and 4 developed polyneuropathy on teriflunomide treatment (no such cases on placebo). A similar number of patients on each treatment reported peripheral neuropathy in Pool 1 (2 patients on placebo, 2 on Teri 7 and 3 on Teri 14 in Pool 1). All cases were non-serious. Listings are as follows.

²³ Sawada et al. Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis. *Rheumatology (Oxford)*, 2009 Sep;48(9):1069-72.

²⁴ Successful treatment of leflunomide-induced acute pneumonitis with cholestyramine washout therapy. *J Clin Rheumatol*. 2009 Dec;15(8):389-92.

Listing of patients with neuralgia, polyneuropathy and peripheral neuropathy in Pool 1.

Patient ID	Age/sex. Rel Study day onset. (Duration [(days)] Action taken with drug PT. Outcome/comment
Teri 14	
006049-124-1205-0004	42/F. Day 492 (39). None Neuralgia. Recovered. Also presented paresthesia with onset on Day 476, and carpal tunnel syndrome on Day 566, which did not recover. Intermittent dizziness. Herpes simplex on Day 13-17 and 539-551. Intermittent diarrhea Day 172 to 283 and 306 to 332. Pruritic rash Day 30-52 and eczema with onset Day 415 which did not recover.
006049-152-3803-0010	28/F Day 9 (8). None Neuralgia. Recovered. Oropharyngeal candidiasis Day 41 to 52. Transaminase increase reported Day 41 to 56. Acute sinusitis Day 50-56. Dyslipidemia reported Day 47 did not resolve.
006049-203-4101-0023	51/F. Day 134. (ND). None Neuralgia. Continuing. Oral herpes reported Day 327 to 335. ALT increased Day 384 to 390. Arthralgia Day 379 to 456 (pain on hips and knees).
006049-246-2206-0004	37/F. Day 540 (ND). None Neuralgia. Continuing
006049-792-5003-0005	28/M. Day 543 (105) None Neuralgia. Recovered
006049-152-3805-0005 ¹	48/ F. Day 576. (ND). None Polyneuropathy. Continuing. Patient also has diabetes mellitus.
006049-643-3201-0002	42/ F. Day 104. (27). None Polyneuropathy. Recovered within a month. Did not complete study for other reasons.
006049-643-3210-0003 ²	42/ F. Day 337. (212). Discontinued drug Polyneuropathy. Recovered. 7 months after washout.
006049-124-1209-0037	34 /F. Day 14. ND. None Peripheral neuropathy. Recovered in 5 days. Intermittent reports of paresthesia, facial hypoesthesia, dizziness, nausea, pain in extremity during study. Elevated ALT Day 26 to 33.
006049-203-4101-0019	51/ F. Day 519. ND. None Peripheral neuropathy. Continuing. Had transient neutropenia Day 71-85, and HTN Day 414 to 589.
006049-826-2607-0009	29 /M . Day 256. ND. None Peripheral neuropathy. Recovered after 802 days NCS showed mild slowing of sural sensory conduction velocity. Did not meet criteria for polyneuropathy, but yes for peripheral neuropathy Motor studies were normal. Intermittent upper respiratory infections during study.
Teri 7	
006049-124-1207-0001	28/M. Day 633. ND. None Neuralgia. Continuing
006049-616-3003-0022	39/F. Day 464. ND. None Neuralgia. Continuing
006049-124-1212-0001	47/F. Day 136. ND None Neuralgia. Did not complete study. Unknown outcome
006049-826-2609-0006	43/F. Day 176. ND. None Neuralgia. Did not complete study. Unknown outcome
006049-643-3210-0004 ³	43/ F. Day 173. ND. Discontinued drug Polyneuropathy. Continuing.
006049-380-2812-0003	39/ M. Day 422. ND. None Peripheral neuropathy (ulnar neuropathy). Said to have recovered. Duration not stated. Same day reported arthralgia (ankle pain). Day 699 reported “epicondylitis” lasting 32 days (reported term: ulnar neuropathy due to epicondylitis)
006049-643-3201-0014	24/ F. Day 59. ND. None Worsening of peripheral neuropathy. Recovered after 6 months. NCS reported moderate

	myelinopathy. Alopecia reported on Day 71 (no recovered).
Placebo	
006049-152-3805-0001	54/ F. Day 763. (1). None Peripheral neuropathy. Lasted 1 day. Occurred during washout period..
006049-276-2005-0016	44/ F. Day 463. (1). None Peripheral neuropathy. Irritation of nerve ulnaris, Lasted 1 day.

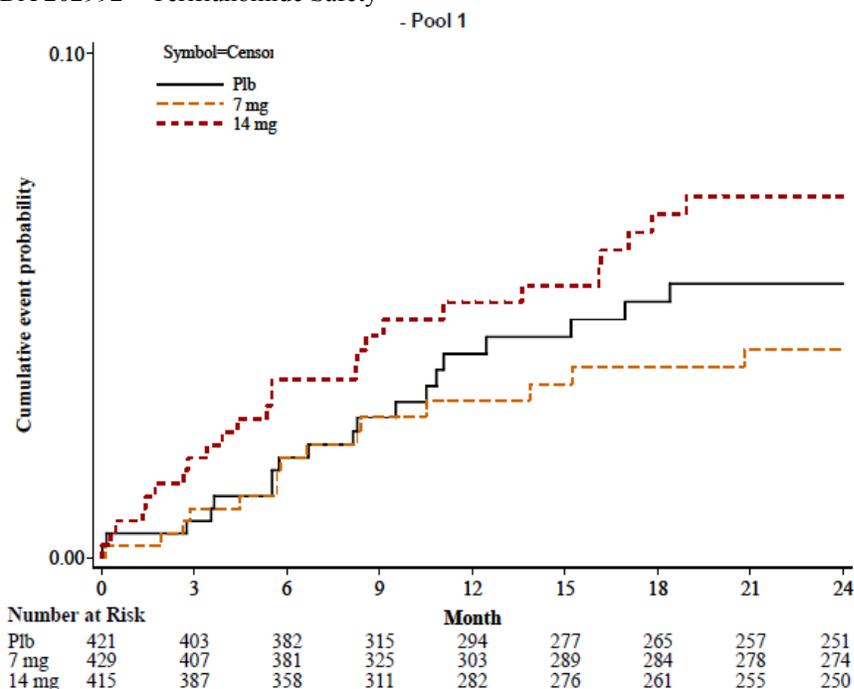
Source: AE datasets.

Neuralgia and polyneuropathy were reported in 11 females, 2 males, ages 28 to 48 years, on teriflunomide treatment only. The mean time to onset of neuralgia was 347.4 (range 9 to 633 days) and of polyneuropathy was 297.5 days (range 104 to 576 days). Three cases of neuralgia recovered within 8 to 105 days without drug discontinuation, four did not recover and two discontinued drug treatment but the outcome is unknown. Two cases of polyneuropathy discontinued study drug (one recovered and one did not), one continued treatment and event did not resolve and one recovered but it is unclear if drug was discontinued or not. Of note, the cases of peripheral neuropathy on placebo lasted 1 day, while the cases on teriflunomide lasted longer or did not recover.

Additionally, patient 002001-124-0018-0011, 28 yo F developed intermittent burning sensation, hypeaesthesia, paresthesia during Teri 14 treatment. She discontinued drug because of alopecia, approximately 4 ½ months into the study. Alopecia resolved several months later, but neuropathy had not resolved at the time of last follow up. None of these events were considered serious.

The following figure shows the Kaplan Meier plot of time to onset of peripheral neuropathy AE in Pool 1 (Sanofi’s analysis).

Figure 6. Kaplan-Meier plot for time to onset of Peripheral Neuropathy Narrow SMQ, Pool 1



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This analysis shows that the risk of peripheral neuropathy (Narrow SMQ) starts within the first month and there is a suggestion of a dose response between Teri 14 and Teri 7 mg/day treatments. Of note, this analysis does not include terms such as disesthesia, paresthesia and mononeuropathy.

FDA Additional analysis of peripheral neuropathy

Sanofi stated they used the Narrow SMQ for Peripheral neuropathy. The search did not include peripheral disaesthesia, paraesthesia and mononeuropathy. These terms are captured with the analyses of HLT (MedDRA high level term) Mononeuropathies and Paresthesias and disesthesias. Some patients had overlapping PT of peripheral neuropathy and carpal tunnel syndrome or paresthesia.

Table 55. More cases of Peripheral neuropathy by selected MedDRA HLT, Pool 1

Peripheral neuropathy HLT Preferred term	Placebo (N=363) n (%)	7 mg (N=379) n (%)	14 mg (N=350) n (%)
Mononeuropathies	3 (0.8)	4 (1.2)	11 (3.1)
Carpal tunnel syndrome	2 (0.6)	2 (0.6)	10 (2.9)
Nerve compression	0	1 (0.3)	0
Peroneal nerve palsy	1 (0.3)	0	1 (0.3)
Mononeuropathy	0	-	1 (0.3)
Paraesthesias and disaesthesias¹	51 (14.1)	55 (15.0)	71 (20.3)
Burning sensation	8 (2.2)	10 (2.7)	10 (2.9)
Dysaesthesia	4 (1.1)	3 (0.8)	7 (2.0)
Formication	0	0	1 (0.3)
Hyperaesthesia	3 (0.8)	0	8 (2.3)

Paraesthesia	36 (9.9)	42 (11.1)	44 (12.6)
Skin burning sensation	0	0	1 (0.3)

Source: FDA analysis of AE datasets in original submission. Includes PTs in the Paresthesias and dysesthesias HLT, except for Lhermitte sign and oral paresthesias. A patient can have more than one AE.

This analysis suggests an increased risk of carpal tunnel syndrome, paresthesias and dysesthesias with teriflunomide (mostly Teri 14) as compared to placebo. Some patients were already included in the applicant analysis of peripheral neuropathy because of coexistent PT terms of peripheral neuropathy or polyneuropathy.

Sanofi provided the following analysis of nerve conduction-confirmed peripheral neuropathy in study 6049/TEMPO:

Table 56. Peripheral neuropathy confirmed by nerve conduction studies in 6049/TEMPO

	Placebo (N=360)	teriflunomide	
		7 mg (N=368)	14 mg (N=358)
Total			
No suspected peripheral neuropathy	327/330 (99.1%)	323/335 (96.4%)	315/324 (97.2%)
Suspected peripheral neuropathy	3/330 (0.9%)	12/335 (3.6%)	9/324 (2.8%)
Suspected but not confirmed	3/330 (0.9%)	8/335 (2.4%)	3/324 (0.9%)
Confirmed by other studies or overall assessment, but not confirmed by electrophysiological nerve conduction studies	0/330	0/335	0/324
Confirmed by electrophysiological nerve conduction studies	0/330	4/335 (1.2%)	6/324 (1.9%)

Source: Appendix 14.2.9.3.1, TEMPO CSR. Total refers to all patients, regardless of baseline presence of suspected or confirmed neuropathy.

As per this analysis, peripheral neuropathy was suspected in 2.8-3.6% of patients on teriflunomide and 0.9% of patients on placebo. Of the suspected peripheral neuropathy, 4/335 (1.2%) of patients on Teri 7 and 6/324 (1.9%) of patients on Teri 14, were confirmed by electrophysiological nerve conduction studies (NCS), as compared to none on placebo.

As per listing included in Appendix 14.2.9.3.2 of the CSR, the patients with peripheral neuropathy confirmed by NCS in study 6049/TEMPO were as follows²⁵:

On Teri 7

- 1802/0005 – at week 60, not confirmed on repeat NCS at week 84
- 3007/0004 – at week 84 and 108 (no FU testing after week 108) (AE term: ulnar entrapment neuropathy, L side)
- 3201/0014- at week 36, not confirmed at week 60 (AE: worsening peripheral neuropathy, resolved)

²⁵ Seven of these 10 patients are included in the listing in page 157 of this review. 1802/0005, 3007/0004 and 1209/0043 are not.

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3210/0004- at week 108 (no FU testing) (AE: acute peripheral neuropathy – led to drug discontinuation)

On Teri 14

1205/0004 – at week 108 (no FU testing) (carpal tunnel syndrome; not recovered)

1209/0043 – at week 108 (no FU testing) (diabetic peripheral neuropathy; not recovered) Also had erythema nodosum, iritis, pancreatic disorder, peripheral edema.

2607/0009 – at week 36 and 60 (no FU testing) (peripheral neuropathy, shimmering sensation), resolved.

3210/0003 – at week 108 (no FU testing) (polyneuropathy led to study dc; other events: hepatic steatosis, treponema test false +)(did not resolve)

3805/0005- at week 60 and 108 (no FU testing) (carpal tunnel syndrome, polyneuropathy; did not resolve)

4101/0019 – at week 84 and 108 (no FU testing) (peripheral neuropathy, did not resolve). Other AE: HTN, transient neutropenia.

As per this listing, only two of the 10 cases of NCS-confirmed peripheral neuropathy resolved (both on Teri 7). In order to evaluate whether peripheral neuropathy could be related to hypophosphatemia, available patient profiles were reviewed. Of the 10 cases listed above, five had available patient profiles (because they were serious or led to study discontinuation). None of the five was associated with hypophosphatemia.

AESI of peripheral neuropathy in Pool 2:

In addition to the events described in Pool 1, there were 2 reports of polyneuropathy (1 in each treatment group: patients # 6050/3201/0001, confirmed with NCS, and # 6050/3805/0005, not confirmed with NCS, thought to be related to MS), 9 reports of peripheral neuropathy (4 in the Teri 7 and 5 in the Teri 14 group) and 5 reports of neuralgia (4 in the Teri 7 and 1 in the Teri 14 group). One of the patients with peripheral neuropathy was confounded by a history of diabetes.

Additionally there was one case of axonal neuropathy (sensory motoraxonal neuropathy) on Day 2215 in a 52-year-old male patient on Teri 14. The patient experienced a tingling sensation in lower extremities that lasted 1.3 years and resolved without treatment discontinuation or corrective treatment.

Additional cases of peripheral neuropathy as IND safety report

- Study LTS 6050 (extension to 6049), Investigator 1038, patient 0002, from U.S. MFR# 2012SA015222. 48 yo F approximately 1.9 months into teriflunomide treatment had foot paresthesias. Patient was taking concomitant cyclobenzaprine, naproxen and hydrocodone. The patient had loss of sensation in both limbs in the glove and sock distribution. Patellar reflexes were normal and the Achilles reflexes were hypoactive. Nerve conduction studies and EMG were compatible with a mild peripheral sensory motor neuropathy. The case was initially reported as non-serious but then changed by the investigator to a serious AESI. *The causal relationship to teriflunomide can not be excluded.*
- Study LTS6048 (extension to 2001) Investigator 0017, Patient 0005. Patient developed peripheral neuropathy 4.2 years into teriflunomide treatment characterized by loss of sensation and reduced

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ankle reflexes. The patient had MS for approximately 8 years before entering the study. Diabetes was diagnosed 1.5 years prior to development of peripheral neuropathy. Patient did have nerve conduction abnormalities as well as examination findings compatible with a length dependent sensory motor predominantly axonal polyneuropathy with mild demyelinating features. By history it was symmetrical. The suggestion of the neuromuscular disorder specialist was to stop the medication for 6 to 12 months to see if the neuropathy improved but the patient was opposed. According to the investigator, there was a reasonable possibility that this non serious AESI was associated with the study medication. Alternative explanation: type II diabetes mellitus, gout, hypertension. *I agree.*

CONCLUSIONS REGARDING PERIPHERAL NEUROPATHY

There was a higher risk of developing events of polyneuropathy, mononeuropathy and neuralgia in the teriflunomide treatment groups, particularly Teri 14, as compared to placebo in Pool 1. The clinical presentation was heterogeneous and many were confounded by the underlying disease (MS) or other concomitant diseases (diabetes mellitus in at least 3 cases). There were 9 cases of neuralgia and 4 of polyneuropathy on teriflunomide treatment in Pool 1. No cases on placebo. There were 5 cases of peripheral neuropathy PT on teriflunomide (3 on Teri 14, 2 on Teri 7) and 2 on placebo. The two cases of peripheral neuropathy on placebo resolved in one day, while the cases on teriflunomide lasted months or did not resolve.

Peripheral neuropathy has been documented with leflunomide in patients with RA with no underlying demyelinating disease.^{26, 27, 28} Age, underlying diabetes and use of other potentially neurotoxic drugs were identified as risk factors.²⁹ No clear correlation has been found between clinical symptoms of peripheral neuropathy and electrophysiological findings.²⁰

The risk of peripheral neuropathy confirmed by nerve conduction studies with onset during the on treatment period in study 6049/TEMPO was 1.9% in patients taking Teri 14 and 0 in patients taking placebo, consistent with teriflunomide-induced peripheral neuropathy. The cases were not considered serious from the regulatory point of view but most had not resolved at the time of last follow up.

Teriflunomide should carry a WARNING for peripheral neuropathy, similar to that of ARAVA. I favor including the information on the analysis of peripheral neuropathy from TEMPO in labeling.

7.3.4.4 AESI of Malignancy

There was no evidence of increased risk of malignancy in this database. However, the database is insufficient to adequately address this question and can not rule out an increased risk of malignancy with long term treatment. See section 7.3.2 of this review. The possibility of

²⁶ Richards et al. Effect of leflunomide on the peripheral nerves in rheumatoid arthritis. *Intern Med J.* 2007 Feb;37(2):101-7.

²⁷ Bonnel and Graham. Peripheral neuropathy in patients treated with leflunomide. *Clin Pharmacol Ther.* 2004 Jun;75(6):580-5.

²⁸ Gabelle et al. Leflunomide-related severe axonal neuropathy. *Rev Neurol* 2005 Nov;161(11):1106-9.

²⁹ Martin et al. Peripheral neuropathy associated with leflunomide: is there a risk patient profile? *Pharmacoepidemiol Dur Saf.* 2007 Jan;(1):74-8.

malignancy with the long term use of teriflunomide should be part of labeling similar to the language in the ARAVA label.

7.3.4.5 AESI of Hypertension

In Pool 1, teriflunomide was associated with a higher risk of hypertension related AEs as compared to placebo. There was no clear dose response between Teri 7 and Teri 14 (see table below).

Table 57. Hypertension AEs by Primary SOC and PT - Safety population - Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Any class	14 (3.3%)	23 (5.4%)	23 (5.5%)
Vascular disorders	9 (2.1%)	16 (3.7%)	19 (4.6%)
Hypertension	9 (2.1%)	15 (3.5%)	18 (4.3%)
Essential hypertension	0	0	1 (0.2%)
Hypertensive crisis	1 (0.2%)	1 (0.2%)	0
Investigations	5 (1.2%)	8 (1.9%)	4 (1.0%)
Blood pressure increased	5 (1.2%)	8 (1.9%)	4 (1.0%)

TEAE: Treatment emergent adverse event, SOC: System Organ Class, PT: Preferred term

MedDRA version: 13.1

n (%) = number and percentage of patients with at least one TEAE

Median time to onset of TEAEs potentially related to hypertension was 197.5 days in placebo, 406.0 days on Teri 7 and 310.0 days on Teri 14. Corrective treatment was administered for 6 of 14 patients in placebo, 15 of 23 patients in Teri 7 and 17 of 23 patients in Teri 14 groups.

There was 1 serious report of hypertension on Teri 14 in Pool 1. The event led to study treatment discontinuation.

- **2001/0021/0002**, 42-year-old female patient with no prior history of hypertension but with BP of 150/90 mmHg at baseline was treated with Teri 14 for about 6 months and experienced hypertension of mild intensity (BP of 160/110 mmHg). No antihypertensive treatment was introduced. The event was regarded as medically important and resulted in the permanent discontinuation of the patient from the study. After completion of drug elimination procedure with cholestyramine high BP of 160/100 mmHg continued to be observed. Blood analysis showed no detectable level of teriflunomide at that time.

Non-serious events of hypertensive crisis were reported in two patients, one on Teri 7 and one on placebo, as follows:

- **6049/3210/0004**. Hypertensive crisis of a few months duration in a patient treated with teriflunomide 7 mg for 5.5 months. There were no records of severe increases in blood pressure consistent with the reported diagnosis (BP during the event was 132/95 mmHg), nor the reports of adverse events suggestive of target organ damage. The patient recovered from the event with antihypertensive treatment.

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- **6049/3205/0020** on placebo.

All other reports of hypertension were non-serious, mild/moderate in severity and did not lead to the study treatment interruption or discontinuation.

Table 58. Analyses of HTN related AESI by gender in Pool 1.

AESI	Placebo (N=421)	teriflunomide		Risk difference (95% CI)	
		7 mg (N=429)	14 mg (N=415)	7 mg vs placebo	14 mg vs placebo
Gender group					
Male	3/108 (2.8%)	5/126 (4.0%)	3/116 (2.6%)	1.43 (0.35 to 5.84)	0.93 (0.19 to 4.51)
Female	11/313 (3.5%)	18/303 (5.9%)	20/299 (6.7%)	1.69 (0.81 to 3.52)	1.90 (0.93 to 3.90)

Source: AESI section, original ISS.

Analyses of HTN related AESI by gender in Pool 1 suggest a slightly greater risk in females than males.

Teriflunomide was associated with an increase in systolic and diastolic blood pressure. At study endpoint (end of treatment visit for completers, value at or prior to last drug intake for discontinued patients) the mean change in systolic blood pressure was 2.6 mmHg on Teri 14 and -1.3 mmHg on placebo. The mean change in diastolic BP was 1.4 mmHg on Teri 14 and -0.9 on placebo. Therefore, at study endpoint, the change in BP from baseline on Teri 14 was 3.9 mmHg higher for systolic BP, and 2.3 mmHg higher for diastolic BP as compared to placebo. Analyses of systolic and diastolic BP in Pool 2 indicate that blood pressure continues to increase over time. Blood pressure analyses are presented in 7.4.3 of this review. Of note, some patients had BP measurement in the supine position and some had it sitting, therefore the measurements are referred to as “supine/sitting” BP. There were no measurements of orthostatic BP in the phase 2/3 trials.

Outlier analyses (PCSA events) showed that 5.6% of patients on Teri 14 and 1.9% of patients on placebo had at least one measurement of systolic BP ≥ 160 mmHg AND ≥ 20 mmHg higher than baseline. And 1.4% of patients on Teri 14 and 0.5 % of patients on placebo had at least one measurement of diastolic BP ≥ 110 mmHg AND ≥ 10 mmHg higher than baseline. *(These are rather strict criteria for identifying potentially relevant events, particularly for diastolic BP. Of note, diastolic BP >110 is the category considered to be hypertensive crisis by the American Heart Association.)*

Narratives for patients with PCSA changes in BP were submitted at the FDA request, on April 17, 2012. The submission included 9 patients on placebo, 19 on Teri 7 and 22 on Teri 14 from TEMSO. The patients on Teri 14 were 18 female, 6 male, ages 34 to 54 years; 9 of the 22 (41%) had a history of hypertension prior to entering the trial; 15 (68%) required new or additional antihypertensive treatment during the study. The patients on placebo were 8 female, 1 male, ages 34 to 52 years; 3 of the 9 (33%) had a history of hypertension prior to entering the trial; 2 (22%) required new or additional antihypertensive treatment.

There were five cardiovascular deaths in this application (one MI, one cardiorespiratory failure, and three unknown cause of death [found dead]) several years into teriflunomide treatment. Two

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of the patients had documented hypertension with diastolic blood pressures >100 during the studies. Modest increases in BP are known to increase long term cardiovascular risk and increase risk of MI and stroke. MI and stroke were not increased as compared to placebo in the controlled database. However, in addition to the CV deaths, three non-fatal MI and one resuscitated cardiac arrest occurred in the extension monotherapy studies. No recent BP values or laboratory values were available in these patients. Additionally, a case of hypertensive encephalopathy with hemorrhagic stroke and acute renal failure was reported as an IND safety report on July 3, 2012 (Patient 003, Inv 348002, TENERE). The patient was a 48 year old male with history of diabetes, HTN and hyperlipidemia. At the time of the event SBP measured by family was 240 mmHg. Laboratory data showed estimated creatinine clearance of 21 ml/min, with increased urea and uric acid. The patient improved and was discharged home five days later, after adjusting his antihypertensive medications. This patient exemplifies the kind of events that one should be worried about with a drug associated with increase in blood pressure and transient acute renal failure, although it is difficult to interpret in the absence of a controlled database. The role of teriflunomide in these serious cardiovascular events can not be ruled out.

In a PK/PD analysis using data from Pool 1 (Study POH0295), an increase in mean teriflunomide trough plasma concentrations was associated with an increase in DBP with a maximum effect relationship.

IN SUMMARY, REGARDING HYPERTENSION RELATED AESI:

Teriflunomide is associated with increase in blood pressure and a diagnosis of hypertension or worsening hypertension requiring new/additional antihypertensive treatment in approximately 70% of cases. At study endpoint, the change in BP from baseline on Teri 14 was 3.9 mmHg higher for systolic BP, and 2.3 mmHg higher for diastolic BP as compared to placebo. If approved, labeling should include a WARNING that recommends regular monitoring and treatment as needed, to maintain BP under control.

7.3.4.6 AESI related to Bone marrow disorders

AESI that were serious or led to study discontinuations were already discussed in sections 7.3.2 and 7.3.3 of this review. Teriflunomide is clearly associated with an increased risk of AE of neutropenia as compared to placebo, but all cases resolved with or without drug discontinuation and no cases appeared to be associated with serious infections.

Bone marrow disorders were considered as potential risks and hematologic parameters were closely monitored during the study. Sanofi used the Narrow “Haematologic cytopenias” SMQ, as well as other relevant hematology parameters related to WBC and differential count, RBC, hemoglobin, and platelets.

The main PT contributors in the teriflunomide groups were neutropenia/neutrophil count decreased, white blood cell count decreased, and lymphopenia/lymph count decreased. However, there were also cases of anemia and thrombocytopenia/ platelet count decreased. There were no reports of pancytopenia. The relative risk for bone marrow disorders for the 14 mg dose as

compared to placebo was 3.32 (95% CI 1.71, 3.43). Patients with bone marrow AESI in Pool 1 are summarized below:

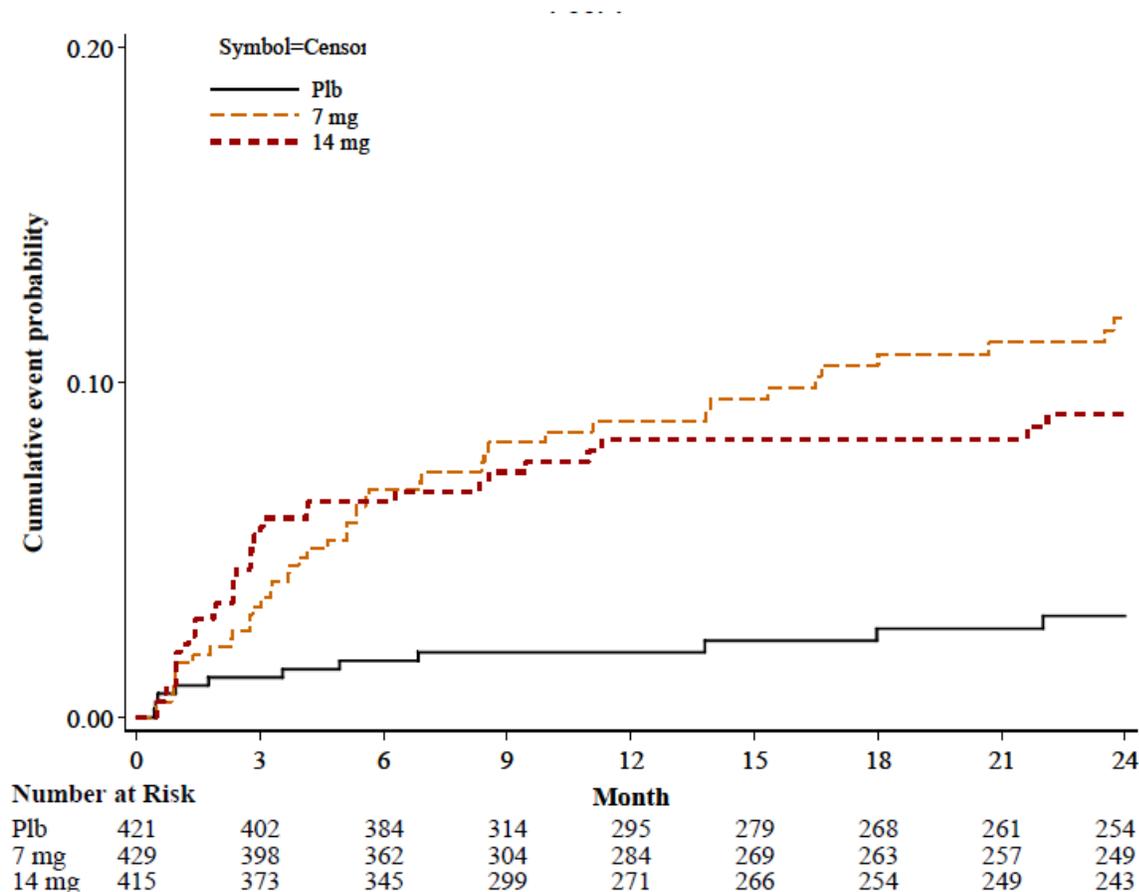
Table 59. Patients with bone marrow AESI, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Any class	11 (2.6%)	44 (10.3%)	36 (8.7%)
Blood and lymphatic system disorders	6 (1.4%)	20 (4.7%)	24 (5.8%)
Neutropenia	2 (0.5%)	10 (2.3%)	19 (4.6%)
Leukopenia	1 (0.2%)	6 (1.4%)	4 (1.0%)
Lymphopenia	2 (0.5%)	4 (0.9%)	4 (1.0%)
Thrombocytopenia	0	3 (0.7%)	2 (0.5%)
Agranulocytosis	1 (0.2%)	0	0
Monocytopenia	1 (0.2%)	0	0
Investigations	5 (1.2%)	25 (5.8%)	14 (3.4%)
Neutrophil count decreased	2 (0.5%)	12 (2.8%)	9 (2.2%)
White blood cell count decreased	0	14 (3.3%)	5 (1.2%)
Lymphocyte count decreased	0	1 (0.2%)	2 (0.5%)
Monocyte count decreased	0	0	1 (0.2%)
Platelet count decreased	0	3 (0.7%)	1 (0.2%)
Red blood cell count decreased	2 (0.5%)	4 (0.9%)	1 (0.2%)
Basophil count decreased	1 (0.2%)	0	0

Source: Table 30, Applicant's ISS. The case of agranulocytosis on placebo had a neutrophil count of 1.35 Giga/L (patient #6049/3509/0008, neutropenia but not agranulocytosis).

Kaplan-Meier analysis showed that the difference between teriflunomide and placebo for AESI related to all bone marrow effects starts within one month of treatment and is observed mostly during the first 6 months but some cases continue to occur after 6 months of treatment. There was no evidence of dose response between Teri 7 and 14.

Figure 7. Kaplan-Meier plots for time to onset of bone marrow AESI, Pool 1



Source: Figure 10, ISS.

The KM analysis was driven by events of neutropenia. Events on Teri 14 occurred mostly within the first 3 months and then stabilized. Events on Teri 7 appear to occur mostly up to 6 months but continued to occur during the 2 year study. Median time to onset of bone marrow disorders TEAEs was 108 days in placebo, 148 days in Teri 7 and 79 days in Teri 14.

The majority of bone marrow disorder events were mild to moderate; 4 and 1 events were considered as severe in the Teri 7 and 14 groups, respectively. Recovery during the observation period of Pool 1 was reported in all of the 11 patients on placebo, 40 of 44 patients on Teri 7 and 34 of 36 patients on Teri 14.

Evaluation of hematologic laboratories are presented in Section 7.4.4.3 of this review. Findings are summarized below.

Measures of central tendency showed a small decrease in mean and median WBC, neutrophil, lymphocyte count, hemoglobin and platelet count. The mean neutrophil count decreases from baseline occurred mainly during the first 6 weeks for both teriflunomide treatment groups compared to placebo, and then stabilized. For lymphocytes, the decrease was mainly during the first 6 weeks but it continued to drop slightly until the end of the 2 year period. Hemoglobin dropped during the first 6 months and remained low thereafter. Platelets showed a maximum drop

of approximately 8% below baseline at 3 months, then showed slow recovery to 5% of baseline by the end of study (week 108).

Outlier analyses in Pool 1 showed at least one measurement of WBC <3 Giga/L in 6.1% of patients on Teri 7, 9.9% on Teri 14 and 1% of those on placebo; neutropenia with absolute neutrophil count (ANC) <1 Giga/L in 2.1% of patients on Teri 7, 2.2% of patients on Teri 14 and 0.5% of patients on placebo; lymphocyte count <0.8 Giga/L in 7.2% of patients on Teri 7, 9.7% of patients on Teri 14 and 4.8% of those on placebo. These analyses support a bone marrow suppressive effect of teriflunomide. On the other hand, absolute eosinophil >0.5 Giga/L was observed in 8.4% of patients on Teri 7, 11.9% on Teri 14 and 7.9% on placebo in Pool 1, suggesting a slightly higher incidence of eosinophilia in teriflunomide-treated patients. Eosinophil count >0.5 Giga/L in Pool 2 was present in 12.8% of patients on Teri 7 and 14.8% on Teri 14.

The proportion of patients CTCAE grade 1 anemia in Pool 1 was slightly higher in the teriflunomide groups than on placebo with a trend for a dose effect (13.3% on Teri 7, 15.5% on Teri 14 and 10.7% on placebo). The proportion of patients with anemia grade 2 was similar between treatment groups. A few patients had anemia grade 3 (one on Teri 7 and 4 on Teri 14). There is very limited information from these patients. As per request for clarification submitted on April 12, 2012, investigators were required to perform adequate testing for any positive diagnosis. However, anemia was not identified as a safety signal in teriflunomide studies and therefore no specific work-up to identify a type of anemia associated to teriflunomide was in place.

In Pool 1, there were 4 cases of platelet count decreased and five cases of thrombocytopenia on teriflunomide (platelet count decreased: 3 on Teri 7, one on Teri 14; thrombocytopenia 3 on Teri 7, 2 on Teri 14). They were 5 female, 3 male, ages 27 to 61. None was considered serious or led to study discontinuation (two of the patients did not complete the study for other reasons). Mean time to onset was 170 days (42 to 658 days). The cases were mild to moderate and recovered without drug discontinuation. Several cases presented intermittent low platelet counts during the base study and extension. There were no such cases on placebo. Two of the patients reported menorrhagia that may or may not have been related to low platelet counts. One of these patients later reported multiple gastric ulcers (patient 002001-124-0019-0002). Additionally one patient had hemorrhoidal bleeding. Two of the cases of thrombocytopenia occurred in patients who also reported low neutrophil counts at some point during the study.

Table 60. Bone marrow AESI in Pool 1, by gender.

AESI Gender group	Placebo (N=421)	teriflunomide		Risk difference (95% CI)	
		7 mg (N=429)	14 mg (N=415)	7 mg vs placebo	14 mg vs placebo
Male	2/108 (1.9%)	8/126 (6.3%)	7/116 (6.0%)	4.5% (-1.3% to 10.3%)	4.2% (-1.7% to 10.1%)
Female	9/313 (2.9%)	36/303 (11.9%)	29/299 (9.7%)	9.0% (4.6% to 13.4%)	6.8% (2.7% to 11.0%)

Evaluation of bone marrow AE by gender suggests an increased risk of bone marrow AESI in female as compared to male treated with teriflunomide, but so it does for placebo-treated patients.

In a PK/PD analysis using data from Pool 1 (Study POH0295), an increase in mean teriflunomide trough plasma concentrations was associated with a decrease in WBC including neutrophils and lymphocytes with a maximum effect relationship.

Available hematologic evaluations from other studies are consistent with those of Pool 1 and 2. Evaluation of AESI in the TOWER study is consistent with findings in Pool 1 (data not shown).

CONCLUSION REGARDING BONE MARROW EFFECTS

Teriflunomide is associated with a dose-related bone marrow suppressive effect on WBC, neutrophils, lymphocytes, hemoglobin and platelets. The drop in neutrophil and lymphocyte count occurred mostly during the first 6 weeks and then appeared to stabilize. The effect on platelet count was observed mostly within the first 3 months and then appeared to stabilize. There was also a 2-3% decrease in mean hemoglobin with teriflunomide, more marked during the first 6 months of treatment, and slightly more patients had anemia on teriflunomide treatments as compared to placebo but the mechanism of hemoglobin decrease is unclear. There was no major decrease in RBC over time as compared to placebo. Perhaps the decreased Hb is associated with blood loss but there was not consistent work up of patients with anemia. Teriflunomide should carry a WARNING for bone marrow suppression, similar to that of ARAVA.

The decrease in WBC including neutrophils and lymphocytes suggests that teriflunomide-treated patients will have a decreased ability to respond to infections and vaccination. The applicant has not formally evaluated whether teriflunomide decreases previously acquired immunity. However, experience with leflunomide indicates that teriflunomide may be associated with opportunistic infections and viral reactivation. Additionally, no clinical data are available on the efficacy and safety of vaccinations, including live vaccines during teriflunomide treatment, but it is reasonable to recommend that live vaccines be avoided during teriflunomide treatment.

The only blood cells that showed increase in teriflunomide treated patients were the eosinophils (11.9% of patients on Teri 14 and 7.9% of patients on placebo had eosinophil count >0.5 Giga/L in Pool 1).

7.3.4.7 Infections and infestations

In Pool 1, risk of AESI related to infections and infestations was 57.5% in placebo, 59.7% in Teri 7 and 61.7% in Teri 14. Based on the patient years of exposure shown in Table 6 of this review (663.5 PYRs for placebo, 680.5 PYRs for Teri 7 and 649.5 for Teri 14) the number of patients

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with any infections and infestations in Pool 1 was 365 per 1000 PYRs on placebo; 376 per 1000 PYRs on Teri 7, and 394 per 1000 PYRs on Teri 14, suggesting a slight increase in the overall risk of infections. Moreover, median time to onset of infections and infestations AEs was shorter for Teri 14 as compared to Teri 7 and placebo (142 days in the placebo group, 117 days in the Teri 7 group and 86 days in the Teri 14 group).

Events with a risk $\geq 1\%$ higher Teri 14 as compared to placebo are shown below.

Table 61. Patients with risk of infections and infestations at least 1% higher on teriflunomide than placebo in Pool 1.

Primary System Organ Class Preferred Term n(%)	14 mg (N=415)	Placebo (N=421)
Total number in SOC	256 (61.7%)	242 (57.5%)
Influenza	49 (11.8%)	39 (9.3%)
Upper respiratory tract infection	45 (10.8%)	38 (9.0%)
Urinary tract infection	44 (10.6%)	40 (9.5%)
Bronchitis	30 (7.2%)	24 (5.7%)
Sinusitis	24 (5.8%)	16 (3.8%)
Pharyngitis	16 (3.9%)	12 (2.9%)
Gastroenteritis viral	15 (3.6%)	5 (1.2%)
Cystitis	14 (3.4%)	5 (1.2%)
Oral herpes	14 (3.4%)	6 (1.4%)
Rhinitis	12 (2.9%)	8 (1.9%)
Tooth infection	8 (1.9%)	2 (0.5%)
Tinea pedis	7 (1.7%)	2 (0.5%)
Tonsillitis	7 (1.7%)	3 (0.7%)
Laryngitis	6 (1.4%)	1 (0.2%)

Source Table 34, ISS

No febrile neutropenia was reported. There was no evidence of a specific trend in white blood cell changes at time of the onset of an infection.

Pool 1, the proportion of patients with AEs related to opportunistic infections by primary SOC and PT was 35 of 421 (8.3%) in placebo, 39 of 429 (9.1%) in teriflunomide 7 mg and 44 of 415 (10.6%) in teriflunomide 14 mg. The main PT contributors were oral herpes and tinea pedis.

Two serious AEs of opportunistic infections were reported:

- **6049/2812/0001**, hepatitis with cytomegalovirus was reported for a 32 year-old male patient in the Teri 14 group (described in the hepatic related AESI).
- **6049/1212/0002**, herpes zoster was reported on Day 681 for a 22-year-old female taking placebo. The patient recovered in 25 days.

Three other opportunistic infections were not considered serious or led to study discontinuation but are worth noting:

- **6049/2402/0021**, 34 yo F on Teri 7, developed bronchitis on day 224 to 295. She had a prior history of several infections including viral meningitis and hepatitis B. She was diagnosed as having “latent TB” on Day 472. Reactivation of TB was not confirmed but she was treated

with rifampin and isoniazide. The event was considered mild, non-serious and not related to teriflunomide by the investigator. She continued treatment with study drug.

The investigator certainly did not think that this was related to teriflunomide, however, it is unclear if she did have active TB in the first place.

- **6049/1802/0005** a 54-year-old female patient developed herpetic keratoconjunctivitis on Day 500 of Teri 7 treatment. Study drug was not discontinued; she recovered after treatment with acyclovir.
- **6049/4604/0003**, a 41 yo male developed fungal infection of the eye, foot and groin area on Day 596. He recovered with appropriate therapy without drug discontinuation.

No systemic opportunistic infections such as pneumocystis, toxoplasma, mucocutaneous candidiasis, histoplasmosis, or aspergillosis were reported in Pool 1.

In Pool 2, the number of patients with TEAEs related to opportunistic infections was 78 (13.3%) on Teri 7 and 77 (14.1%) on Teri 14. These numbers of cases include all cases of oral herpes, tinea pedis, and vulvovaginal mycotic infections. There were no systemic opportunistic infections in Pool 2. One case of latent syphilis was reported in Pool 2 but it is unclear whether she had reactivation of syphilis or not.

Of note, one patient died of gram negative sepsis (described under deaths). In addition to the possible case of TB reported in study 6049, one case of ileal TB and two of pulmonary TB were reported in ongoing studies. Other infections of note in ongoing studies were enterococcal endocarditis and osteomyelitis by anaerobes (see section 7.3.2).

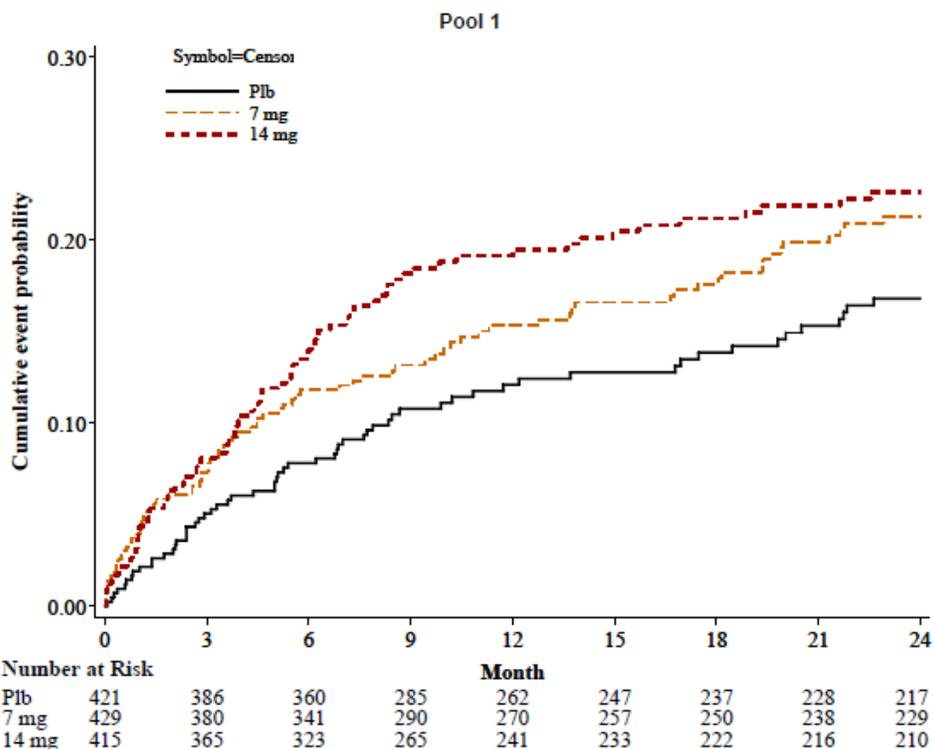
CONCLUSIONS REGARDING INFECTIONS AND INFESTATIONS:

There seems to be a small increase in risk of overall infections with no evidence of increase in serious infections, infections leading to drug discontinuation or systemic opportunistic infections among teriflunomide treated patients as compared to placebo in Pool 1. However, the database is small to rule out an increase in serious and systemic opportunistic infections. Four cases of tuberculosis were identified in this database. Tuberculosis reactivation has been reported with leflunomide. Moreover, it is unclear the extent of evaluation that some of the patients with infections had. No case of progressive PML was identified in the teriflunomide program. However, none of the adverse event reports of MS relapse mentions CSF evaluation. Teriflunomide should carry a WARNING for the potential for serious and opportunistic infections, similar to that in ARAVA.

7.3.4.8 Hypersensitivity

In placebo-controlled Pool 1, the proportion of patients experiencing TEAEs potentially related to hypersensitivity and skin disorders was higher in the 2 teriflunomide treatment groups (19.1% in 7 mg and 20.5% in 14 mg) compared to the placebo group (14.5%). Time to event is shown in the following figure.

Figure 8. Kaplan Meier plots for time to onset of hypersensitivity AE, Pool 1.



Source: Figure 14, ISS.

The median time to onset of TEAEs related to hypersensitivity and skin disorders was 160 days in placebo, 133.5 days in teriflunomide 7 mg, and 129 days in teriflunomide 14 mg.

Hypersensitivity AESI in Pool 1 are summarized below.

Table 62. Patients with Hypersensitivity AESI, Pool 1.

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Any class	61 (14.5%)	82 (19.1%)	85 (20.5%)
Eye disorders	0	2 (0.5%)	0
Eye oedema	0	1 (0.2%)	0
Eyelid oedema	0	1 (0.2%)	0
Vascular disorders	7 (1.7%)	10 (2.3%)	7 (1.7%)
Hypotension	5 (1.2%)	7 (1.6%)	5 (1.2%)
Circulatory collapse	0	0	2 (0.5%)
Flushing	2 (0.5%)	3 (0.7%)	0
Respiratory, thoracic and mediastinal disorders	24 (5.7%)	24 (5.6%)	29 (7.0%)
Cough	17 (4.0%)	19 (4.4%)	20 (4.8%)
Dyspnoea	3 (0.7%)	5 (1.2%)	7 (1.7%)
Asthma	4 (1.0%)	2 (0.5%)	3 (0.7%)
Wheezing	1 (0.2%)	1 (0.2%)	1 (0.2%)
Bronchospasm	0	1 (0.2%)	0
Choking	1 (0.2%)	0	0
Laryngeal oedema	1 (0.2%)	0	0
Skin and subcutaneous tissue disorders	30 (7.1%)	50 (11.7%)	50 (12.0%)
Rash	17 (4.0%)	20 (4.7%)	23 (5.5%)
Pruritus	7 (1.7%)	16 (3.7%)	11 (2.7%)
Erythema	2 (0.5%)	8 (1.9%)	5 (1.2%)
Urticaria	2 (0.5%)	4 (0.9%)	5 (1.2%)
Pruritus generalised	2 (0.5%)	1 (0.2%)	4 (1.0%)
Rash pruritic	0	2 (0.5%)	2 (0.5%)
Generalised erythema	0	1 (0.2%)	0
Rash erythematous	0	1 (0.2%)	0
Rash generalised	0	4 (0.9%)	0
Swelling face	1 (0.2%)	0	0
General disorders and administration site conditions	5 (1.2%)	8 (1.9%)	6 (1.4%)
Chest discomfort	4 (1.0%)	8 (1.9%)	6 (1.4%)
Face oedema	1 (0.2%)	0	0
Investigations	1 (0.2%)	0	0
Blood pressure decreased	1 (0.2%)	0	0

Source: Table 31, ISS. TEAE: Treatment emergent adverse event, SOC: System Organ Class, PT: Preferred term MedDRA version: 13.1. n (%) = number and percentage of patients with at least one TEAE. Table sorted by SOC internationally agreed order and decreasing frequency of PTs in teriflunomide 14mg group.

Of note, this analysis includes a list of terms from several SOCs. The PTs driving the difference in overall AESI are in the Skin and subcutaneous tissue, Respiratory, thoracic and mediastinal disorders, and General disorders SOCs.

However, this search strategy did not include the Immune system disorders SOC, Allergic conditions AEHLGT which included terms such as erythema multiforme, erythema nodosum, hypersensitivity and photosensitivity allergic reaction, all of which occurred in teriflunomide treated patients, and not in placebo treated patients.

List of patients with PT terms in Allergic conditions HLGTT not included in Sanofi’s search of hypersensitivity, Pool 1.

Patient ID	Age/ gender	PT	Rel Day	Duration days	Action	Outcome
Teri 14						
002001-124-0015-0025	42 F	Erythema multiforme	90	120	NONE	Recovered. Discont. after motor vehicle accident.
006049-124-1209-0043	54 F	Erythema nodosum	366	472	NONE	Recovered
006049-616-3002-0005	49 F	Photosensitivity allergic reaction	586	4	NONE	Recovered.
Teri 7						
006049-528-4601-0001	44 M	Hypersensitivity (allergic reaction)	537	4	NONE	Recovered.
006049-528-4602-0004	42 F	Erythema nodosum	69	-	NONE	Continuing.
006049-616-3003-0024	45 F	Hypersensitivity (allergic reaction)	541	-	NONE	Continuing.

Source: NDA AE datasets.

Two events of erythema nodosum and one of erythema multiforme, and two hypersensitivity reactions were reported in patients taking teriflunomide. None led to study drug discontinuation. One case of erythema nodosum and one hypersensitivity reaction were reported to be ongoing at the time of the last report.

EOSINOPHILIA or eosinophil count increased were reported as an AE in 10 patients in pool 1 during the treatment period (3 on Teri 14, 5 on Teri 7 and 2 on placebo). The cases are summarized below:

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Listing of patients with eosinophilia in Pool 1.

Patient ID	Age/gender/ Relative day of onset (duration in days) Action taken with drug. Outcome/other AEs.
Teri 14	
002001-124-0017-0007	36 F. Day 72 (129). None Eosinophil count increased Recovered. Preceded by seasonal allergies which continued. Did not complete study.
006049-250-2414-0004	36 F. Day 224 (33). None Eosinophil count increased. Recovered. Did not complete study
006049-826-2608-0004	34 M. Day 29 (15). None Eosinophil count increased. Recovered. Intermittent cold/flu symptoms during study. Back pain Day 239, continuing. Rash on both legs on Day 659, continuing.
Teri 7	
006049-250-2407-0031	34 M. Day 115 (ND). None Eosinophilia. Continuing. Other AE: fatigue (day 705), hypotension. (day 596)
006049-826-2600-0008	35 F. Day 98 and 463 (16 and 43 days). None Eosinophilia. Recovered. Other AE: eczema (day 190), conjunctivitis (day 287, 597 and 622), gastroenteritis viral (Day 496).
006049-124-1212-0001	47 F. Day 30. (14) None Eosinophil count increased. Recovered. No other AE at the time.
002001-124-0013-0006	56 F. Day 84 (22). None Eosinophil count increased. ALT, GGT and ALP increased at the same time. Recovered without discontinuation.
006049-826-2600-0013	42 F. Day 221 (45). None Eosinophil count increased. Recovered. Preceded by dx of Hay fever, Day 192 continuing. Bil ankle arthralgia and swelling, Day 327, continuing.
Placebo	
006049-250-2407-0026	45 F. Day 86. (252) . None Eosinophilia. Recovered. Other AE: MS and visual field disorder (Day 149)
006049-124-1204-0010	42 F. Day 29 (722). None. Eosinophil count increased. Recovered.

Outlier analyses of eosinophil counts in Pool 1 showed that more patients had increased eosinophil counts in the PCSA range in teriflunomide treated patients as compared to placebo.

Review of the cases with eosinophil count in the PCSA range identified that the patient suspected of having severe DILI in this database had an absolute eosinophil count >1 Giga/L at the time of last available measurement. Of note, eosinophilia was not reported as an AE in this patient. It is unclear if the events of hepatitis and eosinophilia are related or it is just a coincidence. There were no other cases with concomitant ALT elevation >3xULN and eosinophilia in Pool 1.

ARAVA carries a WARNING for skin reactions. Teriflunomide should carry a similar warning.

There is no apparent increase risk of pancreatic disorders in the controlled database using the applicant’s approach. The PT included in the search were those in the Acute pancreatitis Narrow SMQ plus the following PTs: blood amylase increased, lipase increased, pancreatic enzyme abnormality, lipase abnormal, blood amylase abnormal, pancreatic enzymes abnormal, pancreatic enzymes increased, and hyperlipasaemia. The analysis did not include the PT “pancreatic disorder.” Patients with pancreatic AEs in Pool 1 is presented in the following table.

Table 63. Patients with pancreatic disorder AEs, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Any class	12 (2.9%)	14 (3.3%)	9 (2.2%)
Gastrointestinal disorders	1 (0.2%)	0	0
Pancreatitis	1 (0.2%)	0	0
Investigations	11 (2.6%)	14 (3.3%)	9 (2.2%)
Lipase increased	5 (1.2%)	7 (1.6%)	6 (1.4%)
Blood amylase increased	7 (1.7%)	8 (1.9%)	5 (1.2%)
Blood amylase abnormal	1 (0.2%)	0	0
Pancreatic enzymes increased	0	1 (0.2%)	0

Source: Table 28, original ISS.

There is no major difference in the risk of pancreatic related AESI in the teriflunomide groups, as compared to placebo in Pool 1. This approach did not include “pancreatic disorder” and “pancreatic lipomatosis”. Evaluation of the Pancreatic disorders HLT in Pool 1 which includes the PT pancreatic disorder and pancreatic lipomatosis identified 12 unique patients. Two events occurred during the washout period, after discontinuation of Teri 7. The other 10 occurred during treatment. Of those, 3 occurred on Teri 14, 7 on Teri 7 and four on placebo. Therefore, there is no evidence of imbalance for pancreatic disorders in Pool 1.

Pancreatic AESI in TOWER:

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	Placebo (N=363)	teriflunomide	
		7 mg (N=379)	14 mg (N=350)
Any class	0	3 (0.8%)	3 (0.9%)
INVESTIGATIONS	0	3 (0.8%)	3 (0.9%)
HLGT: Gastrointestinal investigations	0	3 (0.8%)	3 (0.9%)
HLT: Digestive enzymes	0	3 (0.8%)	3 (0.9%)
Blood amylase increased	0	2 (0.5%)	1 (0.3%)
Lipase increased	0	3 (0.8%)	2 (0.6%)

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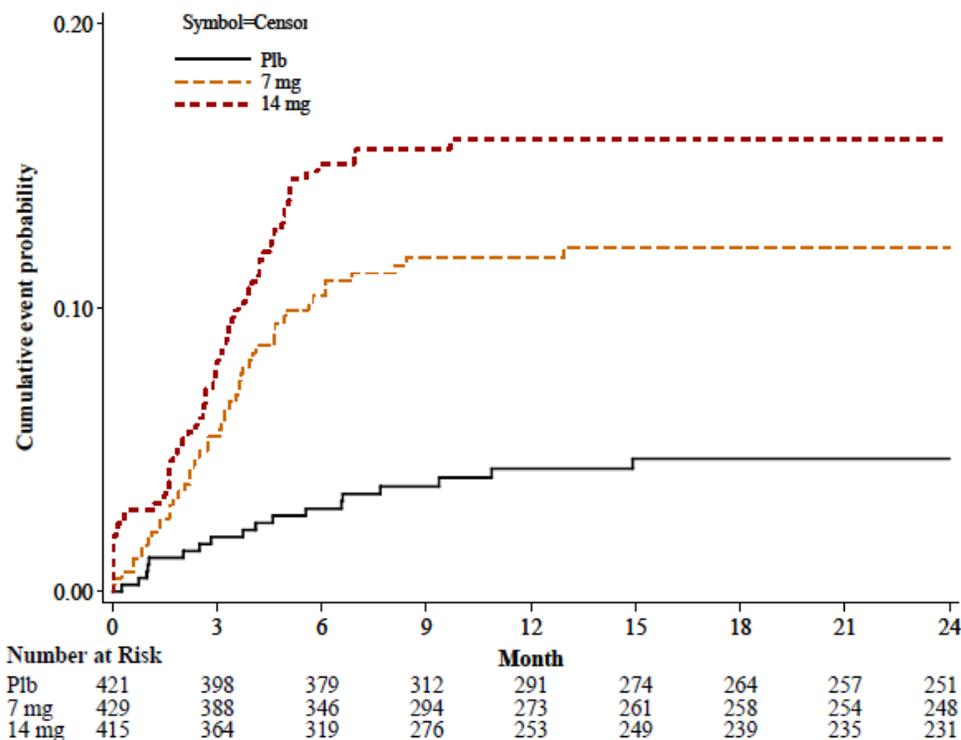
In TOWER, lipase increased was presented by 3 patients in the Teri 7 group and 2 in the Teri 14 group; 2 of the patient sin the Teri 7 and one in the Teri 14 also had amylase increased. There were no such cases on placebo. As per review of the datasets, the increases in lipase and amylase were not associated with serious clinical AEs.

IN SUMMARY, for pancreatic disorders: Non-clinical data suggested that the pancreas was a target organ for teriflunomide. The clinical data in Pool 1 do not suggest an increased risk of pancreatitis/pancreatic disorder with teriflunomide. There is a suggestion of an increased risk of blood amylase and lipase elevation in TOWER. The numbers are small and the elevated values were not associated with serious clinical adverse events. I would not include this information in labeling but this is an area that will require follow up in the postmarketing setting.

7.3.4.10 Alopecia

In Pool 1 alopecia was more frequent in teriflunomide treated patients (11.4% and 15.2% for Teri 7 and Teri 14, respectively) as compared to placebo (4.3%), and the difference started within the first month of treatment. All the alopecia TEAEs were of mild or moderate intensity, except 1 event (verbatim: loss of hair [diffuse]) in the teriflunomide 14 mg group reported as severe (Patient 6049/2003/0005). Of the 112 patients with TEAE of alopecia in the teriflunomide treatment groups, 8 patients discontinued the study treatments (2 patients in teriflunomide 7 mg and 6 patients in teriflunomide 14 mg). Of the 18 patients with alopecia in the placebo group, none discontinued study treatment.

Figure 9. Kaplan-Meier estimate for events of alopecia in Pool 1.



Pool 1. Figure 20 ISS.

The analysis of cumulative incidence showed that most of the AE of alopecia with teriflunomide occurred during the first 6 months of treatment. The median time to onset was 95 days and 90 days in teriflunomide 7 mg and 14 mg, respectively compared to 119.5 days in placebo. The frequency of reporting of alopecia was higher in female patients (18.4% with Teri 14) as compared to males (6.9% on Teri 14).

	Placebo (N=421)	Teriflunomide 7 mg (N=429)	14 mg (N=415)	Relative risk ratio (95% CI) 14 mg vs placebo
Male	0/108	5/126 (4.0%)	8/116 (6.9%)	>9999 (NC)
Female	18/313 (5.8%)	44/303 (14.5%)	55/299 (18.4%)	3.20 (1.92 to 5.32)

The majority of patients recovered during the observation period in Pool 1 (38 of 49 patients in teriflunomide 7 mg and 57 of 63 patients in teriflunomide 14 mg). In the placebo group, 13 of 18 patients recovered.

In a PK/PD analysis using data from Pool 1 (Study POH0295), a logistic regression relationship was observed with an increase in mean teriflunomide trough plasma concentrations associated with a greater probability to have an increase in alopecia.

In Pool 2, as observed in Pool 1, the proportion of patients with alopecia was higher in teriflunomide 14 mg (17.3%) than in teriflunomide 7 mg (12.1%).

CONCLUSION: Alopecia is a frequent AE associated with teriflunomide use. It should be prominently mentioned in the labeling.

7.3.4.11 Cardiac arrhythmia AESI

There were 5 cardiovascular deaths in this application, including three patients who were found dead, all during extension studies. The cases are described under deaths (section 7.2 of this review). As part of the review of AESI of cardiac arrhythmia, Sanofi conducted a search of events within the Cardiac arrhythmias Narrow SMQ.

There was no increase in cardiac arrhythmia narrow SMQ in Safety Pool 1. Two patients developed atrial fibrillation in Pool 1 (one on Teri 7 and one on placebo). The cases are as follows:

- **6049/1502/0004.** 50 yo F experienced atrial fibrillation on Day 614 of Teri 7 treatment. She had a history of hydronephrosis. She had been treated with Rebif and MP before entering the trial. No concomitant meds were reported. She was treated with amiodarone, continued study drug and completed the study. The event was ongoing at time of last follow up. No washout procedure was done.
- **2001/1240013/0013.** 50 yo F experienced atrial fibrillation on Day 223 of placebo. She had a history of hypertension and hypoglycemia. She recovered the same day without intervention. She completed the study and continued into the extension study.

In both cases it is unclear how the diagnosis was made; if the patients were symptomatic or not, and if any workup was done to identify the etiology of the atrial fibrillation. No laboratory measurements are mentioned at the time of the atrial fibrillation.

Analyses of all AE in the Cardiac Disorders SOC in Pool 1, showed a slight increase in the reports of palpitations and tachycardia in teriflunomide groups as compared to placebo. However, most events were non serious and did not lead to study discontinuation, therefore, there is no narrative for these patients.

Table 64. All adverse events in the Cardiac Disorders SOC, Pool 1.

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Cardiac disorders	13 (3.1%)	20 (4.7%)	17 (4.1%)
Palpitations	5 (1.2%)	13 (3.0%)	8 (1.9%)
Tachycardia	2 (0.5%)	4 (0.9%)	6 (1.4%)
Angina pectoris	1 (0.2%)	0	2 (0.5%)
Sinus tachycardia	1 (0.2%)	0	1 (0.2%)
Supraventricular tachycardia	0	1 (0.2%)	1 (0.2%)
Atrial fibrillation	1 (0.2%)	1 (0.2%)	0
Cardiovascular disorder	0	1 (0.2%)	0
Hypertrophic cardiomyopathy	1 (0.2%)	0	0
Myocardial infarction	1 (0.2%)	0	0
Tachycardia paroxysmal	1 (0.2%)	0	0

Source: ISS.

Cardiac arrhythmia in Pool 2

Seven patients reported AE of cardiac arrhythmia in Pool 2 (six in Teri 7 and 1 in Teri 14). All reports were non-serious.

- **6050/2202/0002**, a 49 yo F developed unspecified arrhythmia on Day 578, along with anxiety. Concomitant med included almotriptan. The patient was treated with a selective serotonin reuptake inhibitor (escitalopram) and continued study drug. Arrhythmia resolved.
- **6048/0013/0013** (a 50 yo F) reported extrasystoles on Day 2736 of Teri 7 treatment. She recovered the same day without treatment.
- **6048/0021/0004** (a 36 yo F) reported extrasystoles on 1136 of Teri 7 treatment. She received atenolol and thyroid hormone replacement without interruption of study drug.
- **6048/0019/0006** (a 61 yo male) reported ventricular extrasystoles on Day 590 of Teri 7. Recovered without discontinuation of treatment.
- **6050/3205/0005** (35 yo male) reported ventricular extrasystoles on Day 899 of Teri 7. Recovered without discontinuation of treatment.
- **6048/0017/0009** (49 yo) reported irregular heart rate on Day 687 of Teri 7 treatment. Isolated premature atrial and ventricular contractions were recorded on ECG. He was diagnosed with unspecified cardiomyopathy and discontinued study treatment.
- **6048/0015/0015** (59 yo) reported irregular pulse and ventricular extrasystoles (abnormal ECG) on Day 16 of Teri 14 treatment. The event resolved without corrective treatment and patient or drug discontinuation.

There were 3 cases of ventricular extrasystoles, 2 of extrasystoles and one of irregular heart rate in the extension studies in Pool 2, several years into teriflunomide treatment. Five of them were mild, recovered without treatment and did not lead to study drug discontinuation. One was diagnosed as unspecific cardiomyopathy and led to study discontinuation. The narratives include very limited information about underlying risk factors and concomitant medications. It is difficult to attribute these relatively common asymptomatic events to teriflunomide in the absence of a control group.

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In the adjunctive therapy studies there were three cases of tachycardia (cardiac arrhythmia HLT), one on Teri 14 + INF and two on Teri 14 + glatiramer

- **2764010/004** on Teri 14 + IFN-beta presented an event of tachycardia 5 days into teriflunomide treatment (added to IFN). She had a medical history of hypothyroidism. Concomitant therapy was tolperisone (a muscle relaxant). On Day 1, ECG was read as abnormal, not clinically significant (HR 62 bpm, RR interval 969 ms, PR interval 148 ms, QTcF 388 ms). ECG on the day of the event of tachycardia is not available. The event is reported to have resolved on Day 19. It was considered related to the study drug by the investigator, but treatment continued. She completed the study (339 days of treatment).
- **8401012/1003**, 47 yo F presented intermittent tachycardia 267 days into Teri 14 and glatiramer, apparently during methylprednisolone administration. Concomitant meds included ibuprofen, prednisolone, amoxicillin and tussionex. Vital signs were reportedly normal. She recovered one day later.
- **3805001/1001**, 36 yo F experienced tachycardia 42 days into Teri 14 and glatiramer treatment. It was mild and resolved on Day 74. Vital signs were reportedly normal. There is no mention of any work up done for tachycardia.

The cases of tachycardia appear to be mild but there is very limited information about these cases.

In the clinical pharmacology study, one patient reported cardiac arrhythmia

- **259991702**, a 57 yo healthy female complained of dizziness 3 days after taking a single dose of Teri 7 in a fasted condition. An ECG detected atrial fibrillation on the same day, before discharge. The atrial fibrillation lasted approximately 1 hour and resolved. The patient stayed in the unit for a few hours and received the first dose of the 5-day cholestyramine treatment. During screening she had a normal ECG. ECG one day after the event of atrial fibrillation showed sinus tachycardia and borderline increased QTc (457 ms, compared to 397 at baseline). QTc 2 days after the event was normal. No concomitant meds were reported. Work-up for thyroid disease and electrolyte abnormalities were negative. BP was normal. On Day 7, a cardiologist reported normal clinical exam, ECG, Doppler echocardiography and 24 hour Holter.

Transient atrial fibrillation in a 57 yo female three days after a single dose of Teri 7 appears unlikely related to study drug.

Of note, the Cardiac Arrhythmia Narrow SMQ used by Sanofi did not capture the two events of sudden death (found dead) in Pool 2.

- Cardiac arrhythmias in TOWER

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Table 65. AESI of Cardiac Arrhythmia in TOWER (interim report)

PRIMARY SYSTEM ORGAN CLASS HLGT: High Level Group Term HLT: High Level Term Preferred Term n(%)	teriflunomide		
	Placebo (N=363)	7 mg (N=379)	14 mg (N=350)
	Any class	3 (0.8%)	5 (1.3%)
CARDIAC DISORDERS	2 (0.6%)	5 (1.3%)	5 (1.4%)
HLGT: Cardiac arrhythmias	2 (0.6%)	5 (1.3%)	5 (1.4%)
HLT: Cardiac conduction disorders	2 (0.6%)	3 (0.8%)	1 (0.3%)
Brugada syndrome	0	1 (0.3%)	0
Bundle branch block	1 (0.3%)	0	0
Bundle branch block left	0	1 (0.3%)	0
Bundle branch block right	0	0	1 (0.3%)
Conduction disorder	0	1 (0.3%)	0
Wolff-Parkinson-White syndrome	1 (0.3%)	0	0
HLT: Rate and rhythm disorders NEC Arrhythmia	0	1 (0.3%) 1 (0.3%)	0
HLT: Supraventricular arrhythmias	0	1 (0.3%)	3 (0.9%)
Atrial fibrillation	0	1 (0.3%)	2 (0.6%)
Sinus bradycardia	0	0	1 (0.3%)
HLT: Ventricular arrhythmias and cardiac arrest	0	0	1 (0.3%)
Ventricular extrasystoles	0	0	1 (0.3%)
INVESTIGATIONS	1 (0.3%)	0	1 (0.3%)
HLGT: Cardiac and vascular investigations (excl enzyme tests)	1 (0.3%)	0	1 (0.3%)
HLT: ECG investigations	1 (0.3%)	0	1 (0.3%)
Electrocardiogram PR shortened	1 (0.3%)	0	0
Electrocardiogram QT prolonged	0	0	1 (0.3%)

There seems to be an imbalance in the percentage of patients with Cardiac Arrhythmia in the teriflunomide groups as compared to placebo. However, the numbers are small (6 [1.7%] on Teri 14 versus 3 [0.8%] on placebo).

Cases of atrial fibrillation in TOWER are as follows:

- **276001012** Teri 14. 24 yo F medical hx of epilepsy migraine, asthma. Concomitant meds included sumatriptan. On Day 73 the patient developed atrial fibrillation. She had tachycardia, vertigo, nausea and diarrhea and felt chest tightness. She was hospitalized and treated with metoprolol and enoxaparin. Spontaneous conversion to sinus rhythm occurred. She persisted with position dependent vertigo and nystagmus. Brain MRI showed new inflammatory foci consistent with MS lesion. Echocardiogram showed no atrial enlargement. The reason for the atrial fibrillation was not identified. Urinalysis showed a urinary infection that was treated with oral antibiotic (cotrim forte) for 5 days. She was discharged on Day 78 on stable condition and continued in the study. Event was not considered related to study drug by the investigator.

It is unclear how the diagnosis of atrial fibrillation was made. There is no information on laboratory measurements at the time of the Afib.

The case above was mentioned under SAE in Cardiac SOC in TOWER.

Additionally, there were two non-serious cases of atrial fibrillation as follows:

- **840015009**, 52 yo F, from US presented atrial fibrillation on day 123 of Teri 14 treatment. Medical hx of HTN, mitral valve prolapse, high cholesterol, hypertonic

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bladder, cholecystectomy, headache, depression, anxiety, drug hypersensitivity. She was taking multiple concomitant medications including citalopram, gabapentin, modafinil, metoprolol. On Day 20 laboratory showed serum creatinine 2x baseline with creatinine 159 $\mu\text{mol/L}$ (range: 31 - 101 $\mu\text{mol/L}$). Other blood chemistry values were within normal. On Day 27 she had a urinary tract infection resistant to oral medications (it is unclear which medications she received). On Day 35 she passed out at her daughter's house. She hospitalized with UTI, treated with cefuroxime, bactrim, cefalexin, oxybutynin and levofloxacin. She was placed on telemetry but there is no mention if there were any abnormalities. She recovered from syncope on the same day. On Day 123, the patient experienced intermittent atrial fibrillation. No vital signs data were recorded on that day. No corrective treatments were given. On Day 134, the patient recovered from the atrial fibrillation and the event was considered as not related to the IP by the investigator. On Day 125, the patient experienced AE of elevated creatinine again (creatinine at 177 $\mu\text{mol/L}$). No corrective treatments were given. On Day 168, the patient recovered from the blood creatinine increased (97 $\mu\text{mol/L}$) and the event was considered as not related to the IP by the Investigator.

It is unclear how the diagnosis of atrial fibrillation was made on Day 123 and what the laboratory values were at that time, or on Day 125, when she had increased creatinine. She was placed on telemetry when she had the UTI on Day 35, but there is no mention of whether there were any abnormalities. Patient profile includes laboratory data for scheduled visits and a baseline ECG but no lab data or ECG at time or hospitalization. This is yet another case of transient increase in creatinine (See review of renal function, section 7.7 of this review).

- **840026901** 54 yo F, history of hypothyroidism, MVP, headache, migraine, pneumonia, conduction disorder and BBB right, had atrial fibrillation on Day 498 of Teri 7 treatment. On Day 125 she was hospitalized for abdominal pain and partial small bowel obstruction. LFTs, amylase and lipase and basic metabolic panel were within normal. She was given ketorolac and ondansetron and discharged on stable condition. On Day 498 she had paroxysmal atrial fibrillation. No vital signs data or laboratory data were reported on this date. No corrective treatment was given. The event was considered not related to AP by the investigator. As of the last report, the patient had not recovered. Drug was not stopped.

Again, it is unclear how the diagnosis of paroxysmal atrial fibrillation was made. Whether she had any symptoms that led to obtaining an ECG. It is unclear if any work up was done to evaluate the event. No electrolyte values are available at the time of atrial fibrillation.

In all three cases of atrial fibrillation in TOWER it is unclear how the diagnoses were made, if patients were symptomatic or not, the laboratory values at the time of the diagnoses and what kind of work up was done for evaluation of AFib. All three patients with A Fib continued in the study; two resolved and one did not resolve.

The search for AESI also identified a case of Brugada syndrome, on Teri 7 mg, as follows:

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840074004 Teri 7 – 46 yo male. Brugada syndrome. This patient died in a motor vehicle accident on Day 477 of Teri 7 treatment.

In response to an FDA request for information Sanofi stated that the diagnosis of possible Brugada syndrome was made based on an ECG taken on Visit 2 at baseline, and was never confirmed. No symptoms were reported. This patient died in a motor vehicle accident during a snow storm. It is impossible to determine whether an arrhythmia played a role on his death.

CONCLUSION REGARDING CARDIAC ARRHYTHMIAS

Three patients who were taking teriflunomide were found dead (sudden death) several years into treatment. One additional patient died in the emergency room from an event reported as “cardiac trouble” accompanied by shortness of breath. There is very limited information about these four patients. Particularly, there is no information about their electrolyte status. All four deaths occurred in extension studies.

There is no signal for increased risk of arrhythmias, particularly serious or life-threatening arrhythmias with teriflunomide in the controlled database. However, there several reports of ventricular extrasystoles, atrial fibrillation, and unspecified arrhythmias/heart rate irregular in the extension studies. There is very limited information in the narratives for these patients, whether patients were symptomatic or not, and whether there were any electrolyte abnormalities at the time of the events. Moreover, it is impossible to interpret the clinical relevance of these relatively common rhythm disturbances in the absence of a controlled arm.

ECG in study 2001 and TOWER, and the thorough QT study did not suggest an increase risk of arrhythmias with teriflunomide. Cardiac arrhythmia has not been identified as an event associated with leflunomide in the postmarketing database, however, a relationship between cardiac arrhythmia and teriflunomide can not be ruled out.

Information regarding the five cardiovascular deaths occurring in patients taking teriflunomide should be included in the WARNINGS section of labeling. These deaths could be related to a long-term effects in blood pressure, or perhaps to acute changes in electrolytes (e.g. K or Mg) associated with transient renal failure (see discussion by Dr. Mentari, section 7.7 of this review). On the other hand, sudden death has been reported in patients with MS involvement of the brainstem, therefore, a relationship between CV death and teriflunomide can not be established.

I recommend requesting an epidemiologic, observational study of CV death (including sudden death) and arrhythmias with leflunomide, as a postmarketing requirement for approval of teriflunomide. These endpoints are relatively easy to evaluate in an epidemiologic study. To assess the clinical relevance of the effects on

blood pressure, non-fatal MI and non-fatal stroke should also be included as endpoints for this study.

7.3.4.12 AESI related to Convulsions

Two patients in the teriflunomide 7 mg group (0.5%) and 3 in the teriflunomide 14 mg group (0.7%) had TEAEs related to convulsion versus 1 in the placebo group (0.2%). The patient on placebo had seizures after hemithyroidectomy for thyroid carcinoma. Two of the 5 cases on teriflunomide were discussed in the SAE section of this review (6049/3009/0013 on Teri 7 and 6049/3801/0017 on Teri 14).

The other three were 1 nonserious report of convulsion in a patient treated with 7 mg (2001/0013/0014) and 2 nonserious events of partial seizures with secondary generalization reported in association with MS (6049/3202/0003) and epilepsy (6049/2405/0001) in patients treated with teriflunomide 14 mg. These events did not lead to study treatment discontinuation and patients recovered on study with or without corrective treatment. Both patients in the teriflunomide 14 mg group had a history of the convulsions/epilepsy prior to the study entry.

No difference in incidence of TEAE of convulsions (any class) was observed between the two teriflunomide groups (0.9% and 0.7% in teriflunomide 7 mg and 14 mg, respectively).

There was 1 report of epilepsy in a patient in the 7 mg teriflunomide dose in adjunct to GA (6046/3001/1006). The patient recovered from the event and continued study treatment.

CONCLUSION: Epilepsy is more common in patients with MS than in the general population (2 to 3% of patients, in some studies). There is no evidence that teriflunomide is associated with an increased risk of convulsions in this database. Convulsion has not been identified as an adverse event related to leflunomide, however, concerns about the increased risk of convulsions were raised at the IND stage. The lack of evidence of an increased risk of convulsions in this database does not rule out the possibility. Convulsion is an AE of interest to be followed in postmarketing surveillance.

7.3.4.13 AESI related to Hemorrhages

AESI related to hemorrhages (using the approach presented in Table 46 of this review) were slightly higher in the Teri 14 group (9.4%) as compared to Teri 7 (6.4%) and placebo (7.4%). They are summarized in the following table.

Table 66. Patients with hemorrhage related AESI, Pool 1

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Any class	31 (7.4%)	29 (6.8%)	39 (9.4%)
Blood and lymphatic system disorders	1 (0.2%)	0	0
Spontaneous haematoma	1 (0.2%)	0	0
Ear and labyrinth disorders	0	0	1 (0.2%)
Haematotympanum	0	0	1 (0.2%)
Vascular disorders	1 (0.2%)	4 (0.9%)	2 (0.5%)
Haematoma	0	4 (0.9%)	2 (0.5%)
Haemorrhage	1 (0.2%)	0	0
Respiratory, thoracic and mediastinal disorders	5 (1.2%)	3 (0.7%)	4 (1.0%)
Epistaxis	5 (1.2%)	3 (0.7%)	3 (0.7%)
Haemothorax	0	0	1 (0.2%)
Gastrointestinal disorders	4 (1.0%)	5 (1.2%)	2 (0.5%)
Gastrointestinal haemorrhage	0	0	1 (0.2%)
Rectal haemorrhage	2 (0.5%)	0	1 (0.2%)
Abdominal wall haematoma	0	1 (0.2%)	0
Anal haemorrhage	0	1 (0.2%)	0
Diarrhoea haemorrhagic	0	1 (0.2%)	0
Gingival bleeding	0	1 (0.2%)	0
Haematochezia	1 (0.2%)	1 (0.2%)	0
Haemorrhoidal haemorrhage	1 (0.2%)	0	0
Skin and subcutaneous tissue disorders	0	0	1 (0.2%)
Umbilical haemorrhage	0	0	1 (0.2%)
Musculoskeletal and connective tissue disorders	1 (0.2%)	0	0
Haemarthrosis	1 (0.2%)	0	0
Renal and urinary disorders	2 (0.5%)	1 (0.2%)	2 (0.5%)
Haematuria	2 (0.5%)	1 (0.2%)	1 (0.2%)
Urethral haemorrhage	0	0	1 (0.2%)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.2%)
Post abortion haemorrhage	0	0	1 (0.2%)
Reproductive system and breast disorders	7 (1.7%)	7 (1.6%)	16 (3.9%)
Menorrhagia	2 (0.5%)	4 (0.9%)	9 (2.2%)
Menometrorrhagia	0	0	2 (0.5%)
Metrorrhagia	2 (0.5%)	2 (0.5%)	2 (0.5%)
Vaginal haemorrhage	2 (0.5%)	0	2 (0.5%)
Uterine haemorrhage	1 (0.2%)	1 (0.2%)	1 (0.2%)
Postmenopausal haemorrhage	1 (0.2%)	0	0
Investigations	2 (0.5%)	1 (0.2%)	1 (0.2%)
Blood urine present	2 (0.5%)	1 (0.2%)	1 (0.2%)
Injury, poisoning and procedural complications	11 (2.6%)	10 (2.3%)	11 (2.7%)
Contusion	10 (2.4%)	10 (2.3%)	11 (2.7%)
Traumatic haematoma	1 (0.2%)	0	0

Source: Table 40. ISS.

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The difference was driven by menorrhagia, which was reported in 2.2% of patients in teriflunomide 14 mg respectively, versus 0.5% in placebo.

Median time to onset of hemorrhages was 171 days in teriflunomide 7 mg and 173 days in teriflunomide 14 mg compared to 234 days in placebo. Most of the events were of mild intensity; hemorrhage was considered as severe in 4 of 39 patients in teriflunomide 14 mg and 1 of 31 patients in placebo. Corrective treatment was administered for 6 of 29 patients in teriflunomide 7 mg, and 14 of 39 patients in teriflunomide 14 mg group and 8 of 31 patients in placebo.

In Pool 2, the proportion of patients with hemorrhages was similar between both treatment groups (13.5% and 13.7% in teriflunomide 7 mg and 14 mg, respectively).

CONCLUSION REGARDING HEMORRHAGE: There is no evidence of increase risk of bleeding in the controlled database, except for the increased risk of menorrhagia. It is unclear if menorrhagia is truly related to teriflunomide. Platelet counts/INRs were normal in these patients. Menorrhagia should be mentioned in the teriflunomide labeling. Hemorrhage should be followed in the postmarketing setting as an AE of interest.

7.3.4.14 AESI related to Embolic and thrombotic events

In Pool 1, AEs related to embolic and thrombotic events were reported in 2 (0.4%), 3 (0.7%) and 3 (0.7%) in the Teri 7, Teri 14 and placebo groups respectively.

- 6049/3805/0006 on placebo, 51 yo female, presented myocardial infarction and ventricular fibrillation on Day 96. She was a smoker.
- 002001/124/0018/0006, 40 yo M presented superficial thrombophlebitis on Day 1 of placebo treatment.
- 006049-528-4605-0013, 38 yo female presented phlebitis on right and left arms on Day 474 of placebo treatment.
- 6049/2402/0014. 32 yo female developed venous thrombosis on Day 379 of Teri 7 treatment. On Day 393 on a second visit to the ER, and angio CT scan showed venous thrombosis of the left brachiocephalic trunk, in association with a port-a-cath. IP was temporarily interrupted. She recovered on Day 613.
- 00604/616/3009/0007, 49 yo female developed venous thrombosis on Day 388 of Teri 7 treatment. Drug continued. She recovered.
- 6049/1203/0015 a 27-year-old female on Day 247 of Teri 14 treatment developed a pain in her left shoulder, and was diagnosed with pulmonary embolism and thrombophlebitis of left leg. Concomitant medications included oral contraception. She recovered from the pulmonary embolism on Day 393 and from the thrombophlebitis on Day 432.

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- 6049/4605/0006, a 25 yo male developed thrombosis of the right testicle on Day 600 of Teri 14 treatment. Drug was continued. He recovered.
- 006049-643-3205-0004, a 39 yo female had superficial thrombophlebitis on Day 756. Drug continued. She recovered.

In Pool 2, there were two additional myocardial infarctions and one pulmonary embolism with DVT in patients taking Teri 7 mg. No additional cases on Teri 14.

- 6048/0012/0001, a 52-year-old female with medical of hypertension, hypercholesterolemia, and ex-smoker presented acute myocardial infarction on Day 915 of Teri 7 treatment. Drug was discontinued. The patient recovered in 336 days.
- 6048/0013/0004, a 22-year-old female was diagnosed with pulmonary embolism and deep vein thrombosis on Day 385 of Teri 7 treatment. Concomitant meds included oral contraceptive. She was a smoker. Drug was discontinued. She recovered in 463 days.
- 6048/0013/0009, a 45-year-old female with medical history of coronary artery disease, left heart catheterization, angioplasty, hypertension, dyslipidemia and depression, experienced a fatal myocardial infarction on Day 3281 (9 years). The massive myocardial infarction was considered related to underlying disease.

In study 6045 (adjuvant with INF-beta) a case of DVT occurred in a 34 yo male two months after discontinuation of Teri 7 treatment because of disease progression. This patient had undergone cholestyramine washout and the event is unlikely to be related to teriflunomide.

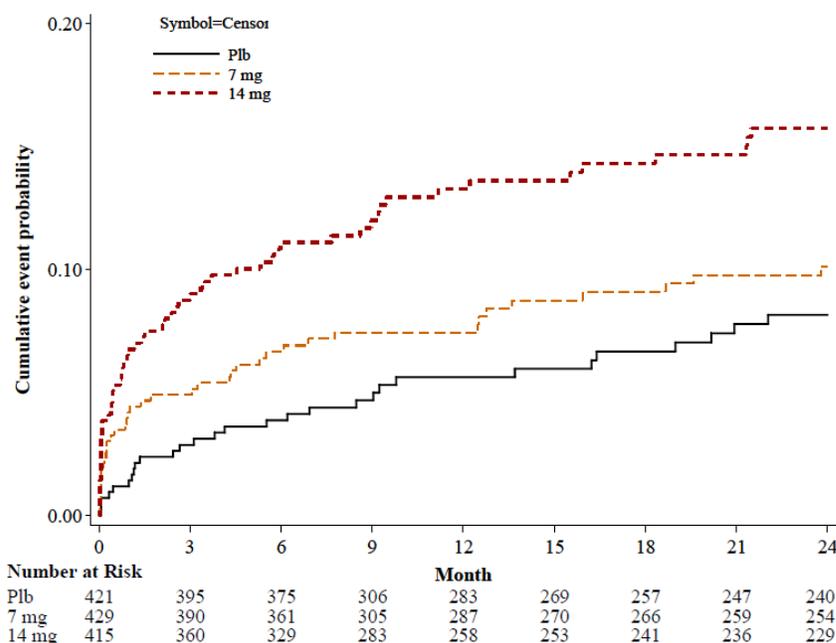
IN SUMMARY: There was a small number and no imbalance in the number of thrombotic/ embolic events in the Pool 1 database (one MI on placebo and no MIs on teriflunomide; no strokes in either treatment group; there was one PE (in a patient taking oral contraceptives) and one thrombosis of the brachiocephalic trunk (in a patient with a port-a-cath) in the teriflunomide group. There were four MI (one fatal) and two PE in the extension monotherapy studies, in patients with additional risk factors. Additionally there was a subclavian vein thrombosis in one of the ongoing studies. Overall, there is no evidence of an increased risk of thrombosis in the controlled database, but the possibility of an increased risk can not be ruled out. This is an area that needs attention during postmarketing surveillance.

7.3.4.15 AESI related to nausea and diarrhea

Nausea and diarrhea were more frequent with teriflunomide than with placebo, with evidence of a dose response. Nausea was reported in 9.3%, and 14.2% and 6.9% on Teri 7, Teri 14, and placebo, respectively. Vomiting was reported in 3.5% and

4.6%, 3.6%, on Teri 7, Teri 14, and placebo, respectively. The maximum effect appears to be within the first 3 months but event continued to occur over time. Median time to onset of nausea was 47 days in Teri 7 and 42 days in Teri 14 as compared to 126 days in the placebo group. Most cases of nausea were of mild intensity. Corrective treatment was administered in approximately 1/3 of patients. All 29 patients on placebo recovered during the observation period in Pool 1, versus 39/40 patients on Teri 7 and 55/59 on Teri 14. One patient discontinued because of nausea from Pool 1 and two from Pool 2. The risk of nausea with teriflunomide versus placebo tended to be greater in patients ≥ 38 years as compared to < 38 years. There was no evidence of increased risk of nausea regarding other intrinsic factors. The figure below shows a Kaplan-Meier plot for time to onset of nausea.

Figure 10. Kaplan-Meier plot for time to onset of nausea AE, Pool 1

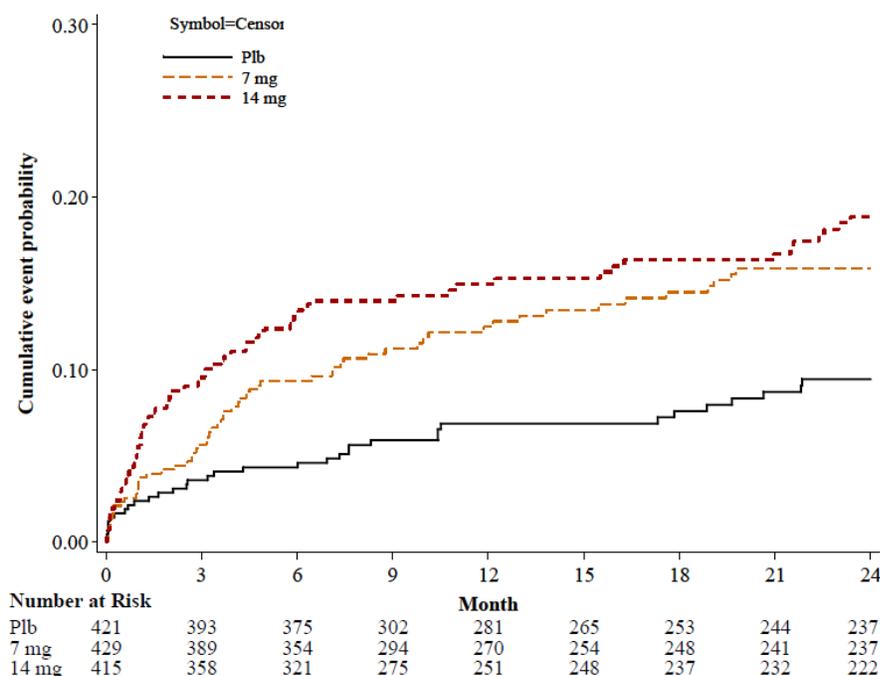


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Source: Figure 4, original ISS.

Diarrhea was evaluated by using the MedDRA “Diarrhea” HLT (high level term). In Pool 1, 15.2%, 17.3% and 8.3% of patients on Teri 7, Teri 14 and placebo, reported an AE of diarrhea. The majority of first events occurred during the first 3 months of treatment.

Figure 11. Kaplan-Meier plot of time to onset of diarrhea, Pool 1



Source: Figure 5, original ISS.

Diarrhea was considered as serious in 1 patient in the teriflunomide 14 mg group.

- **6049/2202/0007** experienced diarrhea starting 20 days after first intake of teriflunomide 14 mg, which led to hospitalization for a diagnostic colonoscopy procedure (no results provided) on day 606. The treatment with teriflunomide was continued despite persistence of the event during the extension study. The patient was considered recovered 3 months later.

Diarrhea led to treatment discontinuation in 2 patients (1 in each teriflunomide group).

- **6049/2607/0002** had 2 episodes of diarrhea (4 days and 7 days after starting treatment with Teri 7, managed with loperamide. The AE soft/loose stools led to permanent discontinuation of study drug. Five months later and the patient was considered recovered.
- **6049/2003/0010** had a history of hepatic steatosis. He had 4 episodes of diarrhea while treated with Teri 14. The first episode was reported after 3 days of treatment; the last episode occurred after 6.8 months of treatment, and led to the discontinuation of the study medication. The patient recovered from each episode with loperamide.

One patient had serious diarrhea with electrolyte disturbances and hypovolemia, leading to hospitalization, about 2.1 years into Teri 14 treatment. Treatment was interrupted. The patient recovered in 3 months, then Teri was re-started without recurrent event.

IN SUMMARY: nausea and diarrhea were common events in teriflunomide studies, with evidence of a dose response. In general, they were mild but occasionally led to hospitalization or discontinuation of study drug. It is unclear if any of these cases of diarrhea underwent work up to rule out an infectious diarrhea.

7.3.5 Submission Specific Primary Safety Concerns

Major safety concerns with teriflunomide are liver toxicity, teratogenicity, potential for immunosuppression, skin reactions, pulmonary toxicity and peripheral neuropathy. For specific safety concerns the reader is referred to the section on AESI.

In addition to adverse events previously identified with leflunomide, the risk of acute, reversible renal failure with teriflunomide has been identified in this application (see section 7.7 of this review).

The other newly identified area of concern is the potential increase in cardiovascular risk. There have been five CV deaths in this application among approximately 2600 patients exposed, all of them during extension studies. One was a myocardial infarction in a patient with multiple CV risk factors. The cause of death for the other four patients remains unknown. Sudden death and neurogenic pulmonary edema have been reported in patients with MS and brainstem involvement. However, a causal relationship to study drug can not be ruled out. Additionally, three non fatal MI and one resuscitated cardiac arrest were observed in the phase 2/3 database. I recommend a postmarketing epidemiologic study to assess the risk of CV death, MI and stroke and arrhythmia in patients taking leflunomide (ARAVA) and enhanced surveillance of CV events with teriflunomide.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Most common adverse events in ISS studies

For purposes of placement in the adverse reactions section of labeling, adverse event risk are usually defined as frequent (risk of >1/100 patients); infrequent (1/100 to 1/1000 patients), and rare (less than 1/1000 patients). In Pool 1, the SOC with the most frequently reported TEAEs (with incidence $\geq 1\%$ in any treatment group) and greater than placebo by decreasing frequency (in teriflunomide 14 mg) were Infections and infestations, Gastrointestinal disorders and Nervous system disorders. The individual PTs with incidence of at least 10% and greater than placebo were Nasopharyngitis, Influenza, Urinary tract infection, Paresthesia, Diarrhea, Nausea, Alopecia and ALT increased. Adverse events with incidence $\geq 5\%$ and greater than placebo in Safety Pool 1 are presented below.

Table 67. Adverse events with incidence $\geq 5\%$ and greater than placebo, Safety Pool 1.

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	Teri 7 mg (N=429)	Teri 14 mg (N=415)
Any class	377 (89.5%)	390 (90.9%)	382 (92.0%)
Infections and infestations	242 (57.5%)	256 (59.7%)	256 (61.7%)
Influenza	39 (9.3%)	41 (9.6%)	49 (11.8%)
Urinary tract infection	40 (9.5%)	34 (7.9%)	44 (10.6%)
Bronchitis	24 (5.7%)	18 (4.2%)	30 (7.2%)
Sinusitis	16 (3.8%)	19 (4.4%)	24 (5.8%)
Gastroenteritis	21 (5.0%)	22 (5.1%)	23 (5.5%)
Nervous system disorders	189 (44.9%)	194 (45.2%)	187 (45.1%)
Paraesthesia	33 (7.8%)	41 (9.6%)	44 (10.6%)
Cardiac disorders	13 (3.1%)	20 (4.7%)	17 (4.1%)
Palpitations	5 (1.2%)	13 (3.0%)	8 (1.9%)
Gastrointestinal disorders	145 (34.4%)	170 (39.6%)	188 (45.3%)
Diarrhoea	35 (8.3%)	60 (14.0%)	72 (17.3%)
Nausea	29 (6.9%)	40 (9.3%)	59 (14.2%)
Abdominal pain	24 (5.7%)	20 (4.7%)	25 (6.0%)
Abdominal pain upper	19 (4.5%)	21 (4.9%)	22 (5.3%)
Skin and subcutaneous tissue disorders	92 (21.9%)	124 (28.9%)	154 (37.1%)
Alopecia	18 (4.3%)	48 (11.2%)	61 (14.7%)
Rash	17 (4.0%)	20 (4.7%)	23 (5.5%)
General disorders and administration site conditions	115 (27.3%)	117 (27.3%)	112 (27.0%)
Pain	4 (1.0%)	10 (2.3%)	9 (2.2%)
Investigations	107 (25.4%)	138 (32.2%)	125 (30.1%)
ALT increased	30 (7.1%)	54 (12.6%)	58 (14.0%)

At least 0.5% greater than placebo. Source: Table 1.5.2.1, ISS.

Common adverse events in TOWER were consistent with those in Pool 1.

Of interest, the risk of neutropenia in TOWER was 9.4% in the Teri 14 group, 6.9% on Teri 7 and 2.5% on placebo. The risk of nephrolithiasis was 0.6% on Teri 14, 2.1% on Teri 7 and 0 on placebo. An AE of Blood CK increased was reported in 9 (2.6%) of patients on Teri 14 and 2 (0.6%) of Teri 7 and placebo groups.

7.4.2 Other potentially relevant events

7.4.2.1 AE with excess in teriflunomide treated groups

Evaluation of all AE regardless of seriousness or whether they led to drug discontinuation in Pool 1 identified potential areas that may warrant further evaluation, as follows.

The risk of an AE of hypercholesterolemia was slightly higher among patients treated with teriflunomide (1.6% and 1.2% on Teri 7 and Teri 14, respectively), as compared

to 0.5% on placebo. It is unclear if this difference contributed to an increased CV risk in the teriflunomide population. There were no clinically relevant changes from baseline for cholesterol and triglycerides in Pool 1.

Hypokalemia was reported in 3 patients on Teri 14 and no patients in other treatment groups.

Vit B12 deficiency was reported in 1 and 3 patients on Teri 7 and Teri 14, respectively, and no patient on placebo. Vitamin B12 deficiency may have been related to the higher incidence of diarrhea in teriflunomide treated patients.

Cardiac disorders were slightly higher in the teriflunomide treatment groups as compared to placebo, driven by palpitations and tachycardia. None of the events of palpitations and tachycardia were reported serious or led to study drug discontinuation. The clinical significance of this finding is unclear.

Table 68. Cardiac disorders SOC, in Pool 1.

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Cardiac disorders	13 (3.1%)	20 (4.7%)	17 (4.1%)
Palpitations	5 (1.2%)	13 (3.0%)	8 (1.9%)
Tachycardia	2 (0.5%)	4 (0.9%)	6 (1.4%)
Angina pectoris	1 (0.2%)	0	2 (0.5%)
Sinus tachycardia	1 (0.2%)	0	1 (0.2%)
Supraventricular tachycardia	0	1 (0.2%)	1 (0.2%)
Atrial fibrillation	1 (0.2%)	1 (0.2%)	0
Cardiovascular disorder	0	1 (0.2%)	0
Hypertrophic cardiomyopathy	1 (0.2%)	0	0
Myocardial infarction	1 (0.2%)	0	0
Tachycardia paroxysmal	1 (0.2%)	0	0

Source: Appendix 1.5.2.1

The incidence of AE in the Skin and subcutaneous tissue disorders SOC was higher in patients taking teriflunomide as compared to placebo. The difference was driven by alopecia related terms, but there was also a slightly higher incidence of skin hypersensitivity/allergic reactions (rash, pruritus, erythema, urticaria, dermatitis atopic). Events with incidence of $\geq 1\%$ in this SOC are shown below:

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Table 69. Adverse events in Skin and subcutaneous disorders SOC, Pool 1 (events with incidence $\geq 1\%$)

Primary System Organ Class Preferred Term n(%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Skin and subcutaneous tissue disorders	92 (21.9%)	124 (28.9%)	154 (37.1%)
Alopecia	18 (4.3%)	48 (11.2%)	61 (14.7%)
Rash	17 (4.0%)	20 (4.7%)	23 (5.5%)
Eczema	8 (1.9%)	9 (2.1%)	12 (2.9%)
Acne	5 (1.2%)	5 (1.2%)	11 (2.7%)
Pruritus	7 (1.7%)	16 (3.7%)	11 (2.7%)
Dry skin	8 (1.9%)	6 (1.4%)	5 (1.2%)
Erythema	2 (0.5%)	8 (1.9%)	5 (1.2%)
Urticaria	2 (0.5%)	4 (0.9%)	5 (1.2%)
Dermatitis allergic	4 (1.0%)	2 (0.5%)	4 (1.0%)
Hypoesthesia facial	3 (0.7%)	3 (0.7%)	4 (1.0%)
Night sweats	1 (0.2%)	2 (0.5%)	4 (1.0%)
Pruritus generalised	2 (0.5%)	1 (0.2%)	4 (1.0%)

Source: Table 1.5.2.1, original ISS.

7.4.2.2 Use of rapid elimination process

Rapid elimination (washout) with cholestyramine or activated charcoal was conducted in most patients who discontinued treatment (either due to early discontinuation or completion of studies for patients who did not enter an extension). For instance, approximately 85% of patients who discontinued prematurely from TEMSO underwent rapid elimination.

Utilization of rapid elimination in teriflunomide studies is summarized below.

Table 70. Percentage of patients who underwent rapid elimination procedure in teriflunomide studies

Study	% of pts who had washout among pts who discontinued early	% of patients with washout among all patients exposed
2001	25%	3 %
LTS6048	41%	22 %
6049/TEMSO	85%	27 %
LTS6050	90%	22 %
PDY6046+LTS6047	94%	94 %
TOWER	80 %	17 %
Clinical pharmacology	100%	100%

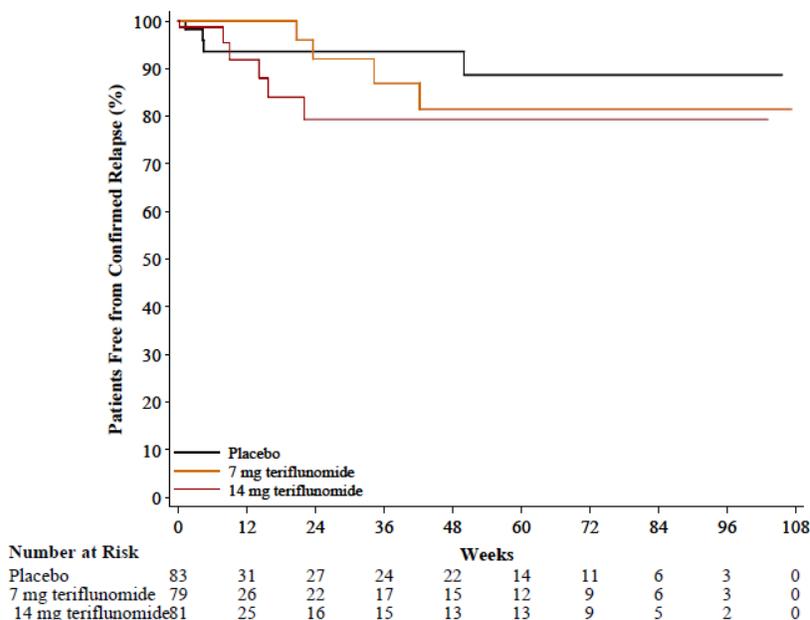
Source: response to FDA request for information submitted 11/14/11. (Numbers are rounded)

The proposed teriflunomide label includes a section that describes time to recovery of ALT after drug discontinuation. However, it should also mention that most patients underwent rapid elimination along with drug discontinuation.

As per a response to the FDA request for information, the incidence of relapse after drug discontinuation and rapid elimination was slightly higher among patients in the teriflunomide treatment group, as compared to placebo, but the number of patients is small. By week 48 only 15 and 13 patients were available for evaluation in the Teri 7 and 14 mg groups.

Figure 12. Time to MS relapse after drug discontinuation and washout in Pool 1.

Figure 2 - Kaplan-Meier plot of time to first MS relapse after treatment discontinuation - Discontinued patients with washout drug (ITT population)



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Source: Figure 2. 4/20/12 response to FDA request for information.

7.4.2 Laboratory Findings

7.4.2.1 Chemistry: metabolic, renal function and electrolytes

Monotherapy studies (Pool 1 and 2)

- Measures of central tendency in Monotherapy studies

Mean and median changes from baseline in values of metabolic functions (glucose, total cholesterol, triglycerides, albumin), renal (BUN, creatinine, creatinine clearance) and electrolytes (sodium, potassium, chloride, phosphorus) were minimal over time and did not vary between treatment groups in Pools 1 and 2. There were no changes in mean/median values for serum calcium (only measured in study 2001). There was no measurement of bicarbonate or magnesium in any study.

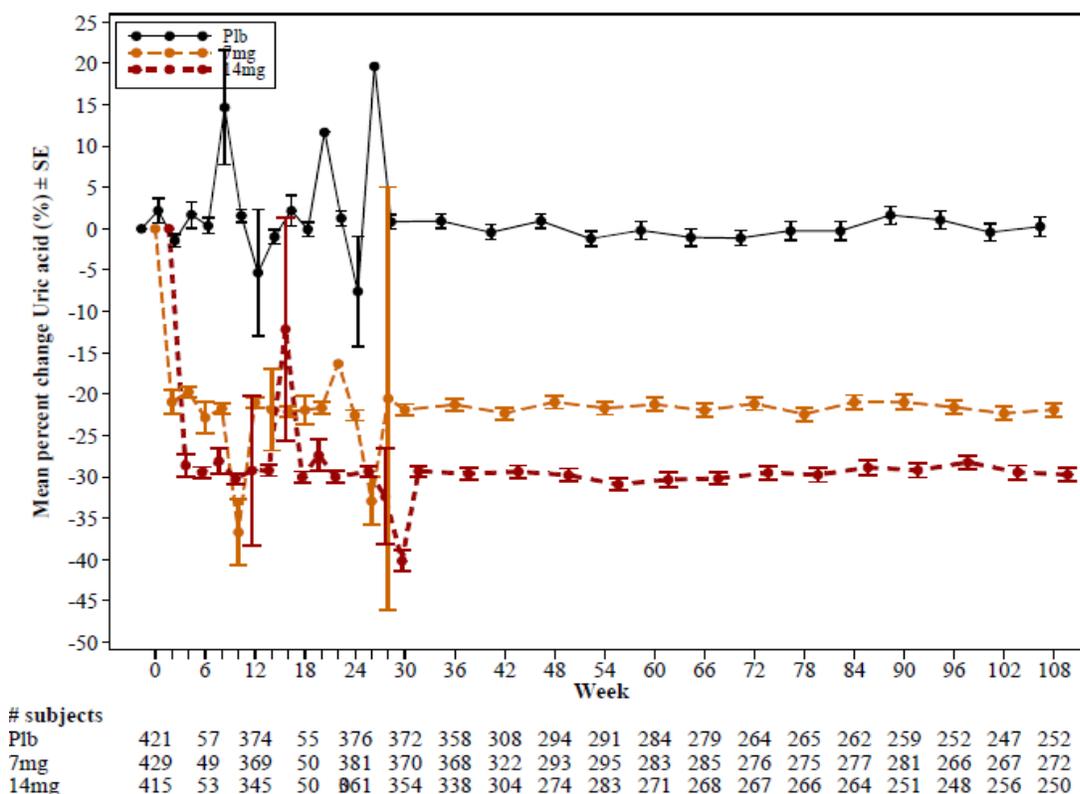
The only two measurements that showed a change from baseline in mean/median values were uric acid and creatine phosphokinase.

- Uric acid levels

There was a clear dose related decrease in serum uric acid levels in most clinical studies. The normal range for uric acid levels: 124.9 to 428.2 umol/L. In Pool 1, the mean changes from baseline in uric acid levels at endpoint (end of treatment visit for completers, last value prior to the last drug intake for discontinued patients) were: -77.8 umol/L on Teri 14, -58.3 umol/L on Teri 7 and -3.8 umol/L on placebo. Analyses in Pool 2 were consistent with those of Pool 1.

The figure below shows that in Pool 1, uric acid levels dropped down to 20-30% of baseline values within the first 2-3 weeks of treatment, with evidence of a dose-response between Teri 7 and 14.

Figure 13. Uric acid percentage change from baseline, Pool 1



Source: Figure in section 1.6.2.1.35 of original ISS.

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- Serum Creatine Phosphokinase (CK) changes

CK was not measured in TEMSO, but it was measured in study 2001 and extension (approximately 60 patients per treatment group).

CK in study 2001 showed a mean change from baseline at endpoint of -2.89 U/L in the placebo group, -2.62 U/L in the Teri 7 group and +10.77 U/L in the Teri 14 group. (Normal CK values for study 2001 were 0 – 190 U/L.) Changes in CK in study 2001 are shown below.

Table 71. Creatine Phosphokinase in study 2001.

Treatment	Statistic	Baseline	Week 6	Week 12	Week 18	Week 24	Week 30	Week 36	Endpoint	Change
Creatine phosphokinase (U/L)										
Placebo	N	61	57	52	56	56	57	57	61	61
	Mean	86.03	81.89	82.73	84.14	75.11	92.98	86.44	83.15	-2.89
	SD	60.355	53.151	70.732	70.498	41.852	75.859	47.079	46.497	42.174
	Median	72.00	65.00	60.00	64.00	65.50	70.00	77.00	74.00	2.00
	Min	26.00	31.00	26.00	26.00	28.00	34.00	27.00	27.00	-180.00
	Max	430.00	345.00	478.00	442.00	259.00	434.00	268.00	268.00	131.00
7 mg Teriflunomide	N	61	51	50	50	56	56	58	61	61
	Mean	95.85	94.02	92.54	90.12	92.66	92.16	95.36	93.23	-2.62
	SD	67.475	61.472	48.227	46.772	58.176	62.668	57.755	56.333	65.135
	Median	76.00	74.00	79.50	84.00	78.50	72.00	73.00	73.00	-1.00
	Min	29.00	26.00	26.00	28.00	26.00	39.00	32.00	32.00	-285.00
	Max	425.00	366.00	243.00	255.00	315.00	432.00	256.00	256.00	144.00
14 mg Teriflunomide	N	57	54	50	51	48	46	46	57	57
	Mean	83.19	95.02	97.36	103.10	105.73	88.91	97.54	93.96	10.77
	SD	48.830	61.088	66.270	93.755	86.960	52.772	63.454	57.749	46.884
	Median	68.00	74.50	73.00	74.00	77.00	72.00	76.50	76.00	9.00
	Min	26.00	38.00	44.00	33.00	36.00	35.00	39.00	35.00	-97.00
	Max	273.00	361.00	344.00	516.00	597.00	269.00	344.00	344.00	219.00

Source: Table T216, study 2001 CSR.

The changes from baseline in study 2001 suggests that teriflunomide, particularly 14 mg/day is associated with an increase in CK levels. The clinical significance of this small increase in mean CK values is unclear. This could be an incidental finding related to multiple analyses in a small database or to a true effect in muscles. The analysis of outliers in Pool 1 did not confirm an increased risk of CK increase. However, analyses of CK in TOWER suggested increased CK elevation >5xULN with Teri 14 as compared to placebo.

Mean changes in lactate dehydrogenase (LDH) in study 2001 were -0.43 U/L in the placebo group, +17.89 U/L in the Teri 7 group and +15.98 U/L in the Teri 14 group. LDH has multiple origins, such as muscle and liver. (Normal LDH levels in study 2001 were 0 - 479 U/L.) *Again, the clinical significance of this small increase in LDH is unclear.*

- Analyses of outliers for laboratory evaluations Pool 1 and 2

Analyses of laboratory metabolic and electrolyte abnormalities based on PCSA (potentially clinically significant abnormalities) are presented below.

Table 72. Outliers for metabolic and electrolyte laboratory abnormalities, Pool 1

Laboratory parameter Baseline by PCSA criteria n/N1 (%)	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)
Glucose (regardless of fasting status)			
Total ^a			
≤3.9 mmol/L and <LLN	82/420 (19.5%)	89/428 (20.8%)	93/413 (22.5%)
≥11.1 mmol/L	8/420 (1.9%)	7/428 (1.6%)	6/413 (1.5%)
Total cholesterol (regardless of fasting status)			
Total ^a			
≥7.74 mmol/L	30/420 (7.1%)	34/428 (7.9%)	27/413 (6.5%)
Triglycerides (regardless of fasting status)			
Total ^a			
≥4.6 mmol/L	28/420 (6.7%)	29/428 (6.8%)	28/413 (6.8%)
Albumin			
Total ^a			
≤25 g/L	1/420 (0.2%)	1/428 (0.2%)	0/413
CPK^b			
Total ^a			
> 3 ULN	2/61 (3.3%)	1/61 (1.6%)	2/57 (3.5%)
> 10 ULN	1/61 (1.6%)	1/61 (1.6%)	0/57
Sodium			
Total ^a			
≤129 mmol/L	2/420 (0.5%)	2/428 (0.5%)	2/413 (0.5%)
≥160 mmol/L	1/420 (0.2%)	1/428 (0.2%)	5/413 (1.2%)
Potassium			
Total ^a			
<3 mmol/L	0/420	1/428 (0.2%)	3/413 (0.7%)
≥5.5 mmol/L	38/420 (9.0%)	38/428 (8.9%)	33/413 (8.0%)
Chloride			
Total ^a			
<80 mmol/L	1/359 (0.3%)	1/367 (0.3%)	0/356
>115 mmol/L	6/359 (1.7%)	3/367 (0.8%)	2/356 (0.6%)
Phosphorus^b			
Total ^a			
<LLN	40/420 (9.5%)	99/428 (23.1%)	115/413 (27.8%)
>ULN	17/420 (4.0%)	10/428 (2.3%)	13/413 (3.1%)

Based on PCSA values: Potentially clinically significant abnormalities. ^a Regardless of baseline status. ^b CPK Only collected in studies 2001+LTS6048. Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once in the TEAE period. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline by baseline PCSA status. For Phosphorus there was no PCA definition; analyses of out of normal range criteria were used for analysis. Source: Appendix 1.6.2.3 of original ISS.

The analyses of metabolism and electrolyte laboratories by PCSA were unremarkable, except for phosphorus. There was a higher percentage of patients who presented phosphorus levels below normal (23% and 27% of patients in Teri 7 and Teri 14), as compared to placebo (9.5%) (no definitions for PCSA values were available for phosphorus in the table above).

Analyses by CTCAE (common terminology criteria adverse events) were generally consistent with PCSA analyses.

In the sponsor table summarizing abnormalities in serum phosphorus in Pool 1 by CTCAE criteria, no subject had a reported serum phosphorus level below 0.3 mmol/L (which is considered to be clinically severe hypophosphatemia).³⁰

³⁰ Hypophosphatemia. Access Medicine, Q&H.Quick Answers. McGraw-Hill.

Table 73. Phosphorus – number of patients with abnormalities (CTCAE) according to baseline status – safety population – Pool 1

Laboratory parameter	teriflunomide		
	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)
Baseline			
by CTCAE criteria n/N1 (%)			
Phosphorus			
Total^a			
≥ 0.6 and <LLN	36/420 (8.6%)	77/428 (18.0%)	91/413 (22.0%)
≥ 0.3 - <0.6 mmol/L	4/420 (1.0%)	22/428 (5.1%)	24/413 (5.8%)
<0.3 mmol/L	0/420	0/428	0/413
Normal/Missing			
≥ 0.6 and <LLN	30/412 (7.3%)	73/422 (17.3%)	89/410 (21.7%)
≥ 0.3 - <0.6 mmol/L	4/412 (1.0%)	21/422 (5.0%)	24/410 (5.9%)
<0.3 mmol/L	0/412	0/422	0/410
≥ 0.6 and <LLN			
≥ 0.6 and <LLN	5/7 (71.4%)	4/6 (66.7%)	2/3 (66.7%)
≥ 0.3 - <0.6 mmol/L	0/7	1/6 (16.7%)	0/3
<0.3 mmol/L	0/7	0/6	0/3
≥ 0.3 - <0.6 mmol/L			
≥ 0.6 and <LLN	1/1 (100%)	0/0	0/0
≥ 0.3 - <0.6 mmol/L	0/1	0/0	0/0
<0.3 mmol/L	0/1	0/0	0/0

CTCAE: Common Terminology Criteria for Adverse Events.

^a Regardless of baseline

Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once in the TEAE period. The denominator (N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline by baseline CTCAE status.

PGM=PRODOPS/HMR1726/OVERALL/OSR_2011/REPORT/PGM/fda_lab_ctcaephosphor_s_t.sas
 OUT=REPORT/OUTPUT/fda_lab_ctcaephosphor_s_t_p1_i.rtf (06JAN2012 - 19:17)

Source: Page 7 of the Sponsor response submitted to NDA 202992 on January 11, 2012.

The applicant claims that the low uric acid and phosphorus have no relevant clinical consequences. However, uricosuric agents are known to be associated with increased risk of lithiasis. More patients presented urinary tract infections and nephrolithiasis in the teriflunomide treatment groups in the monotherapy studies as well as in the TOWER study.

The following are facts about hypophosphatemia^{28, 31}

Moderate hypophosphatemia (1.0–2.4 mg/dL [or 0.32–0.79 mmol/L]) occurs commonly in hospitalized patients and may not reflect decreased phosphate stores.³² It is usually asymptomatic and does not require treatment. Severe hypophosphatemia (< 1 mg/dL [or 0.32 mmol/L]) is associated with impaired tissue oxygenation and cell metabolism. Patients with

³¹ Current diagnosis and treatment: nephrology and Hypertension. Chapter 7 (Keith A. Hruska)

³² Access Medicine uses a lower limit of normal for serum phosphate of 0.79 mmol/L. The normal range of serum phosphate level for the central lab used in the teriflunomide application was 0.71-1.65 mmol/L.

severe or refractory hypophosphatemia are usually symptomatic and will require therapy, including intravenous phosphate.

- Acute, severe hypophosphatemia may cause tissue hypoxia and
 - o It can lead to rhabdomyolysis (increased muscle enzymes), weakness, numbness, paresthesias, and encephalopathy (irritability, confusion, dysarthria, seizures, and coma). (*Evaluation of phosphate levels from 5 out of 10 patients with nerve conduction study-confirmed peripheral neuropathy in TEMSO did not show that patients with peripheral neuropathy had hypophosphatemia. However, phosphate data for the other five were not available.*)
 - o Respiratory failure or failure to wean from mechanical ventilation may occur as a result of diaphragmatic weakness.
 - o Arrhythmias and heart failure are uncommon but serious manifestations. Severe hypophosphatemia has been associated with a cardiomyopathy characterized by a low cardiac output, a decreased ventricular ejection velocity, and an elevated left ventricular end-diastolic pressure. (*One death in a patient with “cardiac trouble” and three sudden deaths occurred in this application in patients taking teriflunomide during extension studies. However, there was no evidence of increased risk of life-threatening arrhythmias in the controlled database.*)
 - o Hematologic manifestations include acute hemolytic anemia from erythrocyte fragility, platelet dysfunction with petechial hemorrhages, and impaired chemotaxis of leukocytes (leading to increased susceptibility to gram-negative sepsis). A decrease in the red cell content of 2,3-diphosphoglycerate and ATP leads to increased rigidity and, in rare instances, hemolysis. Hemolysis is usually provoked by unusual stress on the metabolic requirements of the red cell, such as severe metabolic acidosis or infection. In experimental hypophosphatemia there thrombocytopenia and a reactive megakaryocytosis. In addition, there is an impairment of clot retraction and a hemorrhagic tendency, especially involving gut and skin. (*Teriflunomide inhibits pyrimidine synthesis and is associated with bone marrow suppression; it is difficult to evaluate whether hypophosphatemia contributes to the blood cell count effects of teriflunomide.*)

- Chronic severe depletion may cause anorexia, pain in muscles and bones and osteomalacia. (*Evaluation of all serious and non-serious fractures in Pool 1 and TOWER showed that the percentage was similar among treatment groups.*)

Additionally, severe hypophosphatemia and phosphate depletion affect the balance and serum concentrations of various electrolytes. This may produce changes in cardiovascular function as described above, as renal hemodynamics affect renal tubular transport processes and induce marked changes in renal cell metabolism. A marked increase in urinary calcium excretion occurs during phosphate depletion proportional to the severity of phosphate depletion and the degree of hypophosphatemia. (*No cases of severe hypophosphatemia were identified in this application. Urinary calcium was not measured in teriflunomide studies.*)

Hypophosphatemia may be caused/worsened by decreased intestinal absorption, increased urinary losses, or transcellular shift from the extracellular to the intracellular space. Phosphaturic

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drugs such as theophylline, diuretics, bronchodilators, corticosteroids and calcitonin may lead to or worsen hypophosphatemia.

Review of phosphorus levels in the laboratory datasets did not find any patient with levels <0.3 MMOL/L. As per review of the lab datasets, five patients had serum phosphorus levels below 0.5. None had AE typically associated with hypophosphatemia.

Of note, magnesium and bicarbonate levels were not submitted/analyzed in the ISS. As per a response for information submitted on January 2012, bicarbonate levels were not measured in any of the teriflunomide trials. Of note, a case report of leflunomide-induced Renal Tubular Acidosis (RTA) that resolved after cholestyramine washout has been published in the literature.³³ RTA is characterized by metabolic acidosis (low bicarbonate levels). The patient in the report was asymptomatic.

ARAVA carries the following information, under Laboratory tests:

“Due to a specific effect on the brush border of the renal proximal tubule, ARAVA has a uricosuric effect. A separate effect of hypophosphaturia is seen in some patients. These effects have not been seen together, nor have there been alterations in renal function.”

The proposed Teriflunomide label reads as follows, in the Pharmacodynamics section:



Sanofi has attributed the low uric acid levels to uricosuria due to inhibition of urate transport through the apical urate/anion exchanger. However, no explanation was provided for the effects on phosphorus.

Several conditions characterized by either single or multiple tubular ion transport defects have been characterized in which phosphorus reabsorption is decreased. In Fanconi syndrome, patients excrete not only an increased amount of phosphorus in the urine but also increased quantities of amino acids, uric acid, and glucose, resulting in hypouricemia and hypophosphatemia. Several drugs have been associated with Fanconi syndrome, including anti-retroviral therapy, ifosfamide and tetracycline.

In response to a request for information Sanofi searched for evidence of Fanconi syndrome in the teriflunomide database. The concluded that “The overall effect of teriflunomide is that of

³³ Evans et al. Renal tubular acidosis associated with leflunomide. Letter to the Editor. Rheumatology. Oxford Journals. 2007;46:1040.

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incomplete Fanconi syndrome without any relevant effects on glucose, pH and protein excretion in urine. No clinical complications of the modest effect of teriflunomide on phosphate and uric acid excretion have been detected.” (Response submitted on 10/10/2012.)

Sanofi also stated that the urinary elimination of phosphorus has not been evaluated as part of teriflunomide development program but that in a study of leflunomide in 38 patients with rheumatoid arthritis, decreases in serum urate and phosphate levels were observed with parallel increases in clearances of urate and in fractional excretion of urate, and a reduction in tubular reabsorption of phosphate.³⁴ Sanofi states that the “clearance of creatinine did not change significantly” and that the experience with teriflunomide and the results of the above-mentioned leflunomide study support the statement in the label. However, Sanofi admits that “the specific tubular target for phosphate elimination has not been investigated, and no evidence is available on whether the mechanisms of hypophosphatemia and hypouricemia are independent or not.” (Response submitted on 4/6/2012.)

- Hyperkalemia in Pool 1

As per Table 72 of this review, there were a few more cases of hypernatremia and hypokalemia in the Teri 14 group as compared to Teri 7 and placebo. However, although the table of outliers based on PCSA for potassium does not show a strong imbalance, when analyzed by baseline potassium levels there is an imbalance in hyperkalemia. As shown below, the frequency of treatment-emergent hyperkalemia >7.0 mmol/L among patients with normal or missing potassium values at baseline was greater in teriflunomide-treated subjects (4/421 or 1.0% of teriflunomide 7 mg subjects and 4/408 or 1.0% of teriflunomide 14 mg subjects, compared to 1/414 or 0.2% of placebo-treated subjects).

³⁴ Perez-Ruiz F, Nolla JM. Influence of leflunomide on renal handling of urate and phosphate in patient with rheumatoid arthritis. Clin Rehum 2003;0(4)215-8.

Table 74. Number of subjects with hyperkalemia (CTCAE categories) according to baseline status. Pool 1 Safety population.

Laboratory parameter	teriflunomide		
	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)
Baseline			
by CTCAE criteria n/N1 (%)			
Potassium (hyperkalemia)			
Total^a			
>ULN - ≤5.5 mmol/L	16/420 (3.8%)	18/428 (4.2%)	12/413 (2.9%)
>5.5 - ≤6.0 mmol/L	23/420 (5.5%)	19/428 (4.4%)	18/413 (4.4%)
>6.0 - ≤7.0 mmol/L	2/420 (0.5%)	1/428 (0.2%)	3/413 (0.7%)
>7.0 mmol/L	3/420 (0.7%)	4/428 (0.9%)	4/413 (1.0%)
≥3.0 mmol/L and <LLN			
>ULN - ≤5.5 mmol/L	0/0	0/2	0/0
>5.5 - ≤6.0 mmol/L	0/0	0/2	0/0
>6.0 - ≤7.0 mmol/L	0/0	0/2	0/0
>7.0 mmol/L	0/0	0/2	0/0
Normal/Missing			
>ULN - ≤5.5 mmol/L	16/414 (3.9%)	18/421 (4.3%)	12/408 (2.9%)
>5.5 - ≤6.0 mmol/L	21/414 (5.1%)	18/421 (4.3%)	16/408 (3.9%)
>6.0 - ≤7.0 mmol/L	2/414 (0.5%)	1/421 (0.2%)	3/408 (0.7%)
>7.0 mmol/L	1/414 (0.2%)	4/421 (1.0%)	4/408 (1.0%)
>ULN - ≤5.5 mmol/L			
>ULN - ≤5.5 mmol/L	0/0	0/1	0/3
>5.5 - ≤6.0 mmol/L	0/0	0/1	1/3 (33.3%)
>6.0 - ≤7.0 mmol/L	0/0	0/1	0/3
>7.0 mmol/L	0/0	0/1	0/3
>5.5 - ≤6.0 mmol/L			
>ULN - ≤5.5 mmol/L	0/6	0/4	0/2
>5.5 - ≤6.0 mmol/L	2/6 (33.3%)	1/4 (25.0%)	1/2 (50.0%)
>6.0 - ≤7.0 mmol/L	0/6	0/4	0/2
>7.0 mmol/L	2/6 (33.3%)	0/4	0/2

Source: Table 44, ISS, page 309-310. Submitted to NDA 202992 on 8/18/2011.

Narratives and patient files for Pool 1 treatment-emergent hyperkalemia ≥7 mmol/L were reviewed. Three teriflunomide-treated subjects had hyperkalemia with acute renal failure. Other than these three subjects, narratives did not discuss possible causes of hyperkalemia, and possible causes of hyperkalemia remained unclear. (None were apparent after reviewing lists of concomitant medications and adverse events.) No hemolysis was documented in any of the 9 cases of hyperkalemia >7mmol/L in Pool 1.

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For Pool 1, outlier analyses of urine pH,³⁵ serum calcium,³⁶ urine protein,³⁷ and urine glucose³⁸ were balanced between treatment groups.

Calcium levels were not evaluated in TEMSO, but were done in study 2001. Analyses of PCSA showed that 3/61 (4.9%) of patients on placebo, 0/61 of patients on Teri 7 and 3/57 (5.3%) of patients on Teri 14 had decrease in serum calcium levels of 0.3 mmol/L or more (normal 2.2-2.6 mmol/L) (Source Table T217, 2001 CSR).

- Outlier analyses of renal function in Pool 1

Table 75. Outliers for renal function laboratory abnormalities, Pool 1

Laboratory parameter Baseline by PCSA criteria n/N1 (%)	teriflunomide		
	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)
Creatinine			
Total ^a			
≥150 μmol/L	0/420	4/428 (0.9%)	4/413 (1.0%)
≥30% change from baseline	34/420 (8.1%)	29/428 (6.8%)	31/413 (7.5%)
≥100% change from baseline	0/420	5/428 (1.2%)	5/413 (1.2%)
>3*Baseline or >3 ULN	0/420	3/428 (0.7%)	3/413 (0.7%)
>6 ULN	0/420	0/428	1/413 (0.2%)
Creatinine clearance			
Total ^a			
<30 ml/min (severe renal impairment)	0/420	3/428 (0.7%)	4/413 (1.0%)
≥30-<50 ml/min (moderate renal impairment)	1/420 (0.2%)	2/428 (0.5%)	3/413 (0.7%)
≥50-≤80 ml/min (mild renal impairment)	137/420 (32.6%)	109/428 (25.5%)	107/413 (25.9%)
Uric Acid			
Total ^a			
<120 μmol/L	17/420 (4.0%)	75/428 (17.5%)	121/413 (29.3%)
>408 μmol/L	52/420 (12.4%)	18/428 (4.2%)	12/413 (2.9%)

Based on PCSA values: Potentially clinically significant abnormalities. ^a Regardless of baseline status. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline by baseline PCSA status. Source: Appendix 1.6.2.3 of original ISS.

As shown in this table, overall, increased creatinine above the PCSA criterion was presented by 9.6% of patients on Teri 7, 10.6% of those on Teri 14 and 8.1% of patients on placebo. Ten patients (5 on Teri 7 and 5 on Teri 14) presented doubling of serum creatinine from baseline as compared to none on placebo. Of those with doubling creatinine, six had increase in creatinine 3xULN. Also, three patients in the Teri 7 group and four in the Teri 14 group presented severe renal impairment (defined as creatinine clearance <30 ml/min). These analyses suggest a deleterious effect of teriflunomide in renal function.

³⁵ Available for EFC4049 only. See Table 3 on page 10 of the Sponsor response submitted to NDA 202992 on 10 Jan 2012.

³⁶ Available for 2001 only. See Table 7 on pp. 19-20 of the Sponsor response submitted to NDA 202992 on 10 Jan 2012.

³⁷ See Table 14 on p. 30 of the Sponsor response submitted to NDA 202992 on 10 Jan 2012.

³⁸ See Table 15 on p. 30 of the Sponsor response submitted to NDA 202992 on 10 Jan 2012.

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As per Sanofi's 11/29/11 response to a FDA request for information, each of these seven subjects with estimated creatinine clearance <30ml/min (patient # 006049-124-1209-0023, # 006049-643-3207-0004, # 006049-643-3207-0010, # 006049-643-3208-0004, # 006049-804-3508-0007, # 006049-528-4602-0007 and # 006049-208-4802-0002) was exposed to teriflunomide for over 3 years, and most of them are still participating in the extension study. The creatinine clearance value <30 mL/min was linked to a one-time measurement of abnormal creatinine, which was never confirmed by the retest, and subsequent values were within normal range. In some cases, concomitant AEs were reported, with one patient who temporarily discontinued study drug, waiting for the re-test which was normal. In each case, the re-test showed creatinine values within the normal range and the low value of calculated creatinine clearance (<30 mL/min) was never confirmed.

Sanofi's position is that a single unconfirmed value of elevated creatinine does not raise a safety signal regarding the renal function of patients exposed to teriflunomide. However, all cases occurred on teriflunomide and none on placebo.

A detailed evaluation of the renal effects of teriflunomide was conducted by Dr. Evelyn Mentari, nephrologist, DNP Safety Team (Section 7.7 of this review). Her findings are summarized as follows:

Evaluation of renal function identified 10 patients (2 males, 8 females, ages 19 to 51 years of age), with serum creatinine above normal and nadir creatinine clearance of 8 to 96 cc/minute in Pool 1. Seven of the 10 subjects had creatinine clearances < 30 cc/minute. These measurements occurred between 12 weeks and 2 years after first dose of teriflunomide; most occurred about 1 year after first dose. In each of the 10 subjects the serum creatinine level was normal on the next reported measurement (6 to 48 days later).

All of the 10 subjects had other laboratory tests that corroborated the diagnosis of acute renal failure (e.g., increases blood urea nitrogen, serum phosphorus, and serum uric acid as compared to previous measurements). These multiple laboratory measurements consistent with acute renal failure make laboratory error an unlikely explanation for the increased frequency of serum creatinine $\geq 100\%$ from baseline in teriflunomide-treated subjects. Moreover, three of the 10 patients had serum potassium levels of 6.7 to 7.3 mmol/L (normal 3.4 to 5.4 mmol/L) at the time of the increased serum creatinine. Four of the 10 had missing potassium values.

Renal failure has been described with other drugs that cause hyperuricosuria, as well as in patients with hereditary hyperuricosuria. Acute exercise-induced renal failure has also been described with hereditary hyperuricosuria. The degree of hyperkalemia seen in some of the subjects with acute renal failure in this database is associated with an increased risk of cardiac arrhythmia and death. Data in the teriflunomide database points to the likelihood that there will be cases

of untreated hyperkalemia, accompanied by an increased risk of cardiac arrhythmia, in patients treated with teriflunomide.

Dr. Mentari recommended that information regarding cases of acute renal failure and accompanying hyperkalemia be included in the WARNINGS and PRECAUTIONS section of labeling as well as collecting more detailed information from subjects with reported acute renal failure or elevated serum creatinine in ongoing studies and in the postmarketing setting.

- Urinalysis

Study 2001.

The majority of subjects had normal findings at baseline and endpoint. Abnormal findings for glucose and nitrite were reported in no more than 5 subjects in any single treatment group. Protein in urine was found in similar percentage of patients per treatment group (18.6%, 13.6% and 19.3%) on placebo, Teri 7 and Teri 14. Positive blood in urine was found in 17.0%, 31.9%, 25.0%, of patients on placebo, Teri 7 and Teri 14, respectively, but were mostly transient.

There were no clinically relevant differences between the treatment groups for any of the analytes. Hematuria was reported as a TEAE in 1 subject in the placebo group, but was assessed as not related to study medication.

Study 6049/TEMISO

Review of laboratory data from TEMISO identified hundreds of pages for analyses and listing of pH and specific gravity. No mention of sediment or abnormal findings.

7.4.3.1.2 Chemistry laboratories in other studies

- Pool 2

Chemistry analyses in Pool 2 were consistent with Pool 1. There was no evidence of dose response between Teri 7 and 14, except for the effect in uric acid levels (18.8% had levels <120 umol/L in the Teri 7 group as compared to 27.8% in the Teri 14 group).

Additionally, a PK/PD analysis using data from Pool 1 (study POH02925) showed that an increase in mean teriflunomide trough plasma concentration was associated with a decrease in uric acid and phosphates with a maximum effect relationship. At study endpoint, regardless of gender, the effect was similar for the 7 and 14 mg/day doses: for uric acid the median of mean trough concentration was approximately 26 % of baseline values. For phosphate, there was a decrease of 8-11% of baseline values.

- Adjunctive therapy studies

Chemistry evaluations in adjunctive therapy studies were consistent with the monotherapy studies. There was clear decrease in inorganic phosphorus and uric acid levels in both studies (approximately 10% decrease in plasma levels). No evidence of effect in other parameters.

In Study TES10852, teriflunomide was administered at the dose of 70 mg QD for 4 days followed by 14 mg QD for 8 days to 61 subjects, placebo was administered for 12 days to 65 subjects and a third group of 68 subjects received placebo for 11 days and moxifloxacin the 12th day. Blood samples for creatinine, uric acid, and phosphorus determination were taken at Day-2, Day 5, Day 10, and Day 13, and then during rapid elimination procedure (Day 16, Day 20, Day 24) and EOS visit. A 24-hour urine collection and a blood sampling were performed at Day -2 and Day 10 to investigate creatinine and uric acid clearance.

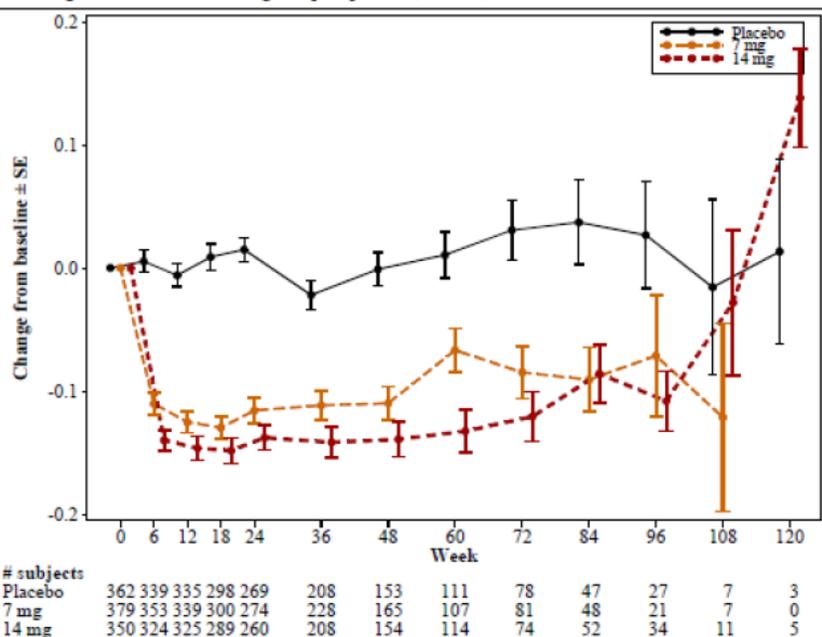
In this study there was no change in serum creatinine and creatinine clearance as compared with placebo. During teriflunomide treatment, serum uric acid decreased by 71 to 82 $\mu\text{mol/L}$ between Day 5 and Day 13 post administration. The values then progressively increased during rapid elimination procedure to baseline values at Day 24 (end of rapid elimination procedure). There was no relevant decrease in serum phosphorus levels from baseline. No urine measurements of phosphorus were done.

The pooling of all repeated-dose studies confirmed the data with a 33 % decrease in uric acid and a slight decrease phosphorus (by 5% maximum). The applicant states that no change in glomerular renal function assessed by creatinine, creatinine clearance or BUN was observed with teriflunomide treatment in the clinical pharmacology studies.

- Ongoing studies (TOWER).

Laboratory results in TOWER were consistent with findings in Pool 1 and 2. Mean changes and outlier analyses showed decreased uric acid and phosphorus serum levels. Percentage of patients with low phosphorus was 8.8% and 14% on Teri 7 and 14 respectively; and 4.1% on placebo. No difference from placebo was observed in change from baseline in creatinine or creatinine clearance, or electrolytes. Analyses of urinalyses showed no effects on pH and specific gravity. No analyses were provided for urine electrolytes, protein or glucose. Of note, the drop in mean serum phosphorus concentration with was very obvious in TOWER, with maximum effect within the first six weeks of treatment (see figure). It is interesting to note that no changes from baseline in mean phosphorus concentrations had been observed in Pool 1.

14.2.8.1.12 Plot of mean change from baseline in Inorganic phosphorus (mmol/L) over time



Best Available Copy

- CK analyses in TOWER

Outlier analyses showed a similar number with increase 3xULN in placebo and Teri 7 group (1.9% each) but higher in the Teri 14 group (3.4%). Analyses of CK by CTCAE are consistent with the outlier analysis (see below).

Table 76. CK elevations in TOWER

14.2.8.4.2 Metabolic function - Number of patients with abnormalities (CTCAE) according to baseline status - Safety population				
Laboratory parameter	Baseline	teriflunomide		
		Placebo (N=363)	7 mg (N=379)	14 mg (N=350)
by CTCAE criteria n/N1 (%)				
CPK				
Total ^a				
>1 - ≤2.5 ULN		60/362 (16.6%)	67/377 (17.8%)	69/350 (19.7%)
>2.5 - ≤5 ULN		4/362 (1.1%)	7/377 (1.9%)	11/350 (3.1%)
>5 - ≤10 ULN		0/362	3/377 (0.8%)	5/350 (1.4%)
>10 ULN		4/362 (1.1%)	0/377	3/350 (0.9%)

Source: Table 14.2.8.4.2. TOWER interim report.

CK increase >5x ULN regardless of baseline CK: 0.8% on Teri 7; 2.3% on Teri 14; 1.1% on placebo. This is consistent with the finding of CK increase for Teri 14 only in study 2001.

Analyses of Glucose level outliers suggest a tendency to mild increased risk of hyperglycemia and less likelihood to develop hypoglycemia in Teri groups (data not shown). Evaluation of mean/median cholesterol, triglycerides, amylase and lipase did not suggest consistent changes from baseline.

IN SUMMARY, chemistry evaluations for renal, metabolic function and electrolytes showed a decrease in uric acid and inorganic phosphorus levels in the monotherapy phase 2&3 studies, clinical pharmacology, adjunctive studies and TOWER study. Drop in uric acid level was 10-30% from baseline and drop in phosphorus was 5-10% from baseline, depending on the study.

There were no consistent changes in glucose, sodium, potassium and chloride. There was a suggestion for CK elevation in patients taking Teri 14 in study 2001 and TOWER, but not in Pool 1. There were no changes in calcium levels in study 2001.

Evaluation of renal function in Pool 1 identified 10 patients with serum creatinine above normal in Pool 1, associated with decreased creatinine clearance. Seven of the 10 subjects had nadir creatinine clearance calculated as less than 30 cc/minute. In each of the 10 subjects, the serum creatinine level was normal on the next reported measurement. The time from abnormal serum creatinine measurement to reported follow-up measurement ranged from 6 to 48 days. All of the 10 subjects had other laboratory tests that corroborated the diagnosis of acute renal failure (e.g., increases blood urea nitrogen, serum phosphorus, and serum uric acid as compared to previous measurements). These multiple laboratory measurements consistent with acute renal failure make laboratory error an unlikely explanation for the increased frequency of serum creatinine $\geq 100\%$ from baseline in teriflunomide-treated subjects. Moreover, three of the 10 patients had serum potassium levels above 6 mmol/L (normal 3.4 to 5.4 mmol/L) and four of the 10 had missing potassium values at the time of the increased creatinine. Renal failure has been described with other drugs that cause hyperuricosuria, as well as in patients with hereditary hyperuricosuria. Acute exercise-induced renal failure has also been described with hereditary hyperuricosuria. (For details regarding renal function, see review by Dr. Mentari, section 7.7 of this review.)

An effect in renal function was not observed in the adjunctive studies, clinical pharmacology and TOWER studies but the exposure to teriflunomide in these patients was shorter.

There were no analyses of serum magnesium and bicarbonate levels or urine electrolytes in Pool 1 or TOWER. Evaluation of urinary pH did not suggest an acid-base balance disorder.

7.4.3.2 Chemistry, Liver related laboratory evaluations

- Monotherapy studies

- Measures of central tendency in Pool 1 and 2

There were no clinically relevant differences between teriflunomide and placebo, or between teriflunomide doses, in changes from baseline in liver enzyme values (ALT, AST, ALK P, Total BR) over time in Pool 1 or 2 (see below; other data not shown). Changes from baseline in ALT values in Pool 1 were slightly greater in the teriflunomide groups as compared to placebo, but did not appear to be clinically relevant.

- Changes from baseline in ALT in Pool 1.

Table 77. Changes from baseline in ALT over time, Pool 1.

	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Baseline			
Value			
Number	421	429	415
Mean (SD)	0.527 (0.259)	0.544 (0.255)	0.520 (0.245)
Median	0.450	0.471	0.467
Q1 : Q3	0.353 : 0.618	0.372 : 0.618	0.353 : 0.618
Min : Max	0.17 : 1.97	0.08 : 1.73	0.18 : 1.71
Week 108			
Value			
Number	251	267	249
Mean (SD)	0.522 (0.241)	0.638 (0.394)	0.611 (0.288)
Median	0.465	0.529	0.529
Q1 : Q3	0.382 : 0.581	0.412 : 0.735	0.419 : 0.735
Min : Max	0.21 : 2.00	0.24 : 3.63	0.21 : 1.86
Change from baseline			
Number	251	267	249
Mean (SD)	0.009 (0.233)	0.112 (0.368)	0.095 (0.310)
Median	0.029	0.088	0.029
Q1 : Q3	-0.059 : 0.116	-0.029 : 0.206	-0.070 : 0.209
Min : Max	-1.00 : 0.82	-1.24 : 2.88	-0.77 : 1.41
Endpoint value			
Value			
Number	420	424	411
Mean (SD)	0.808 (1.720)	0.805 (1.095)	0.847 (1.788)
Median	0.471	0.534	0.559
Q1 : Q3	0.382 : 0.629	0.412 : 0.767	0.412 : 0.765
Min : Max	0.13 : 19.83	0.21 : 11.79	0.20 : 32.38
Change from baseline			
Number	420	424	411
Mean (SD)	0.280 (1.718)	0.263 (1.079)	0.326 (1.776)
Median	0.029	0.070	0.088
Q1 : Q3	-0.067 : 0.133	-0.047 : 0.206	-0.047 : 0.267
Min : Max	-1.00 : 19.57	-1.24 : 11.35	-1.03 : 31.71

Appendix 1.6.3.1.1

The following table showed outlier analyses of liver-related laboratory evaluations.

- Outliers/evaluation by CTCAE criteria

Table 78. Liver related lab evaluations by CTCAE in Pool 1

Laboratory parameter	teriflunomide			
	Baseline by CTCAE criteria n/N1 (%)	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)
ALT				
Total ^a				
>1 - ≤3 ULN		124/420 (29.5%)	204/428 (47.7%)	205/413 (49.6%)
>3 - ≤5 ULN		15/420 (3.6%)	15/428 (3.5%)	16/413 (3.9%)
>5 - ≤20 ULN		9/420 (2.1%)	9/428 (2.1%)	7/413 (1.7%)
>20 ULN		2/420 (0.5%)	1/428 (0.2%)	2/413 (0.5%)
AST				
Total ^a				
>1 - ≤3 ULN		72/420 (17.1%)	137/428 (32.0%)	141/413 (34.1%)
>3 - ≤5 ULN		2/420 (0.5%)	7/428 (1.6%)	6/413 (1.5%)
>5 - ≤20 ULN		11/420 (2.6%)	5/428 (1.2%)	5/413 (1.2%)
>20 ULN		0/420	0/428	1/413 (0.2%)
Alkaline Phosphatase				
Total ^a				
>1 - ≤2.5 ULN		36/420 (8.6%)	45/428 (10.5%)	36/413 (8.7%)
>2.5 - ≤5 ULN		1/420 (0.2%)	0/428	2/413 (0.5%)
>5 - ≤20 ULN		0/420	2/428 (0.5%)	0/413
>20 ULN		0/420	0/428	0/413
GGT				
Total ^a				
>1 - ≤2.5 ULN		58/420 (13.8%)	50/428 (11.7%)	49/413 (11.9%)
>2.5 - ≤5 ULN		10/420 (2.4%)	18/428 (4.2%)	14/413 (3.4%)
>5 - ≤20 ULN		2/420 (0.5%)	9/428 (2.1%)	5/413 (1.2%)
>20 ULN		0/420	0/428	0/413
Total bilirubin				
Total ^a				
>1 - ≤1.5 ULN		30/420 (7.1%)	29/428 (6.8%)	23/413 (5.6%)
>1.5 - ≤3 ULN		14/420 (3.3%)	12/428 (2.8%)	10/413 (2.4%)
>3 - ≤10 ULN		0/420	0/428	1/413 (0.2%)
>10 ULN		0/420	0/428	0/413

Source: Table 27, ISS. Total mean values regardless of baseline values.

As noted in this table, the percentage of patients with ALT elevation ≤ 3x ULN was greater in teriflunomide groups as compared to placebo. However, the incidence of ALT elevations >3xULN was similar among groups: 6.2% on placebo, 5.8% on Teri 7 and 6.1% on Teri 14.

The risk of increased GGT >5x ULN was higher in teriflunomide treated patients (2.1% and 1.2% in the Teri 7 and 14 groups) as compared to placebo (0.5%), suggesting a cholestatic

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component for liver toxicity. There was no difference in the incidence of elevated alkaline phosphatase.

More patients developed BR >1.5xULN in the placebo group as compared to teriflunomide. However, of those, the great majority already had elevated BR at baseline (14 pts on placebo, 10 patients on Teri 7 and 11 patients on Teri 14). (Data not shown)

A Kaplan-Meier plot of time to onset of ALT elevation >3xULN in Pool 1 showed no difference with placebo (data not shown).

- Time to ALT normalization

ALT elevations <3xULN resolved without drug discontinuation in 90% of cases (data not shown).

As per protocol, patients with ALT >3xULN twice were discontinued from the study. Most of these patients also underwent rapid elimination/washout with either cholestyramine or charcoal. In response to a FDA request for information Sanofi clarified that of the patients who discontinued from Pool 1 because of ALT >3xULN, all patients on Teri 14, all patients on placebo and all but 3 patients on Teri 7 underwent rapid elimination with cholestyramine or charcoal (mostly cholestyramine). All cases eventually resolved.

Normalization of ALT elevation among patients who discontinued because $ALT \geq 3x ULN$ or who had $ALT \geq 3x ULN$ at the time of last dose of study drug is presented in the following table.

Table 79. Frequency of normalization (to \leq ULN or return to baseline) for patients discontinued due to ALT \geq 3x ULN or with ALT \geq 3x ULN at time of discontinuation/completion. Pool 1.

	Normalization category	Normalization time after elevation	Placebo (N=17)	Teri 7 (N=14)	Teri 14 (N=14)
All			17	14	14
Underwent washout			17 (100%)	11 (78.6%)	14 (100%)
	After last dose date	\leq 2 weeks	1	0	1 (7.1%)
		>2 - 4 weeks	0	2 (14.3%)	2 (14.3%)
		>4 - 8 weeks	3 (17.6%)	1 (7.1%)	4 (28.6%)
		>8 weeks	5 (29.4%)	6 (42.9%)	3 (21.4%)
	Did not normalize by end of study		8 (47.1%)	2 (14.3%)	4 (28.6%)
Patients did not undergo washout			0	3 (21.3%)	0
	After last dose date	\leq 2 weeks	0	0	0
		>2 - 4 weeks	0	0	0
		>4 - 8 weeks	0	0	0
		>8 weeks	0	1 (7.1%)	0
	Did not normalize by end of study		0	2 (14.3%)	0

Source: table 7. Modified from Table 2 response to request for information submitted 4/23/12.

As per this table, all patients who had ALT \geq 3xULN in the Teri 14 and placebo groups underwent washout. Of those, on Teri 14, 50% of those resolved within 8 weeks, 21% resolved after 8 weeks and 29% (n=4) did not resolve after discontinuation and washout, as compared to 47% who did not resolve on placebo.

A table submitted on 4/23/12 in response to a FDA request for information including the date of last ALT value >3x ULN and the date of last available follow up ALT in these patients shows that the values were obtained only one week to 2 months apart for most patients. The applicant states that ALT elevation eventually resolved to normal or near normal (maximum 1.6 x ULN) in all patients. Evaluation of the narratives of these cases confirms that most of the cases listed as “not resolved” actually resolved, which is reassuring, but raises doubts about the reliability of the ALT analyses of recovery conducted in the NDA application.

- ALT analyses in other studies

Table 80. ALT analyses in TOWER

Laboratory criteria Baseline PCSA criteria n/N1 (%)	Placebo (N=363)	teriflunomide	
		7 mg (N=379)	14 mg (N=350)
ALT			
Total*			
>3 ULN	12/362 (3.3%)	23/377 (6.1%)	18/350 (5.1%)
>5 ULN	8/362 (2.2%)	6/377 (1.6%)	7/350 (2.0%)
>10 ULN	3/362 (0.8%)	1/377 (0.3%)	2/350 (0.6%)
>20 ULN	1/362 (0.3%)	0/377	0/350

Source: Table 40 of TOWER interim report.

The risk of ALT elevation >3xULN in TOWER was greater in patients treated with teriflunomide as compared to placebo. However for elevations >5x ULN it was similar or lower than placebo.

An additional analysis of ALT elevation ≥ 3xULN at least twice during the study was submitted on 4/17/12 at the FDA request.

ALT elevations ≥3x ULN at least twice in TOWER.

ALT criteria	Period	Placebo (N=363)	teriflunomide	
			7 mg (N=379)	14 mg (N=350)
≥3 ULN	Overall	9/362 (2.5%)	11/377 (2.9%)	8/350 (2.3%)
	During treatment	4/359 (1.1%)	4/373 (1.1%)	5/348 (1.4%)
	During wash-out	6/62 (9.7%)	4/76 (5.3%)	4/66 (6.1%)

As per this table, approximately half of the cases occurred during washout.

ALT elevations in TENERE are as follows:

Table 81. Liver enzyme elevation in TENERE.

Laboratory parameter	teriflunomide			
	Baseline by CTCAE criteria n/N1 (%)	7 mg (N=110)	14 mg (N=110)	Rebif (N=101)
ALT				
Total ^a				
>1 - ≤3 ULN		40/110 (36.4%)	47/110 (42.7%)	58/101 (57.4%)
>3 - ≤5 ULN		5/110 (4.5%)	8/110 (7.3%)	12/101 (11.9%)
>5 - ≤20 ULN		2/110 (1.8%)	3/110 (2.7%)	4/101 (4.0%)
>20 ULN		0/110	0/110	0/101
Total bilirubin				
Total ^a				
>1 - ≤1.5 ULN		4/110 (3.6%)	10/110 (9.1%)	3/101 (3.0%)
>1.5 - ≤3 ULN		3/110 (2.7%)	0/110	1/101 (1.0%)
>3 - ≤10 ULN		0/110	0/110	0/101
>10 ULN		0/110	0/110	0/101

Source: Table 32. 120-day SUR.

There seems to be a dose response in the number of patients with ALT elevation between Teri 7 and Teri 14. The number of patients with ALT elevations is greater with Rebif than with Teriflunomide. However, the risk of any increase in total BR was greater in teriflunomide groups (6.3% on Teri 7, 9% on Teri 14) than on Rebif (3%). There were no cases of ALT >3xULN and total BR >2x ULN. This is a small study, not powered to adequately evaluate differences in safety between teriflunomide and Rebif.

7.4.2.3 Hematology parameters

- Measures of central tendency

Mean change from baseline at endpoint value for hemoglobin, WBC, Lymphocytes, neutrophils and platelets are presented as follows

Table 82. Change from baseline at study endpoint for hematology values, Pool 1.

	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
White cell count (Giga/L)			
Baseline			
Value			
Number	419	429	415
Mean (SD)	6.99 (2.11)	6.89 (1.98)	6.79 (1.95)
Median	6.60	6.52	6.46
Q1 : Q3	5.47 : 8.07	5.44 : 7.98	5.38 : 7.73
Min : Max	3.6 : 17.5	3.8 : 16.5	3.4 : 14.5
Change from baseline			
Number	418	424	411
Mean (SD)	-0.01 (2.00)	-0.67 (1.81)	-0.85 (1.80)
Median	-0.00	-0.60	-0.86
Q1 : Q3	-1.00 : 0.92	-1.59 : 0.21	-1.80 : 0.14
Min : Max	-8.5 : 12.4	-8.3 : 9.1	-8.0 : 8.0
Neutrophil count (Giga/L)			
Baseline			
Value			
Number	419	429	415
Mean (SD)	4.45 (1.79)	4.40 (1.70)	4.31 (1.64)
Median	4.02	4.07	3.98
Q1 : Q3	3.21 : 5.27	3.20 : 5.24	3.13 : 5.08
Min : Max	1.5 : 14.6	1.5 : 13.3	1.5 : 11.5
Change from baseline			
Number	418	424	410
Mean (SD)	0.00 (1.87)	-0.47 (1.66)	-0.59 (1.63)
Median	-0.10	-0.45	-0.60
Q1 : Q3	-0.82 : 0.76	-1.28 : 0.27	-1.42 : 0.30
Min : Max	-8.6 : 14.4	-8.5 : 9.8	-7.0 : 7.1
Lymphocyte count (Giga/L)			
Baseline			
Value			
Number	419	429	415
Mean (SD)	1.97 (0.57)	1.94 (0.54)	1.92 (0.57)
Median	1.90	1.88	1.85
Q1 : Q3	1.56 : 2.31	1.55 : 2.25	1.51 : 2.20
Min : Max	0.6 : 4.0	0.7 : 4.3	0.6 : 5.0
Change from baseline			
Number	418	424	411
Mean (SD)	0.00 (0.56)	-0.22 (0.48)	-0.28 (0.47)
Median	0.00	-0.23	-0.29
Q1 : Q3	-0.26 : 0.32	-0.51 : 0.05	-0.54 : -0.03
Min : Max	-1.9 : 4.1	-2.1 : 1.6	-1.8 : 3.4

Source: Appendix 1.6.1.1, original ISS.

Table 81. cont. Change from baseline at study endpoint for hematology values, Pool 1.

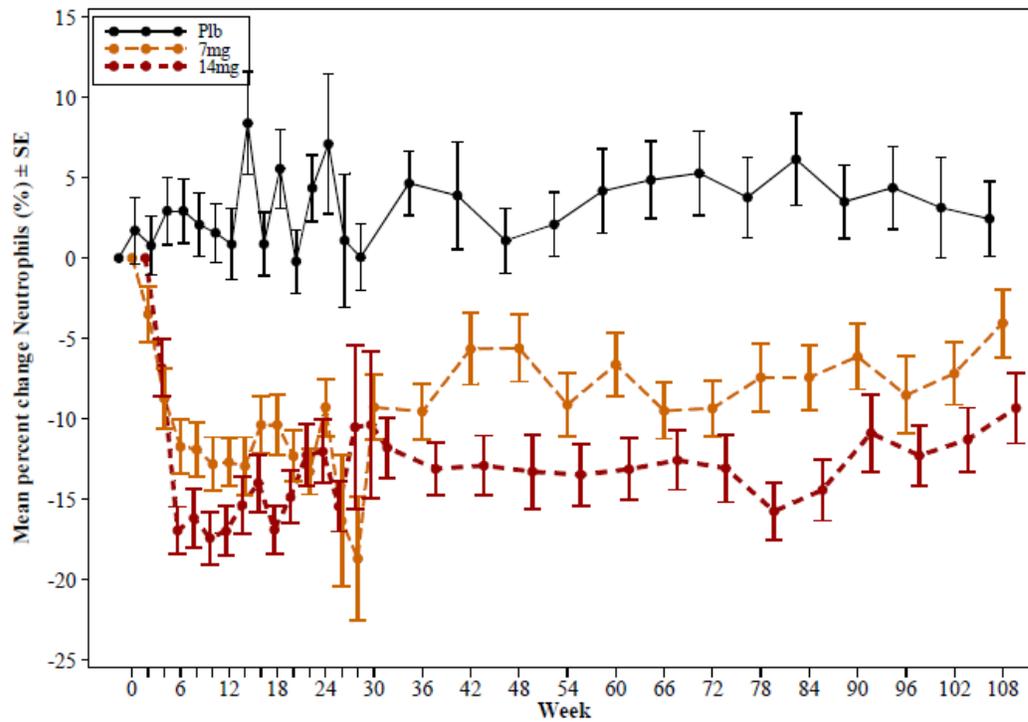
	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
RBC (Tera/L)			
Baseline			
Value			
Number	419	429	415
Mean (SD)	4.698 (0.399)	4.716 (0.434)	4.689 (0.431)
Median	4.700	4.680	4.700
Q1 : Q3	4.400 : 5.000	4.400 : 5.000	4.400 : 4.950
Min : Max	3.66 : 6.60	3.67 : 6.20	3.60 : 6.20
Change from baseline			
Number	418	424	411
Mean (SD)	-0.057 (0.267)	-0.037 (0.275)	-0.033 (0.259)
Median	-0.060	-0.015	0.000
Q1 : Q3	-0.200 : 0.100	-0.200 : 0.100	-0.200 : 0.100
Min : Max	-1.10 : 1.00	-1.20 : 1.20	-0.80 : 1.20
Hemoglobin (mg/L)			
Baseline			
Value			
Number	419	429	415
Mean (SD)	138.6 (13.6)	139.8 (13.0)	138.7 (13.2)
Median	138.0	139.0	138.0
Q1 : Q3	129.0 : 149.0	130.0 : 148.0	131.0 : 148.0
Min : Max	94 : 183	102 : 176	89 : 173
Change from baseline			
Number	418	424	411
Mean (SD)	-1.3 (9.5)	-1.9 (8.9)	-2.4 (8.5)
Median	-2.0	-2.0	-2.0
Q1 : Q3	-7.0 : 4.0	-7.0 : 3.0	-8.0 : 3.0
Min : Max	-49 : 45	-39 : 35	-37 : 44
Platelet count (Giga/L)			
Baseline			
Value			
Number	419	427	412
Mean (SD)	268.5 (61.3)	269.9 (65.1)	265.8 (63.9)
Median	262.0	263.0	254.5
Q1 : Q3	224.0 : 305.0	224.0 : 308.0	219.0 : 303.0
Min : Max	146 : 517	136 : 547	106 : 535
Change from baseline			
Number	418	422	408
Mean (SD)	8.2 (47.2)	-14.1 (40.8)	-14.7 (45.1)
Median	5.0	-13.0	-14.0
Q1 : Q3	-18.0 : 30.0	-40.0 : 11.0	-45.0 : 14.0
Min : Max	-165 : 382	-173 : 118	-205 : 160

Source: Appendix 1.6.1.1, original ISS.

There were no differences in the change from baseline in eosinophils, basophils and monocytes in Pool 1 (data not shown).

The plot of percentage decrease in neutrophil count in Pool 1 is presented below:

Table 83. Neutrophils (%) mean percent change from baseline over time, Pool 1



# subjects	419	359	366	347	368	368	354	304	290	284	277	268	262	260	257	256	248	244	249	
Plb																				
7mg	429	367	365	347	373	369	368	316	296	290	289	279	278	272	279	276	258	268	267	
14mg	415	350	339	337	355	352	341	296	280	283	271	265	267	265	260	248	252	252	247	

Source: Figure 12, original ISS. Only central laboratory values are taken into account in this analysis.

The mean neutrophil count decreases from baseline occurred mainly during the first 6 weeks for both teriflunomide treatment groups compared to placebo, and then stabilized. For lymphocytes, the decrease was mainly during the first 6 weeks but it continued to drop slightly until the end of the 2 year period.

The plot of mean percent change from baseline over time for lymphocyte count in Pool 1 is presented below.

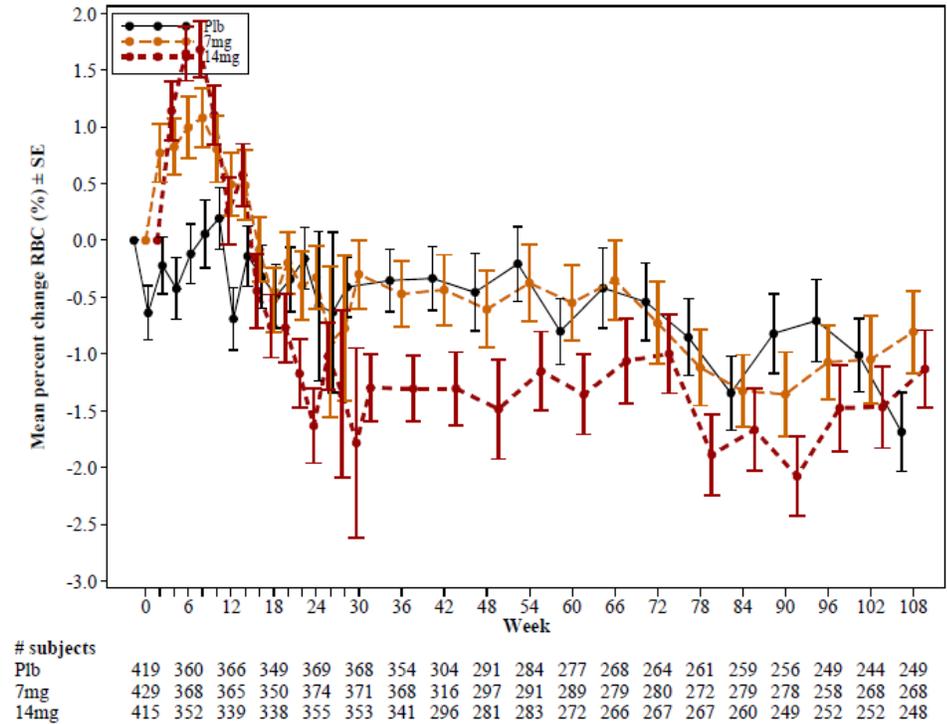
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Evaluation of RBC over time showed an overlap for Teri 7 and placebo. Teri 14 appears to separate from Teri 7 and placebo between weeks 30 and 54, but overall there does not seem to be an effect on RBC as compared to placebo in Pool 1.

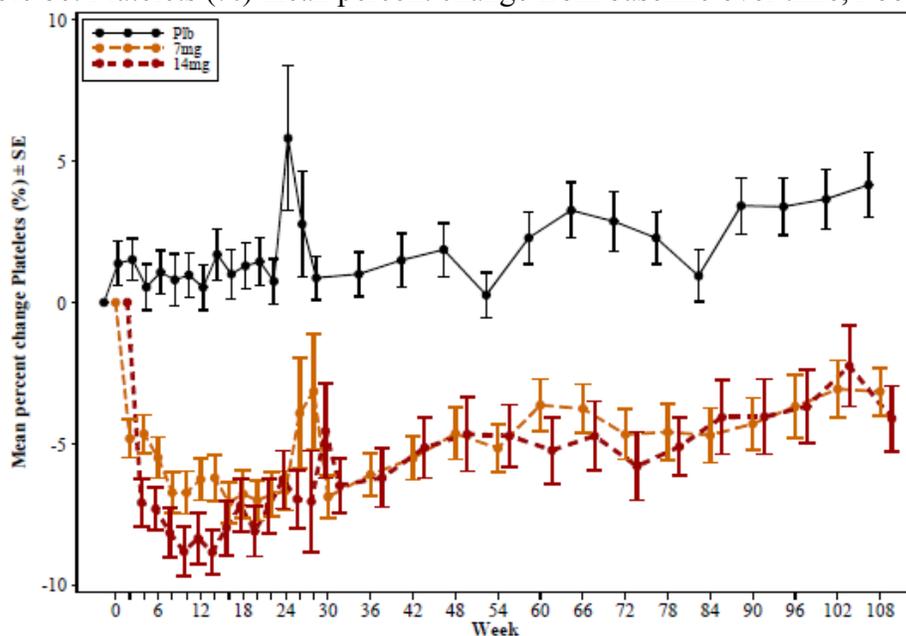
Figure 15. RBC (%) mean change from baseline over time, Pool 1.



Source: Table 1.6.1.1.13, original ISS.

Regarding platelet counts, in Pool 1 there was clear evidence of an effect on platelet counts for teriflunomide 7 and 14, as compared to placebo (see plot below), with no evidence of a dose response.

Table 86. Platelets (%) mean percent change from baseline over time, Pool 1



# subjects	Plb	7mg	14mg
0	419	427	412
6	358	364	347
12	364	361	333
18	344	346	336
24	367	369	349
30	367	368	346
36	351	364	336
42	300	311	290
48	284	290	276
54	280	286	274
60	276	284	267
66	266	273	263
72	263	276	262
78	259	266	262
84	257	276	256
90	251	277	244
96	248	252	248
102	243	264	246
108	249	266	243

Source: Table 1.6.1.1.19 original ISS.

Most changes in platelet count occur during the first 12 weeks, with some stabilization thereafter.

- Outlier analyses for hematologic abnormalities

Analyses of available hematologic parameters by PCSA criteria are shown below.

Table 87. WBC, neutrophil and lymphocyte analyses by CTCAE criteria, Pool 1

Laboratory parameter	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)
Baseline by PCSA criteria n/N1 (%)			
WBC			
Total ^a			
<3 Giga/L (non-black); <2 Giga/L (black)	4/420 (1.0%)	26/428 (6.1%)	41/413 (9.9%)
Neutrophils			
Total ^a			
<1.5 Giga/L (non-black); <1.0 Giga/L (black)	20/420 (4.8%)	43/428 (10.0%)	60/413 (14.5%)
<0.5 Giga/L	0/420	2/428 (0.5%)	0/413
Lymphocytes			
Total ^a			
>4.0 Giga/L	25/420 (6.0%)	9/428 (2.1%)	11/413 (2.7%)
<0.8 Giga/L	20/420 (4.8%)	31/428 (7.2%)	40/413 (9.7%)
<0.5 Giga/L	4/420 (1.0%)	3/428 (0.7%)	8/413 (1.9%)

Source: Appendix 1.6.1.3.3. Original ISS. PCSA: Potentially clinically significant abnormalities.

^a Regardless of baseline. Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once in the TEAE period. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline.

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Analyses of WBC assessments by CTCAE in Pool 1 showed that a higher proportion of patients had grade 1 (<LLN to 3 Giga/L) and grade 2 (<3 Giga/L to ≥ 2 Giga/L) decreases in WBC in the teriflunomide groups as compared to placebo. Cases of neutropenia were discussed in the SAE and discontinuations due to AE sections of this review.

One patient in each teriflunomide group had a grade 4 lymphocyte count decrease (<0.2 Giga/L) versus none in placebo. These cases are as follows:

- **6049/3009/0015**, a 42-year-old female patient receiving teriflunomide 7 mg for approximately 5.5 months, with normal values at baseline, had low lymphocytes at 0.18 Giga/L with normal WBC, Hemoglobin and platelets. Study medication was continued. The retest performed about 1.5 months later was normal. *Possible lab error.*
- **6049/4101/0018**, a 39-year-old male patient with normal values at baseline, developed low lymphocytes at 0.17 Giga/L approximately 1 year into Teri 14 treatment. He had normal WBC, neutrophils, hemoglobin and platelets. The patient discontinued the study due to lack of efficacy and no other hematology results were recorded. No concomitant AEs were reported in this patient. *Event possibly drug related.*

Eosinophilia in Pool 1

As noted above, there was a higher percentage of patients with leukopenia, neutropenia and lymphopenia in teriflunomide treated patients, as compared to placebo. The only blood cells that showed a higher percentage of patients with increased counts in teriflunomide treated patients were the eosinophils. The table below shows patients with increased absolute eosinophil counts that fulfill the definition of potentially clinically significant abnormality in Pool 1.

Table 88. Patients with potential clinically significant increase in eosinophil count, Pool 1¹

Placebo (N= 421)	Teriflunomide 7 (N= 429)	Teriflunomide 14 (N= 415)
33/420 (7.9%)	36/428 (8.4%)	49/413 (11.9%)

¹Eosinophil count > 0.5 Giga/L independent of baseline value. Includes study 6049 and 2001. Source: Appendix 1.6.1.3.3. Original ISS.

The criterion for potentially clinically significant abnormality in study 2001 was slightly different than in study 6049, and consisted of an increase of 0.37 Giga/L from baseline. In this analysis, 4.9% of patients on Teri 7, 8.8% of patients on Teri 14 and 1.6% of patients on placebo presented eosinophil counts in the range of PCSA, out of approximately 60 patients per treatment group (Source, Table 18, study 2001 CSR, data not shown).

As per listings of patients with eosinophil counts in the range of PCSA submitted on 5/1/12 at the FDA request, most patients did not have concurrent adverse events or laboratory abnormalities at the time of the elevated eosinophil count, and a few patients had symptoms consistent with an allergic reaction (e.g. urticaria). I reviewed the AE datasets for cases with reported absolute eosinophil count >1 Giga/L (three patients in study 6049).

- 6049/3201/0009:** 35 yo F on Teri 14. At baseline all laboratory values were normal, including an eosinophil count of 0.08 Giga/L, normal electrolytes and liver enzymes. Patient started treatment on 11/8/2005. ALT was minimally elevated at visit 8 (43 U/L, normal up to 34) and eosinophil count was normal. A diagnosis of **toxic hepatitis** was made on 4/4/2006 (Day 148) of treatment, based on ALT of 1101 U/L (normal up to 34), AST 691 U/L (normal up to 34), Total bili 36 UMOL/L (normal up to 21) and ALP 326 U/L (normal up to 106). Her absolute eosinophil count on that day was **1.03 Giga/L**. This is the patient with suspected DILI discussed in the SAE section of this review. ALT and BR normalized on 9/13/2006 after 5 weeks of hospitalization, plasmapheresis and cholestyramine washout. No further eosinophil count is available. (Neither there are albumin or PT values during hospitalization.)

Of note, this patient is listed as having no data regarding concomitant AE or abnormal laboratories in the listing submitted on 5/1/12.

- Patients 6049/2407/0031 and 2415/0004** did not have AEs consistent with drug allergy.

The presence of eosinophilia and ALT elevation in patient 6049/3201/0009 could favor a hypersensitivity reaction to teriflunomide. However, the other two patients with eosinophil count >0.5 Giga/L did not have AE consistent with a drug hypersensitivity reaction.

Anemia in Pool 1

Table 89. Patients with CTCAE abnormalities for hemoglobin, Pool 1

Laboratory parameter Baseline by CTCAE criteria n/N1 (%)	teriflunomide		
	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)
Hemoglobin (anemia)			
Total ^a			
≥100 g/L and <LLN	45/420 (10.7%)	57/428 (13.3%)	64/413 (15.5%)
≥80 - <100 g/L	19/420 (4.5%)	9/428 (2.1%)	13/413 (3.1%)
<80 g/L	0/420	1/428 (0.2%)	4/413 (1.0%)

Source: Appendix 1.6.1.2.1. CTCAE: Common Terminology Criteria for Adverse Events. ^aRegardless of baseline

Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once in the TEAE period. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline by baseline CTCAE status.

For CTCAE including condition based only on change from baseline, the denominator is restricted on patients having a baseline and a post-baseline values.

The proportion of patients with CTCAE grade 1 anemia in Pool 1 was slightly higher in the teriflunomide groups than in placebo with a trend for a dose effect (teriflunomide 7 mg: 13.3%; teriflunomide 14 mg: 15.5%; placebo 10.7%). The proportion of patients with anemia

grade 2 was similar between treatment groups. Five patients had anemia grade 3 on teriflunomide (one on Teri 7 and 4 on Teri 14).

- **6049/1209/0005**. 33 yo F had normal baseline Hb. She presented low Hb count on Day 218, with nadir of 78 Giga/L approximately 1 ½ years into Teri 7 treatment. She was treated with ferrous sulfate. She also had an AE of vitamin B12 deficiency that required treatment. The patient continued teriflunomide treatment.

The narrative for this patient refers to a diagnosis of hepatic steatosis but does not mention any work up done for the anemia.

The 4 patients with a grade 3 anemia (Hb <80 g/L) in the teriflunomide 14 mg group were:

- **6049/3005/0009**, A 45-year-old female patient on Teri 14 with normal baseline hematology parameters had an isolated hemoglobin value of grade 3 anemia (Hb 69 G/L) on Day 422, reported as non-serious. Study medication was continued and the patient recovered in 8 weeks. A grade 2 isolated anemia recurred 3 month later (Day 547) and persisted for 6 month. The anemia recurred on Day 1359 (grade 3, Hb 63 G/L) in the extension study and recovered in 7 months. Mean corpuscular volume (MCV) suggested a microcytic anemia. Other blood cell lines remained normal. The patient continued treatment and entered in the extension study.

There is no mention of work up done to evaluate a whether a source of bleeding could be found. Additional information submitted on April 12, 2012 indicates that the patient was referred to a hematologist for further work up of anemia but the final diagnosis is not available.

- **6049/3210/0003**, A 42 yo F on Teri 14 had CTCAE grade 1 anemia at baseline, and anemia grade 3 with hemoglobin value of 69 G/L, 3 months into the study, concomitant with grade 2 neutropenia (1.32 Giga/L), grade 2 lymphopenia (0.67 Giga/L), and normal platelets. Study medication was continued and the retest 1 week later showed hemoglobin back to baseline value with improving values for neutrophils and lymphocytes. The patient continued the study treatment.
- **6049/1209/0021**, A 32 yo F had hemoglobin of 79 g/L 6 months into Teri 14 treatment, along with grade 1 neutropenia (1.76 Giga/L) and grade 1 platelet count decrease (134 Giga/L). Study medication was continued and all these parameters were back to normal range at a retest 2 days later. *There is no mention of concurrent infection or concomitant medications. These lab results may have been a lab error.*
- **6049/2401/0005**, A 50 yo M had a SAE leading to drug discontinuation. He had an ANC of 0.90 Giga/L, associated with Hb of 40 g/L and platelets of 89 giga/L on Day 364 (11 months) into Teri 14 treatment. This appears to be a case of pancytopenia. However, the event did not lead to study drug discontinuation. He recovered 1 month later and continued in the study for more than 5 years with all subsequent normal WBCs. *Again, there is no mention of concurrent infection or concomitant medications. The counts recovered without drug discontinuation. These lab results may have been a lab error. If not an error, the event does not appear related to teriflunomide.*

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Thrombocytopenia/low platelet count in Pool 1

In Pool 1, there were 4 cases of platelet count decreased and five cases of thrombocytopenia on teriflunomide (platelet count decreased: 3 on Teri 7, one on Teri 14; thrombocytopenia 3 on Teri 7, 2 on Teri 14). They were 5 female, 3 male, ages 27 to 61. None was considered serious or led to study discontinuation (two of the patients did not complete the study for unrelated reasons). Mean time to onset was 170 days (42 to 658 days). The cases were mild to moderate and recovered without drug discontinuation. Several cases presented intermittently during the base study and extension. There were no such cases on placebo.

Two of the patients reported menorrhagia (heavy periods) that may or may not have been related to low platelet counts. One of these patients later reported multiple gastric ulcers (patient 002001-124-0019-0002). Additionally one patient had hemorrhoidal bleeding. The cases of thrombocytopenia/platelet count decreased in Pool 1 are summarized below.

Pt ID	Age sex	PT	Rel Day onset	Duration (days)	Comments (based on datasets)
Teri 7					
002001-124-0019-0002	44 F	Platelet count decreased	42	54	Continued to have intermittent low platelet count during extension. One episode of menorrhagia on Day 128 to 161 and multiple gastric ulcers on Day 998, ongoing at time of last FU.
002001-124-0019-0006	61 M	Platelet count decreased	86 182	14 15	Continued to have intermittent low platelet count Day 280-339 and 350 to 422, and Day 967 til last FU. Also low neutrophil count Day 407 to 422. Burning sensation bil legs, R flank and shin Day 1147 to 1195.
006049-616-3008-0002	53 M	Platelet count decreased	113	43	Platelets down to 102 Giga/L. ALT 2xULN Day 57-113. Cervical myelopathy Day 124-764. Low platelets again on Day 771 to 848. No bleeding or infection.
006049-246-2202-0001	31 F	Thrombocytopenia	168	41	Neutropenia/leukopenia Day 26-54, Day 114-208. Flu/otitis/sinusitis Day 51 to 64. Cervical radiculopathy L arm started Day 9. Cervical radiculopathy R arm started Day 70. Low phosphorus Day 82. Paresthesia of feet Day 92-100. Alopecia Day 114-205 led to permanent discontinuation.
006049-276-2005-0006	36 F	Thrombocytopenia	211	8	Herpes exacerbation, Day 43. Elevation of PTT Day 85 and 253. Intermittent paresthesia leg; Day 255; fingers Day 589; facial Day 1290. Intermittent headache and vertigo.
006049-616-3007-0004	32 M	Thrombocytopenia	84	15	Bronchitis Day 45, ulnar entrapment neuropathy L side Day 594. Continued with intermittent thrombocytopenia Days 784-798 and Days 924-966. Hemorrhoidal bleeding on Day 1622.

Teri 14					
006049-792-5005-0003	27 M	Platelet count decreased	29	603	Described as moderate. No other events.
002001-124-0015-0001	34 F	Thrombocytopenia	127	72	Day 29: contusion (skin bruises legs and arms) no end date. Menorrhagia (heavy periods) started Day 51, no end date. Flu Day 103, upper resp infect Day 103.
006049-276-2004-0019	39 F	Thrombocytopenia	658	9	Upper resp infections. Abdominal rash started on Day 252; joint pains started Day 396.

AE datasets, original ISS.

Thrombocytopenia/platelet count decreased occurred on teriflunomide but not on placebo. Two of the cases of thrombocytopenia occurred in patients who also reported low neutrophil counts at some point during the study.

Outlier analysis of platelet counts was consistent with bone marrow suppressive effect of teriflunomide (see table)

Table 90. PCSA in platelet counts, Pool 1

Laboratory parameter Baseline by PCSA criteria n/N1 (%)	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Platelets Total ^a			
<100 Giga/L	0/420	4/428 (0.9%)	3/413 (0.7%)
<75 Giga/L	0/420	1/428 (0.2%)	0/413

Source: Appendix 1.6.1.3.1, original ISS.

There was no evidence of increased risk of bone marrow AESI based on most intrinsic (age, race, BMI, baseline EDSS) or extrinsic (region, previous disease modifying MS therapy, selected concomitant medications) factors. Evaluation of bone marrow AESI by gender suggests that the risk was greater in females.

7.4.3.4 Coagulation parameters

7.4.3.4.1 Coagulation in monotherapy studies (Pool 1 and 2)

Coagulation parameters were not collected in Studies 2001 and LTS6048. Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) data were collected in 6049/TEMPO and LTS6050.

PT and APTT in study 6049/TEMPO

- Measures of central tendency

There was no difference in mean and median change from baseline in PT and PTT in teriflunomide treated patients as compared to placebo at the endpoint value (data not shown). (Source: Table 14.2.8.1.12, and 14.2.8.1.13, Study 6049 CSR.)

- Outlier analyses

There was no difference in the number/percentage of patients with CTCAE increase in APTT in study 6049.

A similar number of patients presented low aPTT values at least once during the study in the teriflunomide and placebo groups. Lower number of patients presented high aPTT values at least once during the study in the teriflunomide groups (see below), but the difference is small and the clinical significance of this finding is unclear.

Table 91. Number of patients with out of normal range values during the treatment period, study 6049, safety population.

Laboratory criteria Baseline status Post-baseline	Placebo (N=360)	teriflunomide	
		7 mg (N=368)	14 mg (N=358)
aPTT			
Total*			
Low	274/355 (77.2%)	274/361 (75.9%)	266/350 (76.0%)
High	122/355 (34.4%)	116/361 (32.1%)	101/350 (28.9%)

Source: Table 14.2.8.1.14. *Total: regardless of baseline.

7.4.2.3.2 Coagulation in other studies

Laboratory evaluations identified a slight decrease in activated partial thromboplastin time values over time in both teriflunomide groups (endpoint values: -0.28 seconds and -0.51 seconds for 7 mg + IFN- β and 14 mg + IFN- β groups, respectively), while a slight increase was observed in the placebo + IFN- β group (0.55 seconds).

Similarly, there was a slight decrease in activated partial thromboplastin time values over time in both teriflunomide groups (endpoint values: -1.61 seconds and -0.89 seconds for 7 mg + GA and 14 mg + GA groups, respectively), while a slight increase was observed in the placebo + GA group (0.13 seconds). *The clinical significance of this decrease in APTT is unclear.*

7.4.3 Vital Signs

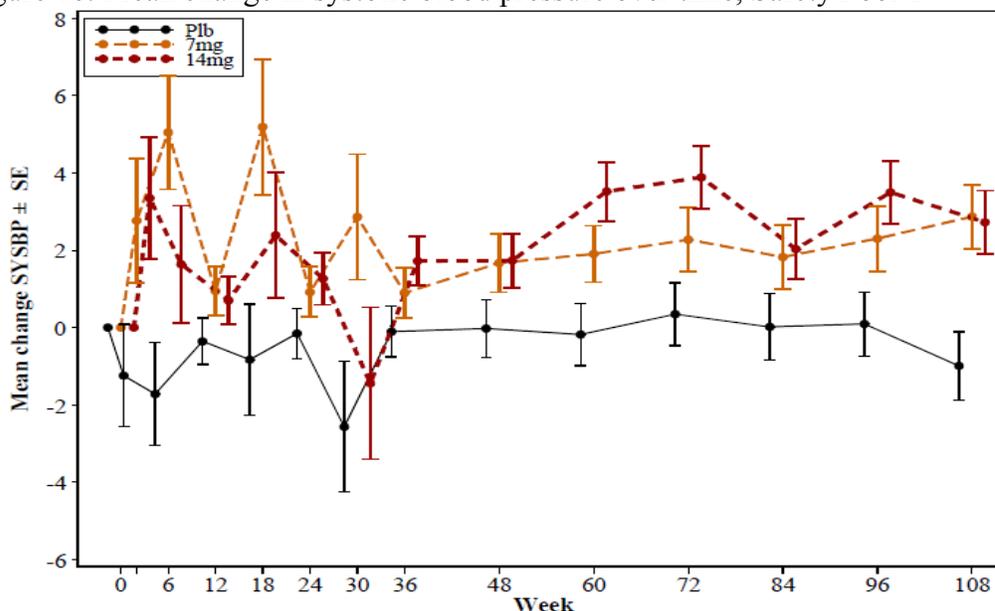
7.4.3.1 Blood pressure

Analyses of systolic and diastolic BP changes in Pool 1 are summarized below. Of note, some patients had it supine and some had it sitting, therefore the measurement is referred to as “supine/sitting” BP.

Mean change in systolic BP over time is presented in the following figure.

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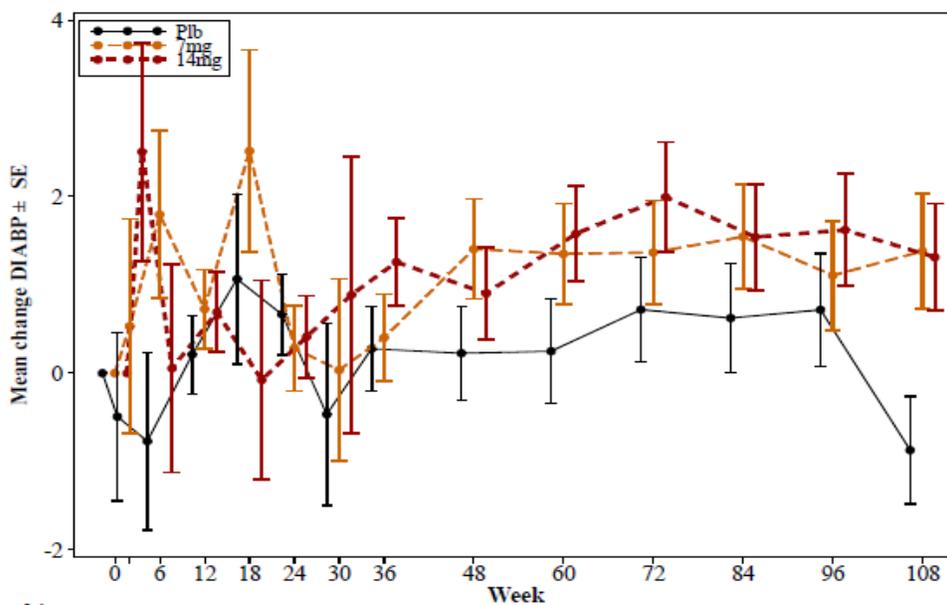
Figure 16. Mean change in systolic blood pressure over time, Safety Pool 1



# subjects	421	61	402	60	381	58	369	300	286	275	269	259	257
Plb	421	61	402	60	381	58	369	300	286	275	269	259	257
7mg	429	59	410	58	386	58	376	305	294	288	278	277	275
14mg	415	55	390	52	361	45	347	287	281	274	269	262	261

Source: Appendix 1.7.1.3 original ISS. Refers to supine/sitting BP.

Figure 17. Mean change in diastolic blood pressure over time, Safety Pool 1



# subjects	421	61	402	60	381	58	369	300	286	275	269	259	257
Plb	421	61	402	60	381	58	369	300	286	275	269	259	257
7mg	429	59	410	58	386	58	376	305	293	288	278	277	275
14mg	415	55	390	52	361	45	347	287	281	274	269	262	261

Source: Appendix 1.7.1.9. Refers to supine/sitting BP.

Table 92. Change from baseline in systolic and diastolic blood pressure, Pool 1

Systolic BP			
	Placebo (N=421)	teriflunomide	
		7 mg (N=429)	14 mg (N=415)
Baseline			
Value			
Number	421	429	415
Mean (SD)	118.2 (14.1)	117.9 (13.7)	117.1 (13.0)
Median	118.0	117.0	115.0
Q1 : Q3	110.0 : 126.0	110.0 : 126.0	110.0 : 125.0
Min : Max	80 : 180	80 : 166	85 : 163
Endpoint value			
Value			
Number	406	412	397
Mean (SD)	116.8 (13.6)	120.3 (14.7)	119.9 (13.8)
Median	115.0	120.0	120.0
Q1 : Q3	108.0 : 126.0	110.0 : 130.0	110.0 : 128.0
Min : Max	80 : 157	80 : 174	90 : 170
Change from baseline			
Number	406	412	397
Mean (SD)	-1.3 (13.7)	2.2 (13.7)	2.6 (12.8)
Median	0.0	2.0	1.0
Q1 : Q3	-10.0 : 8.0	-5.5 : 10.0	-5.0 : 10.0
Min : Max	-45 : 40	-43 : 40	-39 : 60
Diastolic BP			
Baseline			
Value			
Number	421	429	415
Mean (SD)	75.2 (9.7)	75.6 (9.2)	75.4 (9.4)
Median	75.0	75.0	75.0
Q1 : Q3	70.0 : 80.0	70.0 : 80.0	70.0 : 80.0
Min : Max	50 : 109	50 : 104	52 : 110
Endpoint value			
Value			
Number	406	412	397
Mean (SD)	74.2 (9.6)	76.6 (10.8)	76.9 (9.7)
Median	74.0	78.0	78.0
Q1 : Q3	70.0 : 80.0	70.0 : 82.0	70.0 : 81.0
Min : Max	48 : 99	47 : 124	48 : 110
Change from baseline			
Number	406	412	397
Mean (SD)	-0.9 (9.7)	1.1 (10.5)	1.4 (9.7)
Median	0.0	0.0	0.0
Q1 : Q3	-8.0 : 5.0	-5.0 : 8.0	-5.0 : 10.0
Min : Max	-30 : 27	-29 : 46	-29 : 30

Source: Appendix 1.7.1.1 and 1.7.1.7, original ISS. Endpoint value: last value on drug.

At study endpoint (end of treatment visit for completers, value at or prior to last drug intake for discontinued patients) the mean change in systolic blood pressure was 2.6 mmHg on Teri 14 and -1.3 mmHg on placebo. The mean change in diastolic BP was 1.4 mmHg on Teri 14 and -0.9 on placebo. Therefore, at study endpoint, the change in BP from baseline on Teri 14 was 3.9 mmHg higher for systolic BP, and 2.3 mmHg higher for diastolic BP as compared to placebo.

Analyses of systolic and diastolic BP in Pool 2 indicate that blood pressure continues to increase over time, although there is no placebo to compare.

Table 93. Changes from baseline in systolic and diastolic BP in Pool 2.

Change in Systolic BP at endpoint	teriflunomide	
	7 mg (N=587)	14 mg (N=548)
Change from baseline		
Number	565	529
Mean (SD)	3.5 (14.2)	5.3 (12.9)
Median	3.0	5.0
Q1 : Q3	-5.0 : 12.0	-2.0 : 12.0
Min : Max	-49 : 55	-30 : 60
Change in Diastolic BP at endpoint		
Change from baseline		
Number	565	529
Mean (SD)	2.5 (10.4)	3.4 (10.6)
Median	2.0	4.0
Q1 : Q3	-4.0 : 10.0	-3.0 : 10.0
Min : Max	-39 : 36	-40 : 47

Source: Appendix 1.7.1.2 and 1.7.1.8, original ISS.

Outlier analyses of BP by Sanofi’s defined PCSA in Pool 1 are as follows:

Table 94. Patients with potentially clinically relevant changes in blood pressure, Pool 1

Vital signs parameter (regardless of baseline status) Sanofi’s PCSA criteria	Placebo (n=421)	Teri 7 (n=429)	Teri 14 (n=415)
Supine/sitting Systolic Blood Pressure			
≤ 95 mmHg and decrease from baseline ≥20 mmHg	27/416 (6.5%)	25/425 (5.9%)	17/414 (4.1%)
≥ 160 mmHg and increase from baseline ≥20 mmHg	8/416 (1.9%)	18/425 (4.2%)	23/414 (5.6%)
Supine/sitting Diastolic Blood Pressure			
≤ 45 mmHg and decrease from baseline ≥10 mmHg	2/416 (0.5%)	2/425 (0.5%)	3/414 (0.7%)
≥ 110 mmHg and increase from baseline ≥10 mmHg	2/415 (0.5%)	7/425 (1.6%)	6/414 (1.4%)

Source: Appendix 1.7.2.1, ISS.

As seen in this table, 5.6% of patients on Teri 14 and 1.9% of patients on placebo had at least one measurement of systolic BP ≥ 160 mmHg AND ≥ 20 mmHg higher than baseline. And 1.4% of patients on Teri 14 and 0.5 % of patients on placebo had at least one measurement of diastolic BP ≥ 110 mmHg AND ≥ 10 mmHg higher than baseline.

7.4.3.2 Heart rate

Change from baseline in heart rate in placebo-controlled study 2001 based on ECGs was 2.2 bpm, -0.2 bpm and -0.2 bpm in the placebo, the 7 mg and the 14 mg group at Week 36, and 2.1 bpm, 0.3 bpm and 0.4 bpm at endpoint. In the analysis of pooled data from Study 2001+LTS6048, changes from baseline at Week 468 were 2.0 bpm and 8.6 bpm for the 7 mg and the 14 mg groups. Endpoint values for mean change of heart rate from baseline in pooled data were -0.2 bpm and 2.7 bpm for the 7 mg and the 14 mg groups.

ECGs were not done in study 6049/TEMPO. Analyses of HR from this study were not submitted.

7.4.3.3 Weight

In Pool 1, baseline weight values were comparable across groups with a mean of 70 (± 17) and median of 68.0 kg, 69.0 kg, and 67.6 for placebo, teriflunomide 7 mg, and teriflunomide 14 mg, respectively.

Teriflunomide treatment was associated with weight loss. Weight decreased (PT) was reported in 4 patients on placebo (1.0%), 12 patients on teriflunomide 7 mg (2.8%), and 10 patients on teriflunomide 14 mg (2.4%). A decrease from baseline of $\geq 5\%$ occurred in 26.6% for placebo, 39.1% for Teri 7 and 44.4% for Teri 14.

The maximal decrease occurred within the first 6 months and stabilized thereafter. The mean loss of weight at week 24 was 0, - 1.1 and - 1.4 kg for placebo, Teri 7 and Teri 14, respectively. The mean loss of weight at study endpoint (last available value on treatment) was +0.7, - 0.8 and - 1.3 kg for placebo, Teri 7 and Teri 14, respectively.

In Pool 2, weight decreased was reported in 18 patients (3.1%) on Teri 7 and 13 patients (2.4%) on Teri 14.

Outlier analysis using PCSA values for weight (increase or decrease in $\geq 5\%$) in Pool 1 is as follows.

Table 95. Outlier analysis of weight changes in Pool 1

Vital signs parameter Baseline Status PCSA criteria	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)
Weight			
Total ^a			
$\geq 5\%$ increase from baseline	149/417 (35.7%)	84/425 (19.8%)	84/414 (20.3%)
$\geq 5\%$ decrease from baseline	111/417 (26.6%)	166/425 (39.1%)	184/414 (44.4%)

Source. Appendix 1.7.2.1, ISS.

The cause of weight loss is unclear. Decreased appetite was reported as an adverse event twice on Teri 14 as compared to placebo. Nausea and diarrhea may contribute to weight loss too.

7.4.4 Electrocardiograms (ECGs)

ECG controlled data came from completed study 2001, a 6-month study with approximately 60 patients per treatment group (placebo, Teri 7 and Teri 14). ECG data were not collected in TEMPO/6050. Additional data came from the clinical pharmacology studies, ongoing study 6048 and ongoing TOWER study.

Change from baseline in heart rate in placebo-controlled study 2001 was 2.2 bpm, -0.2 bpm and -0.2 bpm in the placebo, the 7 mg and the 14 mg group at Week 36, and 2.1 bpm, 0.3 bpm and 0.4 bpm at endpoint. Mean change from baseline for QTcB at endpoint of Study 2001 were 2.72 ms, 0.43 ms and 3.28 ms and mean change from baseline for QTcF were 0.92 ms, -0.03 ms and 2.73 ms for placebo, teriflunomide 7 mg and 14 mg. Evaluation of PCSA showed no patients with prolonged PR or QRS. Very few patients presented prolonged QT interval, with a small and similar number of patients in each treatment group.

A summary of Potentially Clinically Significant ECG abnormalities (PCSA) in study 2001 are shown in the following table.

Table 96 ECG. Number of patient with PCSA abnormalities, study 2001

ECG parameter	teriflunomide		
	Placebo (N=61)	7 mg (N=61)	14 mg (N=57)
Baseline Status			
PCSA criteria			
Heart Rate			
Total ^a			
≤ 50 bpm and decrease from baseline ≥ 20 bpm	0/61	0/60	0/57
≥120 bpm and increase from baseline ≥ 20 bpm	0/61	0/60	1/57 (1.8%)
PR			
Total ^a			
≥220 ms and increase from baseline ≥ 20 ms	0/61	0/60	0/57
QRS			
Total ^a			
≥120 ms	0/61	0/60	0/57
QTc Bazett			
Total ^a			
Borderline: 431-450 ms (Male);451-470 ms (Female)	4/61 (6.6%)	3/60 (5.0%)	1/57 (1.8%)
Prolonged: >450 ms (Male); >470 ms (Female)	1/61 (1.6%)	3/60 (5.0%)	0/57
≥ 500 ms	0/61	0/60	0/57

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 QTc Bazett - Change from baseline

Total^a

Borderline: Increase versus baseline ≥ 30 and ≤ 60 ms	4/61 (6.6%)	6/60 (10.0%)	6/57 (10.5%)
Prolonged: Increase versus baseline >60 ms	3/61 (4.9%)	2/60 (3.3%)	2/57 (3.5%)

QTc Fridericia

Total^a

Borderline: 431-450 ms (Male); 451-470 ms (Female)	3/61 (4.9%)	3/60 (5.0%)	1/57 (1.8%)
Prolonged: >450 ms (Male); >470 ms (Female)	0/61	2/60 (3.3%)	0/57
≥ 500 ms	0/61	0/60	0/57

QTc Fridericia - Change from baseline

Total^a

Borderline: Increase versus baseline ≥ 30 and ≤ 60 ms	4/61 (6.6%)	1/60 (1.7%)	4/57 (7.0%)
Prolonged: Increase versus baseline >60 ms	2/61 (3.3%)	2/60 (3.3%)	0/57

Source: Table 46. Original ISS.

There does not seem to be a clinically relevant effect on ECG parameters in the controlled 6-month database.

7.4.4.2 ECG data from Extension study LTS6048

In the analysis of pooled data from Study 2001+LTS6048, changes from baseline in heart rate at week 468 were 2.0 bpm and 8.6 bpm for the 7 mg and the 14 mg groups (based on approximately 15 patients per arm). Endpoint values for mean change of heart rate from baseline in pooled data were -0.2 bpm and 2.7 bpm for the 7 mg and the 14 mg groups (with 79-86 patients per arm).

An increase in mean change in QTcB and QTcF from baseline over time was observed in analysis of pooled data Study 2001+6048. Mean change from baseline for QTcB at endpoint was 11.66 ms and 11.55 ms and mean change from baseline for QTcF was 11.40 ms and 8.48 ms for the 7 mg and 14 mg doses.

Few patients had prolonged QTcF or QTcB (>450 ms in male and >470 ms in female). Of these, 3 patients (3.3%) had QTcB ≥ 500 ms in teriflunomide 7 mg and 1 (1.2%) in teriflunomide 14 mg. Increase from baseline in QTcB >60 ms was recorded in 6 patients in each group. Prolonged QTcF ≥ 500 ms was reported in 1 patient (1.1%) in teriflunomide 7 mg versus none in 14 mg. Increase from baseline >60 ms was recorded in 5 patients (5.6%) in teriflunomide 7 mg and 4 (4.8%) in 14 mg.

This apparent effect on the QT interval is difficult to interpret in the absence of a control arm. No events of ventricular tachycardia or torsades de pointes were observed in the teriflunomide database. However, there were three sudden deaths in uncontrolled studies.

7.4.4.3 ECG in Clinical Pharmacology studies

In Clinical Pharmacology studies, for both the single-dose and repeated-dose pools separately, a summary table of PCSAs for absolute value QTc data from studies with automatic ECGs performed during the on-treatment phase was provided. For the repeated-dose pool summary, data from Study TES10852 (Thorough ECG study) was not included. The summary from Study TES10852 was provided separately.

- Thorough ECG study (TES10852)

The effect of repeated oral doses of teriflunomide (70 mg for 4 days followed by 14 mg for 8 days) on ventricular repolarization, as compared with placebo with moxifloxacin (400 mg single dose) as a positive control was studied in healthy subjects (Study TES10852). The primary objective of this Phase 1, randomized, double-blind double-dummy, 3 parallel-group study in 194 subjects was to assess the effect of teriflunomide on QTcF interval compared with placebo. As per Sanofi's interpretation, the study did not show that teriflunomide prolongs the QTcF interval versus placebo (upper bound of the 90% CI was 6.45 ms). Neither prolonged QTcF >480 ms nor QTcF increase from baseline >60 ms was observed in these conditions. This study is being reviewed by the FDA QT team.

- Other clinical pharmacology studies did not suggest an effect of teriflunomide on ventricular repolarization.

7.4.4.4 ECG in TOWER

On March 19, 2012, the DNP requested Sanofi to submit preliminary ECG results of the ongoing TOWER study, with a cut-off date more advanced than the one used at the time of the original submission. Sanofi responded on March 29, 2012.

The data presented in this response were based on the same patients as the interim analysis (ie, patients randomized up to the cut-off date of 30 November 2010). The interim analysis was based on data collected up to 28 February 2011. As of 26 March 2012, postbaseline ECG data were available for 242 to 282 of the same patients (per treatment group) that were randomized by 30 November 2010 and unblinded by the independent group at Sanofi for the interim analysis. An additional 73 patients were randomized after the cut-off date for inclusion in the patient population for the interim analysis. The treatment codes for these patients remain blinded and they are not included in the analysis for this response.

Summary statistics for ECG variables including heart rate, PR, QRS, QT, QTc (Bazett), and QTc (Fridericia) showed a small dose dependent mean increase in heart rate from baseline to endpoint (0.71 bpm on placebo, 1.85 bpm on teriflunomide 7 mg, and 3.59 bpm on teriflunomide 14 mg) (consistent with the finding in study 2001). There was also a dose dependent decrease in PR from baseline to endpoint (PR: placebo: -0.89 ms, teriflunomide 7 mg: -3.17 ms, and teriflunomide 14 mg: -6.04 ms) (data not shown). No other treatment group differences were observed in the mean change from baseline to endpoint for any ECG parameter.

The increase in HR of a few bpm does not appear to be clinically relevant. The clinical significance of the dose-related shortening in PR is unclear.

The number of patients with ECG PCSA are presented in the following table.

Table 97. Number of patients with at least one post baseline PCSA ECG value in the overall on-treatment period in TOWER.

ECG parameter	Baseline Status	teriflunomide		
		Placebo (N=362)	7 mg (N=379)	14 mg (N=352)
PCSA criteria				
Heart Rate				
Total*				
	≤ 50 bpm and decrease from baseline ≥ 20 bpm	0/242	1/282 (0.4%)	0/261
	≥120 bpm and increase from baseline ≥ 20 bpm	0/242	0/282	1/261 (0.4%)
PR				
Total*				
	≥220 ms and increase from baseline ≥ 20 ms	1/242 (0.4%)	0/282	0/260
QRS				
Total*				
	≥120 ms	2/242 (0.8%)	2/281 (0.7%)	2/260 (0.8%)

ECG parameter	Baseline Status	teriflunomide		
		Placebo (N=362)	7 mg (N=379)	14 mg (N=352)
PCSA criteria				
QTc Bazett				
Total*				
	Borderline: 431-450 ms (Male);451-470 ms (Female)	9/242 (3.7%)	12/281 (4.3%)	10/260 (3.8%)
	Prolonged: >450 ms (Male); >470 ms (Female)	1/242 (0.4%)	3/281 (1.1%)	4/260 (1.5%)
	≥ 500 ms	0/242	0/281	1/260 (0.4%)
QTc Bazett - Change from baseline				
Total*				
	Borderline: Increase versus baseline ≥ 30 and ≤60 ms	22/238 (9.2%)	24/275 (8.7%)	22/254 (8.7%)
	Prolonged: Increase versus baseline >60 ms	0/238	1/275 (0.4%)	1/254 (0.4%)
QTc Fridericia				
Total*				
	Borderline: 431-450 ms (Male);451-470 ms (Female)	3/242 (1.2%)	4/281 (1.4%)	4/260 (1.5%)
	Prolonged: >450 ms (Male); >470 ms (Female)	1/242 (0.4%)	1/281 (0.4%)	2/260 (0.8%)
	≥ 500 ms	0/242	0/281	0/260

QTc Fridericia - Change from baseline

Total*

Borderline: Increase versus baseline ≥ 30 and ≤ 60 ms	8/238 (3.4%)	9/275 (3.3%)	11/254 (4.3%)
Prolonged: Increase versus baseline >60 ms	1/238 (0.4%)	2/275 (0.7%)	0/254

Source: Table 2, March 29, 2012 response to request for information. * Total: irrespective of baseline.

The analysis of ECG PCSA in TOWER does not suggest a significant effect of teriflunomide on ECG parameters. This is an interim analysis. This study is planned to be completed in March 2012.

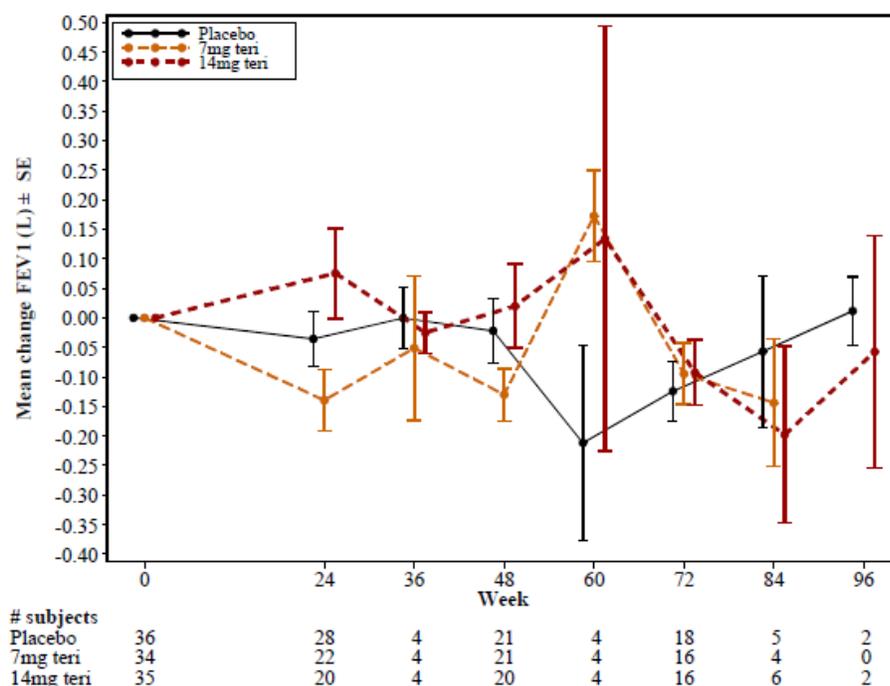
7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies in this application. However, because of the association between leflunomide and interstitial lung disease, pulmonary function tests were conducted in the TOWER study.

- Evaluation of Pulmonary Function Tests.

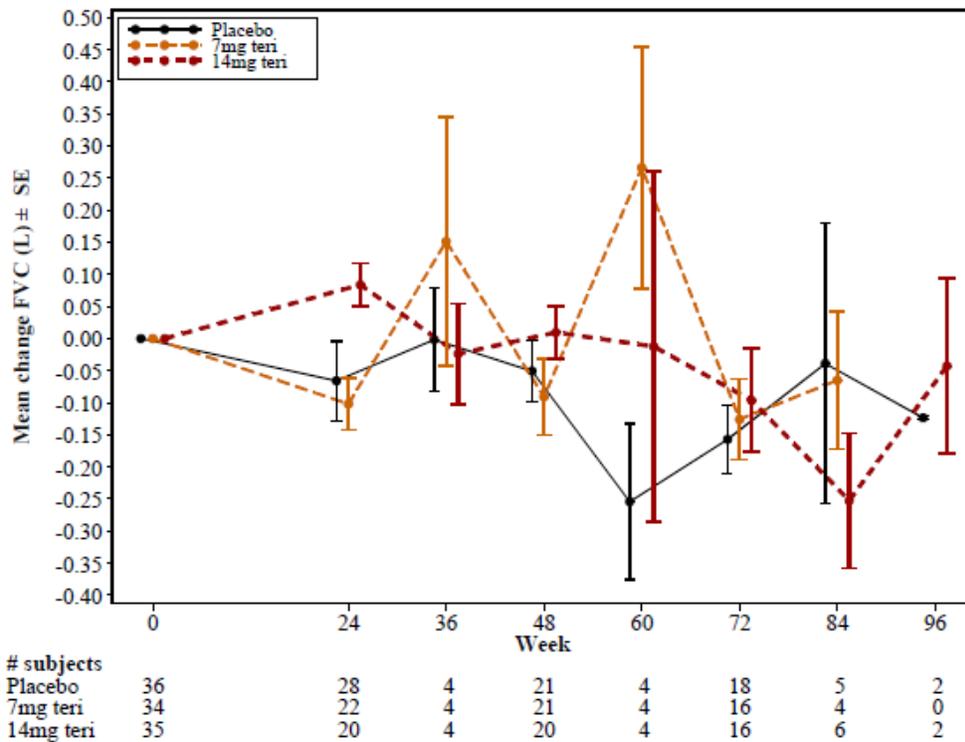
Pulmonary function tests were conducted in a subset of patients in TOWER. A total of 105 patients had PFT assessments at baseline (36, 34 and 35 patients on placebo, Teri 7 and Teri 14, respectively). By week 72 there were 16-18 patients available per treatment group, and by week 84 there were approximately 5 per treatment group. Plots of the mean change from baseline in FEV1, FVC, DLCO in patients who had PFTs in TOWER are shown below.

Figure 18. Change from baseline in FEV1 over time, PFT population, TOWER



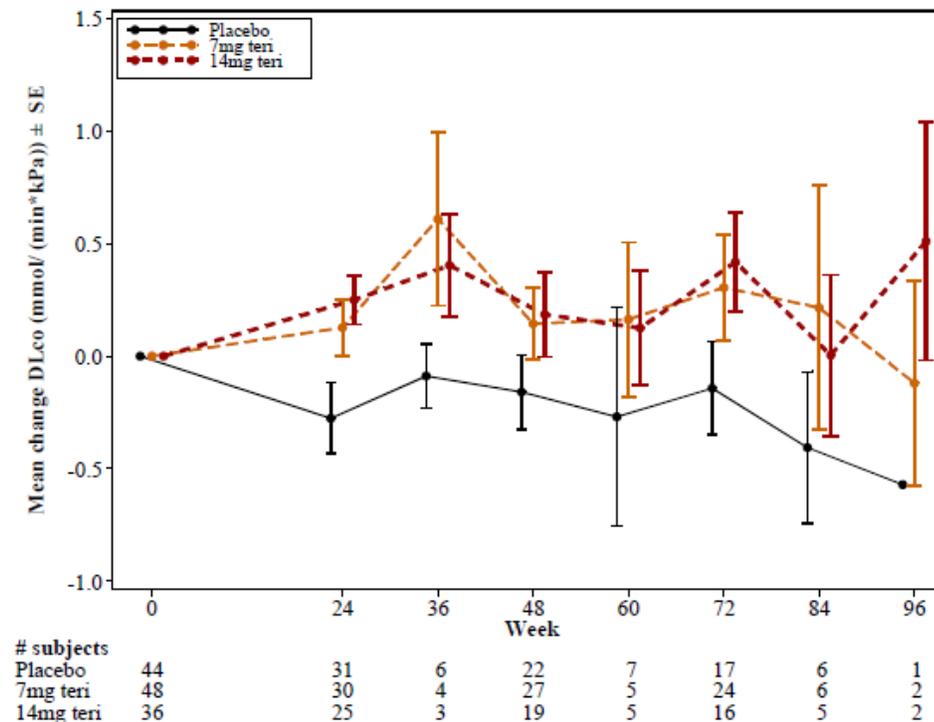
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 Source: Figure 1, 3/29/12 response to FDA request.

Figure 19. Change from baseline in FVC over time, PFT population, TOWER



Source: Figure 2, 3/29/12 response to FDA request.

Figure 20. Change from baseline in DLCO over time, PFT population, TOWER



These analyses do not show worsening lung function with teriflunomide but do not allow definitive conclusions regarding lung toxicity of teriflunomide as they were done in a small subset of patients and only 5-6 patients had available values by week 84.

Sanofi conducted analyses of 50% decrease in FEV1, FVC and DLCO. At the end of treatment endpoint (last value on drug before completion or discontinuation), 33 patients had a greater than 50% decline from baseline in FEV1, with no major difference between treatment groups in the incidence of patients with a decline in FEV1 from baseline (36 to 43 % of patients). Fewer patients in teriflunomide groups had a 50% decline in FVC and DLCO as compared to baseline (data not shown).

Definitive conclusions can not be made regarding lung toxicity of teriflunomide based on these analyses as they were done in a small subset of patients and PFTs may reflect patients with short exposure to drug.

7.4.6 Immunogenicity

Teriflunomide is not a biologic agent and it is not expected to be immunogenic. Some immune mediated diseases were diagnosed in this application (sarcoidosis, rheumatoid arthritis, seronegative arthritis) but the numbers are small and there was no imbalance in controlled studies.

The effect of teriflunomide on the immunologic response to neoantigen and recall antigen, and to cytotoxic responses has not been studied in this application. However, since teriflunomide induces decreased levels of B and T lymphocytes, it is likely to affect all immunologic responses. As per the DSUR, Study PDY11684, a study looking at the antibody response to influenza vaccine in patients with RMS treated with teriflunomide and in a reference population of RMS patients, is ongoing. It is unlikely that such a study will provide adequate assessment of effects of teriflunomide on immunologic responses.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The overall risk of serious events or discontinuations due to AE was similar between teriflunomide 7 and 14 mg/day. However, there was a suggestion of a dose response for some AE (e.g. alopecia, ALT elevation, peripheral neuropathy). There is also evidence of dose response in terms of efficacy (please see review by Dr. Green).

7.5.2 Time Dependency for Adverse Events

Based on observation of Kaplan Meier plots for AESI and percentage change from baseline for laboratory measurements, there was some evidence of time dependency, but it varied for different adverse events. For some events the effect was observed very early, within days (e.g. nausea) while others appeared later (e.g. increase in blood pressure, after 36 weeks). For instance, alopecia was observed within the first few weeks, up to 6 months, then it seemed to stabilize. Peripheral neuropathy started to occur within 1 month and continued to occur over time. Bone marrow AESI were observed within the first 6 weeks with maximum effect at 6 months, then appear to stabilize. Platelet counts dropped up to 12 weeks, then, slowly started to increase (but did not reach normal levels). Hemoglobin dropped steadily up to 30 months then appeared to stabilize.

7.5.3 Drug-Demographic Interactions

Age, gender, race and weight/BMI were identified as significant covariate influencing teriflunomide PK in the population PK analysis. However, these factors did not increase the overall risk of AEs in patients taking teriflunomide as compared to placebo.

There is a suggestion that patients with age <38 years on teriflunomide 14 mg versus placebo had an increased risk of AEs leading to discontinuation compared to the patients with age \geq 38 years (mostly related to ALT elevation), and that nausea was more frequent in patients \geq 38 years than those <38 years. There is also a suggestion of increased risk of liver function abnormalities, neutropenia, hypertension and viral infections in females as compared to males. The numbers are small and do not allow definitive conclusions. Less than 4% of the population was non-Caucasian, therefore, no conclusions can be drawn regarding differential safety based on race.

Weight did not appear to have a great impact in the development of AEs. In terms of steady state exposure, AUC_{0-24SS} increased by 26% on Teri 14 mg for patients weighing less than 59.5 kg (25th percentile) compared to patients weight more than 79.8 kg (75th percentile).

In Pool 1, there was an increased risk of HLTs alopecia and diarrhea in patients with BMI <30 kg/m² compared to patients with BMI \geq 30 kg/m² treated with teriflunomide 7 or 14 mg versus placebo. An analysis of incidence of most common AE by weight submitted on 4/30/12 at the FDA request, did not show that these AE were substantially higher among patients with weight <25th percentile as compared to patients with \geq 25th percentile (data not shown).

7.5.4 Drug-Disease Interactions

No analyses of drug-disease interaction were performed.

7.5.5 Drug-Drug Interactions

In vivo, teriflunomide was a moderate inhibitor of CYP2C8, a weak inhibitor of CYP3A, but not

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of CYP2B6, CYP2C9, CYP2C19, and CYP2D6. Teriflunomide also seemed to be a weak inducer of CYP1A2 in vivo. No major drug interactions are expected, however, drugs metabolized by CYP2C8 should be used with caution during the treatment with teriflunomide.

In a drug interaction study with warfarin, a 25% decrease in peak international normalized ratio (INR) was observed when teriflunomide was coadministered with warfarin as compared with warfarin alone. Therefore, when warfarin is coadministered with teriflunomide, close INR follow-up and monitoring is recommended.

Teriflunomide was studied as add-on therapy to glatiramer or beta interferon therapy. There did not seem to be an increased risk of AE in patients receiving these drugs as compared to teriflunomide alone, however, the database is small. Concomitant use of other immunosuppressors was not allowed in clinical trials. It is anticipated that the use of teriflunomide concomitantly with other immunosuppressors may increase the risk of immunosuppression.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There was no evidence of increased neoplasms in teriflunomide groups as compared to placebo in the controlled database. However, this database is inadequate to assess the long-term immunosuppressive effects of teriflunomide. Most neoplasms were common neoplasms such as breast and skin. Of note, there were three cases of renal cell carcinoma in teriflunomide treated patients and one in a patient not treated with teriflunomide. *See SAE in Neoplasm SOC (Section 7.3 of this review).*

7.6.2 Human Reproduction and Pregnancy Data

All subjects were required to provide written consent to not become pregnant or father a child during study participation. Both female and male subjects of reproductive potential enrolled in teriflunomide studies were informed of the potential teratogenic effect of teriflunomide seen in the animal studies. Recommendations were given to them to use an effective contraceptive method during the entire study period. All the pregnant females should have been discontinued their treatment immediately after they have been made aware of their pregnancies and a rapid elimination treatment procedure using cholestyramine or charcoal been performed. Then discussion of possible alternatives (eg, therapeutic abortion, continuation of the pregnancy) should have been discussed between the subjects and the investigators as warranted after the code was broken. The subject was then followed up for the pregnancy outcome.

As of 01 June 2011, a total of 57 pregnancies were reported to the Pharmacovigilance database in the whole teriflunomide clinical program involving 56 subjects (1 female patient experienced 2 pregnancies).

- 45 pregnancies occurred in female patients aged from 22 to 45 years old.
- 12 occurred in female partners of male patients aged from 18 to 53 years old.

Among a total of 45 pregnancies in female patients the outcome was as follow: delivery of healthy newborns occurred in 10, induced abortion in 21, spontaneous abortion in 9 while 5 were still ongoing pregnancy at time of cut-off. Pregnancy outcomes are summarized in the following table.

Table 98. Pregnancy outcomes in female patients in Teriflunomide NDA (as of 6/1/11)

Outcome	Teriflunomide		Blinded therapy**		β - IFN	Placebo	Study medication not given (screening)	Total
	On-treatment period	Follow up period	On-treatment period	Follow up period				
Female patients (45)								
Live birth	6	1		1*	1	1		10
Induced abortion	12	1	7				1	21
Spontaneous abortion	6	2				1		9
Ongoing pregnancy	1	2	1	1				5
Total	25	6	8	2	1	2	1	45

Live birth: Weight of the babies 3090-3950 grams and gestational age 34-42 weeks; Induced abortions: fetus age 10 days- 2 months; Spontaneous abortions: fetus age few days-3 months. * case occurred during follow up period in TOWER. ** 7 cases in Study EFC10531 and 3 cases in Study EFC6260. Source: Table 49 and 50, ISS.

Among the 10 female patients that delivered live newborns:

- 7 patients received cholestyramine.
- 1 patient received activated charcoal.
- 2 patients (1 patient receiving IFN- β and 1 patient receiving the placebo) did not receive any treatment for rapid elimination procedure.

The median duration of the rapid elimination procedure for female patients with full term pregnancies was 11 days (ranges from 5 to 17 days).

Among the 12 pregnancies in partners of male patients there were 8 live births and one spontaneous abortion.

All 18 newborn babies were healthy without malformation or functional problems as of June 1, 2011.

As per the 120-day SUR, eight additional pregnancies occurred as of September 8, 2011. There were two more live birth (one on treatment, one still blinded), one spontaneous abortion, four induced abortions (still on blinded therapy) and one ongoing pregnancy.

It is anticipated that the pregnancy section of the teriflunomide labeling will be identical to that of leflunomide (Arava®). Sanofi has submitted a summary protocol for a Pregnancy Registry. Review and final recommendations by the Maternal Health Team (MHT) are pending.

7.6.3 Pediatrics and Assessment of Effects on Growth

No studies were done in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant did not find evidence of abuse potential, withdrawal or rebound. The FDA Control Substance Abuse staff concurs with Sanofi. Please refer to the review by CSS staff.

Eight patients were reported to have “drug overdose” in the monotherapy studies. One patient on placebo and one on Teri 7 during the controlled phase; three additional patients on Teri 7 and three on Teri 14 in extension studies. As per review of the narrative of cases of overdose submitted on 4/24/12 at the FDA request, most cases were isolated, accidental overdoses (e.g. taking the drug twice in a day) and the patients were asymptomatic. There was one report of intentional overdose in TOWER as follows.

- **124002001.** A 38 year-old female patient was reported with a non-serious event of “intentional of teriflunomide”(7 mg) coded as **intentional overdose** on Day 470 of treatment with teriflunomide 7mg. No information is available about the quantity of the pills taken or any concomitant symptoms reported. Recovery was stated on the same day. This event of intentional overdose was assessed as not being related to the study drug by the investigator.

There is no evidence of increased risk of abuse potential with teriflunomide.

7.7 Additional Submissions / Safety Issues

Requests for additional information during this review were promptly and timely addressed by Sanofi. Occasional discrepancies between the additional information and the original information required repeated attempts for clarification, particularly related to renal function data. Sanofi’s responses have been incorporated into the body of this review as of June 26, 2012.

7.7.1 Newly identified adverse event: acute renal failure

The following section refers to a newly identified potential safety issue of acute renal failure with teriflunomide, which has been reviewed by Dr. Evelyn Mentari (nephrologist, DNP Safety Team).

Teriflunomide Trials: Increases in Serum Creatinine

Placebo-Controlled Trials

In Pool 1, 10 of 844 (1.2%) of teriflunomide-treated subjects had a creatinine measurement $\geq 100\%$ of their baseline serum creatinine value, compared to 0 of 421 placebo-treated subjects. All of these Pool 1 cases occurred in the Trial EFC6049 (TEMPO).

Table 99.Pool 1: Increased creatinine $\geq 100\%$ from baseline

Laboratory parameter	teriflunomide			
	Baseline by PCSA criteria n/N1 (%)	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)
$\geq 100\%$ change from baseline		0/420	5/428 (1.2%)	5/413 (1.2%)
$>3*$ Baseline or >3 ULN		0/420	3/428 (0.7%)	3/413 (0.7%)
>6 ULN		0/420	0/428	1/413 (0.2%)

Source: NDA 202992 ISS submitted 8/12/2011. Excerpt from Table 45 on page 313.

The Sponsor was asked to provide additional information regarding subjects who had a creatinine measurement $\geq 100\%$ of their baseline serum creatinine value. Findings for individual subjects are summarized in the table below. Nadir creatinine clearances (calculated with the Cockcroft-Gault formula) ranged from 8-96 cc/minute; 7 of the 10 subjects had nadir creatinine clearance calculated as less than 30 cc/minute.

In each of the 10 subjects, the serum creatinine level was normal on the next reported measurement. The time from abnormal serum creatinine measurement to reported follow-up measurement ranged from 6 to 48 days.

Pool 1: Subjects with serum creatinine increased $\geq 100\%$ from baseline

Subject (TEMSo) (teriflunomide dose)	Nadir CrCl (cc/min)	Time to normal creatinine (days)	Inter-vention Y/N	Change serum uric acid	Serum Potassium (mmol/L)	EDSS	T25-FW (seconds)
1209-0023 (7 mg)	25	6	N	-11%	>7.3	2	5.5
1211-0008 (14 mg)	96*	48	N	-25%	missing	4	6.0
2406-0007 (7 mg)	43	15	N	-24%	missing #	1.5	4.2
3003-0022 (7 mg)	93	N/A ∞	N	-40%	3.9	6.5	7.6
3207-0004 (14 mg)	17	9	N	-42%	6.7	2.5	5.0
3207-0010 (14 mg)	22	6	N	-10%	missing #	4	5.5
3208-0004 (7 mg)	25	6	N	+10%	5.2	1.5	4.9
3508-0007 (7 mg)	17	8	N	-57%	missing #	3	6.5
4602-0007 (14 mg)	26	32	N	-28%	5.4	4.5	5.7
4802-0002 (14 mg)	8	28	N	-5%	>7.3	3.5	3.7

The upper limit of quantitation for serum potassium at the central laboratory ^{(b) (4)} was 7.3 mmol/L.

* Subject obese. Baseline creatinine clearance was 250 cc/min. Although calculation of creatinine clearance in the obese patient is overestimate, the difference between baseline and nadir is evident.

∞ Subject's creatinine doubled, but it remained within normal range

Normal range for serum potassium = 3.4-5.4 mmol/L. EDSS = Expanded Disability Status Scale

T25-FW = Timed 25-foot walk. EDSS and T25-FW listed are the most recent measurements prior to the first measurement of increased creatinine. # Specimen with evidence of hemolysis. Change in serum uric acid = last normal serum creatinine value prior to acute renal failure, compared to baseline uric acid measurement

All of the 10 subjects had other laboratory tests that corroborated the diagnosis of acute renal failure (e.g., increases blood urea nitrogen, serum phosphorus, and serum uric acid as compared to previous measurements). These multiple laboratory measurements consistent with acute renal failure make laboratory error an unlikely explanation for the increased frequency of serum creatinine $\geq 100\%$ from baseline in teriflunomide-treated subjects.

These increased creatinine measurements occurred between 12 weeks and 2 years after first dose of teriflunomide; most occurred about 1 year after first dose. Of the 10 subjects with serum creatinine increased $\geq 100\%$ from baseline in the TEMSO trial, 8 were female and 2 were male, and ages ranged from 19-51.

No associated symptoms were documented in any Pool 1 subject with serum creatinine increased $\geq 100\%$ from baseline. None of the subjects had a reported history of renal disease, urologic disease, or urinary lithiases. No known concomitant medications were given that would be likely to contribute to these changes in serum creatinine. No reported dehydration, exercise, or increase in physical activity in the 30 days prior to the adverse event was reported, but this information was not systematically collected.

Despite the low creatinine clearance values and the marked hyperkalemia in Pool 1 subjects with serum creatinine increased $\geq 100\%$ from baseline, the Sponsor determined that these cases were of little clinical significance:

“...the reason for the observed laboratory abnormalities remains unclear. Based on the pattern of isolated increases of laboratory values without clinical symptoms and with rapid spontaneous resolution, the clinical significance of these unexplained findings seems very low.”³⁹

Extension Studies

The table below summarizes the subjects in extension studies with increased creatinine $\geq 100\%$ from baseline.

Table 100. Extension Studies LTS6048 and LTS6050: Subjects with increased creatinine $\geq 100\%$ from baseline

Subject (teriflunomide dose)	Nadir CrCl (cc/min)	Time to normal creatinine (days)	Inter-vention Y/N	Change serum uric acid	Serum Potassium (mmol/L)	EDSS
0014-0050 (0 mg 2001/14 mg LTS6048)	40	5	N	-6.0%	6.0	0
3803-0003 (7 mg EFC6049/7 mg LTS6050)	22	7	Y	-47%	4.0	4

³⁹ Sponsor response submitted to NDA 202992 on March 9, 2012 (page 6).

Subject (teriflunomide dose)	Nadir CrCl (cc/min)	Time to normal creatinine (days)	Inter-vention Y/N	Change serum uric acid	Serum Potassium (mmol/L)	EDSS
1201-0002 (7 mg EFC6049/7 mg LTS6050)	70	>69	Y	-58%	3.7	4

One of 147 (0.7%) of subjects in LTS6048 had an increased creatinine $\geq 100\%$ from baseline while receiving 14 mg of teriflunomide dose; this subject had a clinical course similar to the increased creatinine cases seen in the TEMSO trial (a single increase in serum creatinine with a normal serum creatinine on subsequent measurement).

Two of 742 (0.3%) of subjects in LTS6050 had an increased creatinine $\geq 100\%$ from baseline. Both subjects were in the 7 mg of teriflunomide treatment arm. LTS6050 subject 1201-0002 had an increased serum creatinine for over 2 months during a kidney infection.

LTS6050 subject 3803-0003 was hospitalized for acute renal failure, which resolved after treatment with intravenous saline. The subject had nausea and vomiting “in the last few weeks,” but dates of the nausea and vomiting, as well as timing in relation to her acute renal failure, are unclear.⁴⁰ No adverse event related to nausea or vomiting was documented on the case report form on the day this subject’s increased serum creatinine level was measured. The Investigator attributed the acute renal failure to gastroenteritis leading to dehydration. However, given the unclear time course, the nausea and vomiting may have been a symptom of uremia related to acute renal failure, as opposed to the cause of her acute renal failure. Also, if the nausea and vomiting did precede the acute renal failure, dehydration may have contributed to a drug-related etiology of acute renal failure by increasing the intrarenal concentration of uric acid and leading to renal tubular obstruction by uric acid crystals.

- Hyperuricosuria and renal failure: acute uric acid nephropathy

Increases in renal uric acid clearance have been documented with teriflunomide treatment. Acute uric acid nephropathy is a likely explanation for the cases of transient acute renal failure seen with teriflunomide. Hyperuricosuria can lead to high concentrations of urate in the urine; there is an increased risk of uric acid crystallization, because the undissociated species has poor solubility. Hemodynamic changes can contribute to sudden decreases in renal function, as well as rapid recovery, in patients with hyperuricosuria. For the teriflunomide-treated subjects who had acute renal failure, there was no systematic documentation of whether hemodynamic changes (possibly caused by strenuous activity or dehydration) preceded the events, but it is plausible that these changes may have occurred.

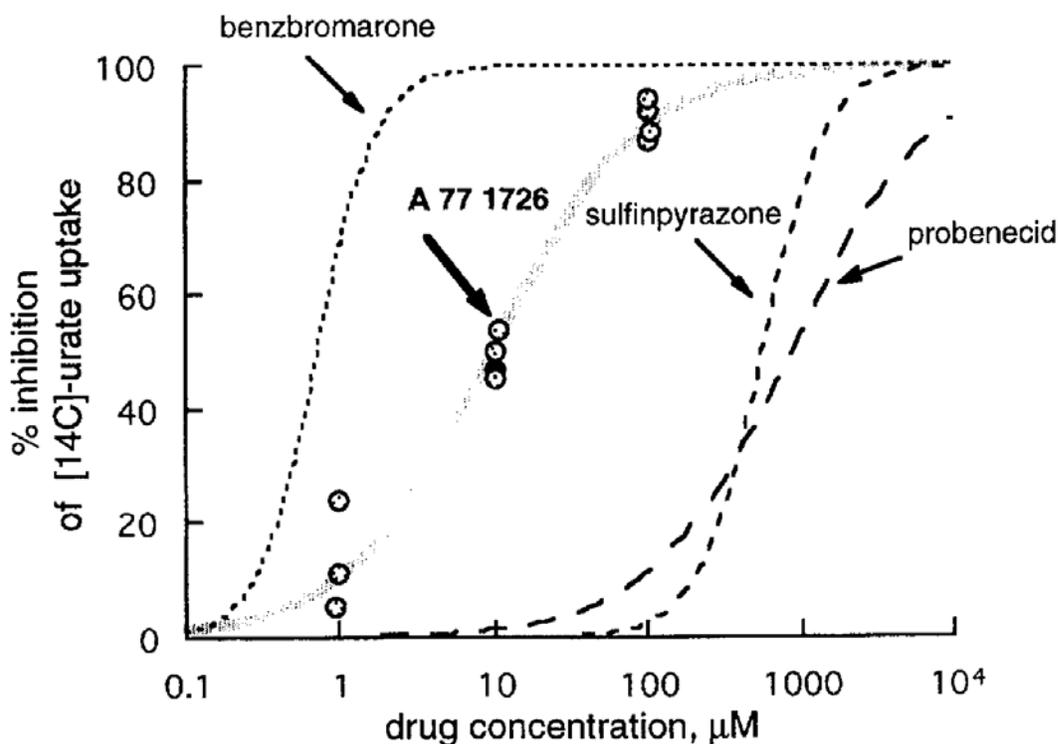
In Pool 1, mean changes in serum uric acid from baseline at endpoint were -3.8 umol/L for placebo, -58.3 umol/L for teriflunomide 7 mg, and -77.8 umol/L for teriflunomide 14 mg. In Study TES10852, after 10 days of treatment with teriflunomide, uric acid clearance was higher

⁴⁰ Sponsor response submitted to NDA 202992 on April 26, 2012 (Question 1).

with teriflunomide treatment (15.48 mL/min, increased 6 mL/min from baseline) than with placebo (9.39 mL/min, no change from baseline).

A marked increase in renal uric acid elimination (linked to the inhibition of the transport of urate through the apical urate/anion exchanger) was demonstrated in vitro (Study DIV151641). In this study, the effect of teriflunomide (a.k.a. A 77 1726) was greater than classical uricosuric drugs probenecid and sulfinpyrazone (see Figure 2 from the DIV1516 study report below).

Figure 21. DIV1516 Study Report Figure 2. Log-concentration inhibitory effect of teriflunomide (A 77 1726), benzbromarone, sulfinpyrazone, and probenecid.



Data for benzbromarone, sulfinpyrazone, and probenecid were taken from Roch-Ramel et al, *J Pharm Exp Ther* 280, 839-845-1997. The effects of 1, 10, and 100 μM of teriflunomide were measured in Study DIV1516.

Renal failure has been described with other drugs that cause hyperuricosuria, as well as in patients with hereditary hyperuricosuria.

Suprofen (brand name Suprol), a nonsteroidal anti-inflammatory drug with uricosuric properties, was marketed in early 1986 as an analgesic agent. A syndrome of temporary and reversible acute renal failure, as well as flank pain, was reported to the spontaneous reporting system after about 700,000 persons used the drug in the United States;⁴² these effects were not detected in pre-

⁴¹ A link to the DIV1516 study report is located on p. 316 of the ISS.

⁴² Strom BL, West SL, Sim E, Carson JL. The epidemiology of the acute flank pain syndrome from suprofen. *Clin Pharmacol Ther.* 1989 Dec;46(6):693-9.

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marketing trials. The manufacturer voluntarily removed Suprol capsules from the market in May 1987.

Acute renal failure has also been documented with ticrynafen, a diuretic agent with uricosuric action.⁴³ Sulfapyrazone, a potent uricosuric agent, has been associated with cases of renal failure and renal colic, especially in the initial stages of therapy.⁴⁴

Acute exercise-induced renal failure has also been described with hereditary hyperuricosuria.⁴⁵ These cases sometimes were accompanied by loin pain, abdominal pain, or fever. In these patients, acute renal failure can be severe enough to warrant treatment with hemodialysis, but the renal function typically recovers.

Yeun et al⁴⁶ documented changes in creatinine clearance with exercise in a patient with hereditary hypouricemia, as well as in normal controls (see Figure 1 below). One hour after exercise, both the patient and the controls had significant decreases in creatinine clearance. Twenty four hours after exercise, creatinine clearance had recovered in control subjects, while the creatinine clearance in the patient with hereditary hypouricemia decreased further. Taking allopurinol, 300 mg daily for 5 days, prevented acute renal failure in the patient with hereditary hypouricemia.

⁴³ Paddock GL, Wahl RC, Holman RE, Schorr WJ, Lacher JW. Acute renal failure associated with ticrynafen. JAMA. 1980 Feb 22-29;243(8):764-5.

⁴⁴ Anturane (sulfapyrazone) archived prescribing information. Accessed 5/22/12 at <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=71878>

⁴⁵ Yeun JY, Hasbargen JA. Renal hypouricemia: prevention of exercise-induced acute renal failure and a review of the literature. Am J Kidney Dis. 1995 Jun;25(6):937-46.

⁴⁶ Yeun JY, Hasbargen JA. Renal hypouricemia: prevention of exercise-induced acute renal failure and a review of the literature. Am J Kidney Dis. 1995 Jun;25(6):937-46.

Figure 22. Yeun, et al. Effect of exercise on creatinine clearance in control subjects and patient with hereditary hyperuricosuria at baseline and after allopurinol

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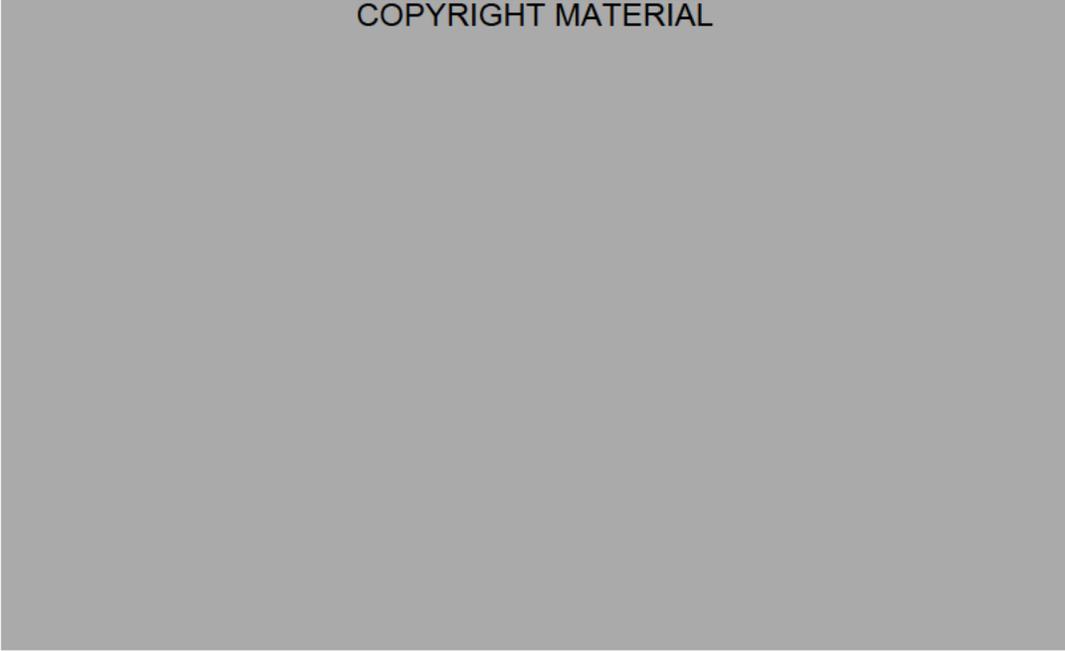


Fig 1. Effect of exercise on C_{Cr} in control subjects and patient with renal hypouricemia at baseline and after allopurinol.

Chronic renal lesions (thickening of the tubular basement membrane and interstitial fibrosis) were documented in a 42-year-old man with hereditary hyperuricosuria who had at least 4 episodes of exercise-induced acute renal failure. ⁴⁷

- Pain as a symptom of acute uric acid nephropathy

Pain (specifically in the loin, flank, back, or abdomen) has been reported to be a symptom that commonly accompanies acute uric acid nephropathy (documented with suprofen,⁴⁸ ticrynafen,⁴⁹ and in patients with hereditary hyperuricosuria.⁵⁰ Narratives for adverse events of loin or flank pain were reviewed. Cases with a clearly stated cause other than uric acid nephropathy (e.g., urolithiasis or pain after a fall) are not included in the cases discussed below. No case of loin or flank pain without a clear cause had documented acute renal failure, but not all subjects had laboratory measurements during the loin or flank pain adverse event. The duration of loin pain events ranged from 1 day to more than 1 year.

47 Ohta T, Sakano T, Igarashi T, Itami N, Ogawa T. Exercise-induced acute renal failure associated with renal hypouricaemia: results of a questionnaire-based survey in Japan. *Nephrol Dial Transplant*. 2004 Jun;19(6):1447-53.

48 Strom BL, West SL, Sim E, Carson JL. The epidemiology of the acute flank pain syndrome from suprofen. *Clin Pharmacol Ther*. 1989 Dec;46(6):693-9.

49 Paddack GL, Wahl RC, Holman RE, Schorr WJ, Lacher JW. Acute renal failure associated with ticrynafen. *JAMA*. 1980 Feb 22-29;243(8):764-5.

50 Ohta T, Sakano T, Igarashi T, Itami N, Ogawa T. Exercise-induced acute renal failure associated with renal hypouricaemia: results of a questionnaire-based survey in Japan. *Nephrol Dial Transplant*. 2004 Jun;19(6):1447-53.

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In Pool 1, 1 of 844 (0.1%) subjects treated with teriflunomide (7 mg dose) and 1 of 421 (0.2%) placebo-treated subjects had flank pain with no clearly documented cause. In Pool 2, 6 of 1135 (0.5%) of subjects reported an adverse event of loin or flank pain with no clearly documented cause. Study 6048 Subject 124-0017-0010 had events of flank pain in September 2004, December 2004, and “renal pain” in December 2006. After the flank pain in December 2004 “IP was discontinued and reintroduced and it was reported that the same event occurred”.⁵¹

While an increased frequency of loin pain associated with acute renal failure has not been documented in teriflunomide-treated subject, symptoms before and after the events of acute renal failure were not systematically documented. Seven of 8 cases of flank pain with no clear cause were reported at Canadian sites (27% of Pool 1 and Pool 2 subjects were from Canada). This variation in reporting may indicate that some cases were not reported.

Reviewer Comment (Dr. Mentari):

While the reductions in renal failure seen with teriflunomide are temporary, some cases are associated with severe decreases in creatinine clearance and marked hyperkalemia.

Only 6 of the 10 Pool 1 teriflunomide-treated subjects with increased creatinine $\geq 100\%$ from baseline had a serum potassium measurement available during the serum creatinine increase; for the other 4 subjects, the serum potassium measurement was missing. Of the 6 subjects with serum potassium measurements, 3 (50%) had marked hyperkalemia (measurements of 6.7, >7.352 , and >7.3 mmol/L).

The degree of hyperkalemia seen in some subjects with acute renal failure causes an increased risk of cardiac arrhythmia and death. In the development program for teriflunomide as monotherapy for the treatment of MS, there were 3 teriflunomide-treated subjects found dead, for whom the cause of death was unclear and cardiac arrhythmia could have been a cause.

Preventing cases of acute renal failure will be difficult, because no clear information is available on any inciting factors in teriflunomide-treated subjects with acute renal failure.

Given the transient nature of the acute renal failure seen with teriflunomide, it is unlikely that regular laboratory monitoring can reliably prevent this adverse event. No associated symptoms were documented in any Pool 1 subject with serum creatinine increased $\geq 100\%$ from baseline, including subjects with hyperkalemia. This clinical trial experience points to the likelihood that there will be cases of untreated hyperkalemia, accompanied by an increased risk of cardiac arrhythmia, in patients treated with teriflunomide.

⁵¹ Page 223 of LTS6048 narratives submitted to NDA 202992 on May 1, 2012.

⁵² The upper limit of quantitation for serum potassium at the central laboratory (b) (4) was 7.3 mmol/L.

The parent drug of teriflunomide, leflunomide, has been marketed for treatment of rheumatoid arthritis since 1998. Of note, there is no description of acute renal failure or loin pain in the leflunomide (Arava) prescribing information, and this reviewer was unable to find any cases documented in the published literature. Strenuous activity may be more difficult in patients with rheumatoid arthritis. Because of musculoskeletal pain associated with rheumatoid arthritis, loin pain may be difficult to identify in that patient population. In addition, the general challenges in identifying cases of acute renal failure apply to rheumatoid arthritis patients taking leflunomide as well.

- Increases in serum creatinine with teriflunomide, recommendations by Dr. Mentari:

I recommend that information regarding cases of acute renal failure, as well as accompanying hyperkalemia, be included in the Warnings and Precautions section.

To gain additional information on acute renal failure with teriflunomide, I recommend systematically collecting additional information in ongoing controlled trials. Having a known denominator of subjects and a comparator group will be critical in characterizing the frequency of these events. I recommend collecting the following information in subjects with reported acute renal failure or elevated serum creatinine $\geq 100\%$ of baseline:

- *Whether the subject had any symptoms, including pain. The timing of these symptoms in relation to the elevated serum creatinine should be documented.*
- *Whether the subject had any dehydration or strenuous activity prior to the elevated creatinine*
- *Assessment of what may have caused the acute renal failure*
- *Subjects should have prompt follow-up, including a full basic metabolic panel and urinalysis.*

The Sponsor should evaluate reported cases of acute renal failure as part of their post-marketing safety reports.

The Sponsor should also evaluate reported cases of loin or flank pain as part of their ongoing studies and postmarketing safety reports.

8 Postmarket Experience

There is no postmarketing experience with teriflunomide. However, there is extensive experience with leflunomide, the parent drug, which has close to 2 million PYRs of exposure. The safety profile of Arava® was described in section 2.4 of this review.

9 Appendices

9.1 Literature Review/References

Literature references have been included as footnotes throughout the review.

9.2 Labeling Recommendations

Labeling recommendations are pending at the time of this review.

9.3 Advisory Committee Meeting

No advisory committee meeting was scheduled for this drug.

9.4 Additional information not presented in the body of the review

Information referred to but not included in the body of this review is presented in the following appendices.

Appendix 1. Clinical Pharmacology studies. Teriflunomide NDA.

Study type	Study code	Teriflunomide dose	Number randomize
In vitro studies			
Intestinal permeability	AIV0202, AIV0213	--	--
Protein binding	HMR008477, HMR010274, HMR015182, HMR014543	--	--
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	--	--
Biopharmaceutical studies			
Bioequivalence tablet (b) (4)	(b) (4) BDR6639	14 mg single dose	27
Bioequivalence tablet (test ^a versus reference)	BEQ10169	7 and 14 mg single dose	94
Food effect (early tablet)	1002	20 mg single dose	16
Food effect (Phase 3 tablet)	ALI6504	7 and 14 mg single dose	30
Pharmacokinetics, pharmacodynamics, and initial tolerability in healthy subjects			
Single dose IV	1024	10 mg single dose	6
Single and multiple ascending dose oral	1001	20 mg SD and 100 mg QD for 2 days	16
Multiple ascending dose	TDR10892	70 mg QD for 14 days	13
Excretion balance, pharmacokinetics, metabolism	BEX6038	70 mg single dose	6
Intrinsic factors			
Mild and moderate impairment	POP6507	14 mg single dose	25
Severe renal impairment	POP11432	14 mg single dose	16
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	21
Effect of teriflunomide on other drugs			
Warfarin (CYP2C9 probe)	INT6040	70 mg QD for 3 days then 14 mg QD for 8 days	14
Midazolam (CYP3A probe)	INT10563	70 mg QD for 3 days then 14 mg QD for 11 days	26 ^e
Cocktail: caffeine (CYP1A2), omeprazole (CYP2C19), and metoprolol (CYP2D6)	INT11720	70 mg QD for 3 days then 14 mg QD for 9 days	36 ^f

Appendix 1. Clinical Pharmacology studies. Teriflunomide NDA (cont)

Study type	Study code	Teriflunomide dose	Number randomized
Repaglinide (CYP2C8) ^g	INT11697	70 mg QD for 4 days then 14 mg QD for 8 days	20
Bupropion (CYP2B6)	INT11932	70 mg QD for 4 days then 14 mg QD for 10 days	17
Oral contraceptives	INT10564	70 mg QD for 4 days then 14 mg QD for 10 days	24 ^h
Pharmacokinetics/pharmacodynamics in healthy subjects			
Thorough ECG	TES10852	70 mg QD for 4 days then 14 mg QD for 8 days	194
Pharmacokinetics in efficacy/safety studies			
	2001	14 or 28 mg QD for 7 days and 7 or 14 mg QD thereafter	179
Monotherapy	LTS6048 (2002)	7 and 14 mg QD	147 ⁱ
	EFC6049/TEM SO (3001)	7 and 14 mg QD	1088
	LTS6050	7 and 14 mg QD	742
	EFC10531/TOWER	7 and 14 mg QD	1110 ^j
Adjunct with IFN-β	PDY6045	7 and 14 mg QD	118
	LTS6047	7 and 14 mg QD	86
Adjunct with glatiramer acetate	PDY6046	7 and 14 mg QD	123
	LTS6047	7 and 14 mg QD	96
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	–	--

Source: Table 1. Applicant’s Summary of Clinical Pharmacology. Original submission.

CYP=cytochrome P450; ECG=electrocardiogram; IFN-β=interferon-β; PD=pharmacodynamic; PK=pharmacokinetic; PopPK=population. pharmacokinetic; QD=once daily.

a without colloidal silica and with increase in film-coating thickness

b PopPK analysis with data from 2001 and EFC6049/TEM SO

c meta-analysis with Phase 1 data. *d* meta-analysis with Phase 2/3 data. *e* 25 subjects received teriflunomide

f 35 subjects received teriflunomide. *g* teriflunomide semen concentrations will be measured at Day 11 on Period 2 before repaglinide treatment and on Day 25 after rapid elimination procedure. *h* 23 subjects received teriflunomide

i enrolled. *j* planned. *k* simulation of population pharmacokinetic model-derived teriflunomide pharmacokinetic

parameters. *l* pharmacokinetic/pharmacodynamic analysis with data from 2001 and EFC6049/TEM SO

Appendix 2. Selection criteria in completed core Phase 2 & 3 clinical studies in patients with relapsing multiple sclerosis

TEMSO (From CSR)	2001 (From CSR)	PDY6045 (From CSR)	PDY6046 (From CSR)
Inclusion criteria			
<p>I 01. Multiple sclerosis patients, aged 18 to 55, who were ambulatory (EDSS of ≤ 5.5).</p> <p>I 02. Exhibiting a relapsing clinical course, with or without progression (relapsing remitting, secondary progressive, or progressive relapsing).</p> <p>I 03. Meeting McDonald’s criteria for MS diagnosis.</p> <p>I 04. Experienced at least 1 relapse over the 1 year preceding the trial or at least 2 relapses over the 2 years preceding the trial .</p> <p>I 05. No relapse onset in the preceding 60 days prior to randomization.</p> <p>I 06. During the 4 weeks prior to randomization, the patients must have been clinically stable, without adrenocorticotrophic hormone (ACTH) or systemic steroid treatment.</p> <p>I 07. Signed the informed consent form and the informed consent for human immunodeficiency virus (HIV) testing.</p>	<p>1. Male or female subjects aged between 18 and 65 years.</p> <p>Female subjects had to be of nonchildbearing potential and fulfill at least 1 of the 3 following criteria:</p> <ul style="list-style-type: none"> - Postmenopausal (at least 2 years since last menses). In subjects <60 years old postmenopausal status had to be verified by follicle stimulating hormone (FSH) test. - Surgically sterilized (hysterectomy, bilateral oophorectomy, bilateral tubal ligation with resection). - Demonstrated not to be pregnant (negative serum pregnancy test) or breast feeding at study entry and agree to undergo serum pregnancy testing every 6 weeks AND <ul style="list-style-type: none"> – Fully informed as to the risks of entering the trial and provide special written consent to enter the trial AND – Agree to maintain adequate means of contraception throughout the study and for 24 months after the discontinuation of study treatment or undergo a washout procedure after discontinuing treatment. High-efficacy contraceptives, (e.g., biphasic and triphasic oral contraceptives with common progestens such as levonorgestrel, noretisterone, or gestodene) and classical combined estrogen and progesten pills with estrogen doses as low as 0.03 mg were considered to be adequate means of contraception. Intrauterine devices, Depo-Provera, and subjects who practiced abstinence or with surgically sterilized partners were also accepted methods of 	<p>1 Males and females, aged 18 to 55 years, meeting McDonald’s criteria for definite multiple sclerosis (MS) diagnosis and who were ambulatory (Expanded Disability Status Scale [EDSS] of less or equal to 5.5).</p> <p>2 Exhibiting a relapsing clinical course, with and without progression (relapsing remitting, secondary progressive or progressive relapsing).</p> <p>3 On a stable dose of IFN-β (employing the dosing regimen of the specific IFN-β used) for at least 26 weeks prior to the screening Visit.</p> <p>4 No onset of MS relapse in the preceding 60 days prior to randomization.</p> <p>5 Clinically stable for 4 weeks prior to randomization.</p> <p>6 Have signed the informed consent form and the informed consent for human immunodeficiency virus (HIV) testing.</p>	<p>1. Males and females, aged 18 to 55 years, meeting McDonald’s criteria for definite MS diagnosis and who were ambulatory (Expanded Disability Status Scale [EDSS] of less than or equal to 5.5).</p> <p>2. Exhibiting a relapsing clinical course, with and without progression (relapsing remitting, secondary progressive or progressive relapsing).</p> <p>3. On a stable dose of GA for at least 26 weeks prior to the screening visit.</p> <p>4. No onset of MS relapse in the 60 days prior to randomization.</p> <p>5. Clinically stable for 4 weeks prior to randomization.</p> <p>6. Have signed the informed consent form and the informed consent for human immunodeficiency virus (HIV) testing.</p>

TEMSO (From CSR)	2001 (From CSR)	PDY6045 (From CSR)	PDY6046 (From CSR)
	<p>birth control. Reliance on barrier methods of birth control was not considered sufficient. Female subjects who were not sexually active also had to be adequately informed about appropriate methods of contraception.</p> <p>Male subjects had to consent to practice contraception during the study and for 24 months after discontinuation of the study medication or were recommended to follow the washout procedure if they wished to father a child after treatment discontinuation.</p> <p>2. Clinically definite MS with at least 2 documented relapses as defined by the Poser criteria. The disease course for each subject was to be defined on the basis of the initial episode, subsequent relapses, and progress assessed by review of clinical history and neurological examinations.</p> <p>3. Clinical disease severity between 0 and 6 inclusively according to the EDSS.</p> <p>4. Screening MRI scan (visit 1) fulfilling the criteria for a diagnosis of MS.</p> <p>5. At least 2 clinical relapses in the 3 years prior to screening with at least 1 relapse in the last year.</p> <p>6. Willingness and ability to participate in a long-term, placebo-controlled trial and provide consistent data needed by the investigators to monitor progress. Subjects also had to be willing to undergo 9 MRI scans within 1 year.</p> <p>Informed consent had to be obtained for all subjects before enrollment in the study.</p>		

TEMSO (From CSR)	2001 (From CSR)	PDY6045 (From CSR)	PDY6046 (From CSR)
Exclusion criteria			
<p>E 01. The patients with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia:</p> <ul style="list-style-type: none"> - Hematocrit <24% and/or - Absolute white blood cell count <4000 cells/mm³ and/or - Platelet count <150000 cells/mm³ and/or - Absolute neutrophil ≤1500 cells/mm³. <p>E 02. The patients with a congenital or acquired severe immunodeficiency, a history of cancer (except for basal or squamous cell skin lesions that had been surgically excised, with no evidence of metastasis), lymphoproliferative disease, or any patient who had received lymphoid irradiation.</p> <p>E 03. Human immunodeficiency virus (HIV) positive subjects.</p> <p>E 04. Known history of active tuberculosis not adequately treated.</p> <p>E 05. Persistent significant or severe infection.</p> <p>E 06. Pregnancy.</p> <p>E 07. Breastfeeding.</p> <p>E 08. The patients wishing to parent children during the course of the trial.</p> <p>E 09. Therapies that were disallowed (minimum of 4 weeks prior to randomization):</p>	<ol style="list-style-type: none"> 1. Significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia. 2. Congenital or acquired severe immunodeficiency, history of cancer (except for surgically excised basal or squamous cell skin lesions with no evidence of metastasis), lymphoproliferative disease, or treatment with lymphoid irradiation. 3. Known HIV positive status. 4. Persistent significant or severe infection in the 4 months before visit 1. 5. Uncontrolled hypertension, uncontrolled diabetes, unstable ischemic heart disease, active inflammatory bowel disease, active peptic ulcer disease, terminal illness, or other medical condition which, in the opinion of the investigator, put the subject at risk to participate in the study. 6. Clinically relevant neurologic disease (including head trauma with residual deficit, stroke, or transient ischemic attack). 7. Clinically relevant cardiovascular, hepatic, endocrine, or other major systemic disease that made implementation of the protocol or interpretation of the study results difficult. 8. Any known condition or circumstance that, in the investigator's opinion, prevented compliance or completion of the study. 9. Pregnancy. 10. Breastfeeding. 11. Women of childbearing potential except if they fulfilled all conditions described in Section Inclusion criteria . 12. Subjects wishing to parent children during the trial or following the trial except if they agreed to the conditions or washout procedure. 13. Likelihood of requiring drugs not permitted by 	<ol style="list-style-type: none"> 1 Significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia: <ul style="list-style-type: none"> - Hematocrit <24% and/or, - Absolute white blood cell (WBC) count <4000 cells/mm³ (µL) and/or, - Platelet count <150 000 cells/mm³ (µL) and/or, - Absolute neutrophil ≤1500 cells/mm³ (µL). 2 Congenital or acquired severe immunodeficiency, a history of cancer (except for basal or squamous cell skin lesions which have been surgically excised, with no evidence of metastasis), lymphoproliferative disease, or any subject who had received lymphoid irradiation. 3 HIV positive status. 4 Known history of active tuberculosis not adequately treated. 5 Persistent significant or severe infection. 6 Pregnancy. 7 Breastfeeding. 8 Wishing to parent children during the course of the trial. 9 Therapies, which are disallowed (minimum of 4 weeks prior to randomization): phenytoin, warfarin, tolbutamine, or cholestyramine. 10 St. John's Wort products containing hyperforin in an unknown percentage or greater than 1% of the extract are disallowed 4 weeks prior to randomization. 11 Have used adrenocorticotrophic hormone (ACTH) or systemic corticosteroids within 4 weeks prior to randomization. 12 Prior or concomitant use of cladribine, mitoxantrone, or the immunosuppressant agents azathioprine, cyclophosphamide, cyclosporin, methotrexate or mycophenolate. 13 Prior use of glatiramer acetate or cytokine therapy in the preceding 24 weeks. 14 Prior use of natalizumab (Tysabri®). 	<ol style="list-style-type: none"> 1. Significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia: <ul style="list-style-type: none"> - Hematocrit <24% and/or, - Absolute white blood cell (WBC) count <4000 cells/mm³ and/or, - Platelet count <150 000 cells/mm³ and/or, - Absolute neutrophil ≤1500 cells/mm³. 2. Congenital or acquired severe immunodeficiency, a history of cancer (except for basal or squamous cell skin lesions which have been surgically excised, with no evidence of metastasis), lymphoproliferative disease, or any subject who has received lymphoid irradiation. 3. HIV positive status. 4. Known history of active tuberculosis not adequately treated. 5. Persistent significant or severe infection. 6. Pregnancy. 7. Breastfeeding. 8. Wishing to parent children during the course of the trial. 9. Therapies, which are disallowed (minimum of 4 weeks prior to randomization): phenytoin, warfarin, tolbutamine, or cholestyramine. 10. St. John's Wort products containing hyperforin in an unknown percentage or greater than

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<p>TEMSO (From CSR)</p>	<p>2001 (From CSR)</p>	<p>PDY6045 (From CSR)</p>	<p>PDY6046 (From CSR)</p>
<p>phenytoin, warfarin, tolbutamide, St. John's Wort, or cholestyramine. E 10. The patients who used ACTH or systemic corticosteroids for 4 weeks prior to randomization. E 11. Prior or concomitant use of cladribine, mitoxantrone, or other immunosuppressant agents such as azathioprine, cyclophosphamide, cyclosporin, methotrexate, or mycophenolate. E 12. Prior use of interferons or cytokine therapy in the preceding 4 months. E 13. Prior use of - glatiramer acetate therapy in the preceding 4 months, -intravenous immunoglobulins in the preceding 6 months. E 14. Prior use of any investigational drug in the preceding 6 months. E 15. Contraindication for MRI, ie, presence of pacemaker, metallic implants in high-risk areas (ie, artificial heart valves, aneurysm/ vessel clips), presence of metallic material (ie, shrapnel) in high risk areas, known history of allergy to any contrast medium, or history of claustrophobia that would prevent completion of all protocol-scheduled MRI. Hip implants were not contraindicated. E 16. Liver function impairment</p>	<p>the study protocol during the study. 14. Treatment with any investigational drug in the 6 months before visit 1. Exceptions to this criterion was made for subjects previously treated in the oral Copaxone® CORAL study. Given the established profile of injectable Copaxone®, and the limited efficacy of the oral therapy, these subjects were allowed to have a screening visit (visit 1) at least 30 days after their last dose of CORAL study medication, provided they had not subsequently received other MS therapies. 15. Treatment with disallowed medications (i.e., phenytoin, warfarin, tolbutamide, or cholestyramine) in the 4 weeks before visit 1. 16. Treatment with systemic, inhaled, intra-articular, or widely applied topical corticosteroids or adrenocorticotropic hormone (ACTH) in the 4 weeks before visit 1. 17. Treatment with interferon, gamma-globulin, or other non-corticosteroid, immunomodulatory therapies in the 4 months before visit 1. 18. Previous treatment with cladribine or mitoxantrone. Treatment with other chemotherapeutic agents such as azathioprine, cyclophosphamide, cyclosporine, or methotrexate in the 6 months before visit 1. 19. History of recent, clinically significant drug or alcohol abuse. 20. Liver function impairment or persisting ALT or direct bilirubin elevations of more than 1.5-fold the upper limit of normal (ULN). 21. Positive serology for hepatitis B or C. 22. Hypoproteinemia (e.g., in severe liver disease of nephrotic syndrome) with serum albumin <3 g/dL. 23. Moderate to severe impairment of renal function with serum creatinine >133 µmol/L (1.5 mg/dL). 24. Mental conditions rendering the subject unable</p>	<p>15 Prior use of intravenous immunoglobulins in the preceding 24 weeks. 16 Prior use of any investigational drug in the preceding 24 weeks. 17 Contraindication for MRI, eg, presence of pacemaker, metallic implants in high-risk areas (ie, artificial heart valves, aneurysm/vessel clips), presence of metallic material (eg, shrapnel) in high risk areas, known history of allergy to any contrast medium, or history of claustrophobia that would prevent completion of all protocol-scheduled MRIs. Hip implants are not contraindicated. 18 Liver function impairment or persisting elevations of serum glutamic pyruvic transaminase (SGPT)/ alanine transaminase (ALT), or serum glutamic oxaloacetic transaminase (SGOT)/ aspartate transaminase (AST), or direct bilirubin >1.5-fold the upper limit of normal (ULN). 19 Persisting elevations of serum amylase or lipase greater than 2-fold the upper limit of normal 20 Known history of chronic active hepatitis. 21 Known history of chronic pancreatic disease or pancreatitis. 22 Hypoproteinemia (eg, in case of severe liver disease or nephrotic syndrome) with serum albumin <3.0 g/dL. 23 Moderate to severe impairment of renal function, as shown by serum creatinine >133 µmol/L (or >1.5 mg/dL). 24 Previous treatment with teriflunomide or leflunomide (ARAVA®) or hypersensitivity to any of the other ingredients or excipients in the investigational product. 25 Likelihood of requiring treatment during the study period with drugs not permitted by the clinical study protocol. 26 Clinically relevant cardiovascular, hypertensive (defined as blood pressure [BP] ≥160/100 mm/Hg), hepatic, neurological, endocrine, or other major</p>	<p>1% of the extract are disallowed 4 week prior to randomization. 11. Have used adrenocorticotropic hormone (ACTH) or systemic corticosteroids within 4 weeks prior to randomization. 12. Prior or concomitant use of cladribine, mitoxantrone, or the immunosuppressant agents azathioprine, cyclophosphamide, cyclosporin, methotrexate, or mycophenolate. 13. Prior use of interferon-β or cytokine therapy in the preceding 24 weeks. 14. Prior use of natalizumab (Tysabri®). 15. Prior use of intravenous immunoglobulins in the preceding 24 weeks. 16. Prior use of any investigational drug in the preceding 24 weeks. 17. Contraindication for MRI, eg, presence of pacemaker, metallic implants in high-risk areas (ie, artificial heart valves, aneurysm/vessel clips), presence of metallic material (eg, shrapnel) in high-risk areas, known history of allergy to any contrast medium, or history of claustrophobia that would prevent completion of all protocol-scheduled MRIs. Hip implants are not contraindicated. 18. Liver function impairment or persisting elevations of serum glutamic pyruvic transaminase (SGPT)/ alanine aminotransferase (ALT), or serum glutamic</p>

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<p>TEMSO (From CSR)</p>	<p>2001 (From CSR)</p>	<p>PDY6045 (From CSR)</p>	<p>PDY6046 (From CSR)</p>
<p>or persisting elevations of serum glutamic pyruvic transaminase (SGPT /ALT), serum glutamic oxaloacetic transaminase (SGOT /AST) or direct bilirubin greater than 1.5-fold the upper limit of normal (ULN). E 17. Known history of active hepatitis. E 18. Hypoproteinemia (eg, in case of severe liver disease or nephrotic syndrome) with serum albumin <3.0 g/dL. E 19. Moderate to severe impairment of renal function, as shown by serum creatinine >133 μmol/L (or >1.5 mg/dL). E 20. Previous treatment with teriflunomide or leflunomide (ARAVA®). E 21. Likelihood of requiring treatment during the study period with drugs not permitted by the clinical study protocol. E 22. Clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the patient at risk by participating in the study. E 23. History of drug or alcohol abuse. E 24. Mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study.</p>	<p>to understand the nature, scope, and possible consequences of the study. 25. Previous treatment with teriflunomide or leflunomide (ARAVA™). Any concomitant disorder (e.g., diabetes mellitus, hypertension, heart disease) had to be controlled before entry into the study by appropriate medication that had to be continued unchanged throughout the study if possible. Any subject who did not fulfill the inclusion criteria at visit 3 could be screened a second time after at least 4 weeks and had to repeat visits 1 and 3. A third screening was not allowed. Any waiver of the inclusion and exclusion criteria had to be approved by the investigator and sponsor on a case-by-case basis and documented with a waiver letter to be filed with the case report form.</p>	<p>systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the subject at risk by participating in the study. 27 History of drug or alcohol abuse. 28 Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study. 29 Severe depressive disorder and/or suicidality. 30 Unlikely to comply with the protocol, eg, uncooperative attitude, inability to return for followup visits, and unlikelihood of completing the study. 31 Subject is the Investigator or any sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol. Patients of reproductive potential Female patients were not to be pregnant or breast-feeding at enrollment in the study. Absence of pregnancy had to be demonstrated by serum testing prior to exposure to the investigational products or any other study procedure and was to be checked by serum pregnancy testing at each study visit. Patients were not to become pregnant or father during the study, up to the close-out visit, because of any low residual drug related substance that could be present more than 2 years after administration. A washout procedure was to be strictly observed at the end of the close-out visit or in case of treatment discontinuation.</p>	<p>oxaloacetic transaminases (SGOT)/ aspartate aminotransferase (AST), or direct bilirubin >1.5-fold the upper limit of normal (ULN). 19. Persisting elevations of serum amylase or lipase greater than 2-fold the ULN. 20. Known history of chronic active hepatitis. 21. Known history of chronic pancreatic disease or pancreatitis. 22. Hypoproteinemia (eg, in case of severe liver disease or nephrotic syndrome) with serum albumin <3.0 g/dL. 23. Moderate to severe impairment of renal function, as shown by serum creatinine >133 μmol/L (or >1.5 mg/dL). 24. Previous treatment with teriflunomide or leflunomide (Arava®) or hypersensitivity to any of the other ingredients or excipients in the investigational product. 25. Likelihood of requiring treatment during the study period with drugs not permitted by the clinical study protocol. 26. Clinically relevant cardiovascular, hypertensive (defined as blood pressure [BP] ≥160/100 mm/Hg), hepatic, neurological, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the subject at risk by participating in the</p>

TEMSO (From CSR)	2001 (From CSR)	PDY6045 (From CSR)	PDY6046 (From CSR)
<p>E 25. The patient unlikely to comply with protocol, eg, uncooperative attitude, inability to return for follow-up visits, or known unlikelihood of completing the study.</p> <p>E 26. The patient who was the Investigator or any subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.</p> <p>E 27. Prior use of natalizumab (Tysabri®).</p> <p>E 28. Persisting elevations of serum amylase or lipase greater than 2 x ULN.</p> <p>E 29. Known history of chronic pancreatic disease or pancreatitis.</p> <p>Patients of reproductive potential</p> <p>The female patients were not allowed to be pregnant or breast feeding at enrollment in the study. Negative pregnancy testing was to be demonstrated prior to exposure to the investigational product or any other study procedure and during each study visit in order to continue the study treatment. The patients were also not allowed to father a child during the study, up to the closeout visit, because of any low residual drug-related substance that could be present more than</p>			<p>study.</p> <p>27. History of drug or alcohol abuse.</p> <p>28. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.</p> <p>29. Severe depressive disorder and/or suicidality.</p> <p>30. Unlikely to comply with the protocol, eg, uncooperative attitude, inability to return for follow-up visits, and unlikelihood of completing the study.</p> <p>31. Subject is the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.</p> <p>Patients of reproductive potential</p> <p>Female patients were not to be pregnant or breast-feeding at enrollment in the study. Absence of pregnancy had to be demonstrated by serum testing prior to exposure to the investigational products or any other study procedure and was to be checked by serum pregnancy testing at each study visit. Patients were not to become pregnant or father a child during the study, up to the close-out visit, because of any low residual drug related substance that could be present more than 2 years after administration. A washout procedure was to be strictly observed at the end of the close-out</p>

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TEMSO (From CSR)	2001 (From CSR)	PDY6045 (From CSR)	PDY6046 (From CSR)
2 years after administration. A washout procedure was to be strictly observed at the close-out visit or in case of treatment discontinuation to accelerate the elimination of teriflunomide.			visit or in case of treatment discontinuation.

Source: Applicant's ISS Table 70.

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Appendix 3. Scheduled efficacy and safety measurements in protocol 6049/TEMSo

Visit name	Screening	MSFC practice	Study treatment period																				Un-scheduled relapse		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22		23	
Week Time point ¹	up to -4 weeks	-5 to -7 days	0 Baseline	4	8	12	16	20	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108 ² Close-out		
Randomization			x																						
Informed consent/ Re-consent	x																								x
Review inc./excl. criteria	x		x																						
Demographics	x																								
Medical & surgical history	x																								
MS diagnosis ³ / MS History ⁴	x		x																						
Chest X-ray ⁵	x																								
Prior/concomitant meds.	x	x	x			x			x		x		x		x		x		x		x		x		x
Kurtzke EDSS	x		x			x			x		x		x		x		x		x		x		x		x
FS score	x		x			x			x		x		x		x		x		x		x		x		x
MSFC	x	x	x						x				x				x						x		
MRI ⁶			x						x				x				x						x		x
FIS			x			x			x		x		x		x		x		x		x		x		x
EQ-5D			x			x			x		x		x		x		x		x		x		x		x
SF-36		x						x				x				x					x				x
PS-MS		x						x				x				x					x				x
WPAI			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Resource utilization ⁷			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x					x					x				x						x				x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood sampling for safety ⁸	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum pregnancy test	X ⁹	x	x			x			x		x		x		x		x		x		x		x		x
Urinalysis sample for safety	x	x				x			x		x		x		x		x		x		x		x		x
Vital signs ¹⁰	x		x ¹¹			x			x		x		x		x		x		x		x		x ¹¹		x
Pharmacokinetic sample		x	x ¹²			x ¹³			x ¹³		x ¹³		x												
Dispense study medication ¹⁴			x			x			x		x		x		x		x		x		x				
Accountability/compliance review						x			x		x		x		x		x		x		x				x

Source: Synopsis. Protocol 6049 CSR.

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EDSS = Expanded Disability Status Scale, MSFC = Multiple Sclerosis Functional Composite practice visit, FS = Functional System, SF-36 = Short Form generic health survey (36 items),

FIS = Fatigue Impact Scale, EQ-5D = EuroQoL, PS-MS = Performance Scales–Multiple Sclerosis, WPAI = Work Productivity and Activities Impairment, MRI = Magnetic resonance imaging

1 Baseline assessments should be completed within 3 days prior to randomization. All post-baseline assessments should be completed within plus or minus 7 days of the scheduled visit date relative to the baseline visit

2 Occurs at Week 108, or as soon as possible after last dose of study drug for withdrawals

3 As per McDonald's criteria for MS diagnosis

4 Multiple Sclerosis history will include presence of a relapsing clinical course, frequency of relapse, current stability of MS, and previous and concomitant MS treatments (within the last 6 months)

5 Chest X-ray need only be performed if the subject has not had one within 1 year of entry into the study

6 MRI will be carried out at baseline and Visits 9, 13, 17 and 23

7 Including number of hospital visits, length of stay by location, emergency room and accident and emergency visits, and consultant visits

8 Including hematology and blood chemistry

9 Postmenopausal female subjects will also undergo a follicle stimulating hormone (FSH) test at screening to verify postmenopausal status

10 Including systolic and diastolic blood pressure (BP), pulse rate (PR), body temperature, and weight

11 Vital signs will also include height at baseline and close-out visit only

12 Drawn at 1-3 hours after the first dosing

13 Trough sample obtained only on subjects who have taken their medication 1 day prior and not on subjects who discontinue their medication. Unscheduled pharmacokinetic sampling may be ordered as necessary for therapeutic monitoring. Pharmacokinetic sampling will not be obtained if the subjects missed ≥ 2 doses of study medication during the week prior to sampling day, unless it is at close out-at the end of the study, or after drop-out.

14 Study medication must not be dispensed until after all baseline procedures have been completed, eligibility has been confirmed, and subject has been randomized via IVRS. Subjects must not take their study medication on the morning of the visit day prior to coming in and will take only their medication after pharmacokinetic samples have been obtained

Appendix 4. Serious AE in studies not included in the ISS

SAE in Clinical pharmacology studies

Table 4.1. Brief narrative of patients with serious adverse events in clinical pharmacology studies

Pt ID	Comment
Pooled Single dose studies	
250001702, ALI6504	57 yo F, asymptomatic isolated atrial fibrillation, 3 days after a single dose of Teri 7 mg (<i>difficult to assess relationship; event is probably not related</i>)
826001005 BEQ10169	25 yo F, sudden severe headache (severity score of 9 out of 10) without any other associated symptoms 20 days after receiving Teri 14 mg . It lasted 24 hours. Computed tomography scan and cerebral spinal fluid examinations were both normal. She was given 1 g paracetamol and the event resolved the following day. (<i>20 days after a single dose, probably unrelated</i>)
0001/0024 BDR6639	22 yo M, appendicitis after a single dose of Teri 14 mg (<i>probably unrelated</i>)
Pooled repeated-dose studies	
826001012, INT6040	24 yo M, viral gastroenteritis, 26 days after last Teri 14 mg treatment and after the accelerated elimination treatment procedure period (<i>probably unrelated</i>)
250001277 TES10852	60 yo F, urticaria (both arms, abdomen, upper back) on Day 11 of Teri 14 treatment. The event resolved within 11 days with corrective antihistaminic treatment. <i>Leflunomide is known to be associated with hypersensitivity. The event seems to have resolved without early drug discontinuation, however, drug was discontinued anyway because of study completion. In my opinion this case may be related to teriflunomide.</i>
250001224, TES10852	20 yo F, increase in ALT > 15.5 x ULN, 8 days after the end of repeated (12 days) Teri 14 , during the accelerated elimination treatment procedure with cholestyramine. ALT returned to close to normal values after 1 month. <i>This occurred during rapid elimination. Perhaps both, teriflunomide and cholestyramine had a role in this ALT increase.</i>
250001227, TES10852	30 yo F on placebo , ALT > 3 x ULN during the accelerated elimination treatment procedure with cholestyramine. <i>This occurred during rapid elimination. Probably related to cholestyramine.</i>

Source: narratives and AE dataset submitted 10/21/11.

In summary, SAE in Clin pharm are consistent with known safety profile (mostly GI, skin, ALT elevation). In three cases the AE (one gastroenteritis, one ALT elevation on Teri, one ALT elevation on placebo) occurred during cholestyramine accelerated elimination and likely related to cholestyramine.

SAE in Ongoing phase 3 studies

- SAE in TOWER

Number of patients with SAE in TOWER is presented in the following table (Interim study report, amendment 1 submission).

Table 4.2. Serious adverse events, safety population. TOWER interim results.

Primary System Organ Class Preferred Term n(%)	Placebo (N=363)	7 mg (N=379)	14 mg (N=350)
Any class	27 (7.4%)	36 (9.5%)	30 (8.6%)
Infections and infestations	5 (1.4%)	8 (2.1%)	6 (1.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.3%)
Blood and lymphatic system disorders*	1 (0.3%)	7 (1.8%)	6 (1.7%)
Metabolism and nutrition disorders	0	1 (0.3%)	0
Psychiatric disorders	1 (0.2%)	3 (0.8%)	2 (0.6%)
Nervous system disorder*	3 (0.8%)	1 (0.3%)	5 (1.4%)
Ear and labyrinth disorders	0	1 (0.3%)	0
Cardiac disorders	1 (0.3%)	0	1 (0.3%)
Vascular disorders	0	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	2 (0.6%)	0	1 (0.3%)
Gastrointestinal disorders	2 (0.6%)	3 (0.8%)	2 (0.6%)
Hepatobiliary disorder*	1 (0.3%)	1 (0.3%)	4 (1.1%)
Skin and subcutaneous tissue disorders	1 (0.3%)	0	0
Musculoskeletal and connective tissue disorders	1 (0.3%)	0	0
Renal and urinary disorders	0	1 (0.3%)	1 (0.3%)
Pregnancy, puerperium and perinatal conditions	0	1 (0.3%)	0
Reproductive system and breast disorders	1 (0.3%)	1 (0.3%)	0
General disorders and administration site conditions	1 (0.3%)	0	0
Investigations	7 (1.9%)	6 (1.6%)	3 (0.9%)
Injury, poisoning and procedural complications	4 (1.1%)	5 (1.3%)	2 (0.6%)

n (%) = number and percentage of patients with at least one treatment emergent SAE.

Note: Table sorted by SOC internationally agreed order. Source Table 14.2.7.2.1 of TOWER Interim CSR.

* SOCs with a greater frequency of events on teriflunomide as compared to placebo.

SOC in which teriflunomide has a higher percentage of SAE than placebo are Blood and lymphatic system disorders, Nervous system disorders and Hepatobiliary disorders. Selected treatment emergent SAEs in TOWER's interim report, by SOC are discussed below.

- SAEs Blood and lymphatic system disorders, TOWER

There was an excess of neutropenia in the teriflunomide groups as compared to placebo, as shown in the table below:

Table 4.3. SAE in Blood and lymphatic system disorders SOC (TOWER interim report)

Primary System Organ Class Preferred Term n(%)	Placebo (N=363)	teriflunomide	
		7 mg (N=379)	14 mg (N=350)
Blood and lymphatic system disorders	1 (0.3%)	7 (1.8%)	6 (1.7%)
Neutropenia	1 (0.3%)	6 (1.6%)	6 (1.7%)
Autoimmune thrombocytopenia	0	1 (0.3%)	0

Source: Table 14.2.7.2.3, TOWER interim report

As per the datasets, all SAE events of neutropenia were considered related to study drug by the investigator (including the case on placebo). Normal range for central lab for WBC is 3.8 - 10.7 Giga/L; for neutrophil count is 1.96 - 7.23 Giga/L. Cases of SAE of neutropenia with absolute neutrophil count (ANC) of ≤ 1 Giga/L are presented below.

Table 4.4. Brief narratives of patients with serious neutropenia in Blood and lymphatic disorders SOC, TOWER interim analysis.

ID	Intensity	Drug withdrawn	Resolved	Comments from narratives
Teri 14				
010531-112-0101-0019	Mild	N	Y	26 yo M on Teri 14 . Hx of respiratory disorder, chronic sinusitis, sinus tachycardia, plasmapheresis. No concomitant meds reported. On day 169 WBC was 3.14 Giga/L, ANC 0.53 Giga/L . Two weeks later WBC resolved but ANC still in the 1.2 Giga/L range. He did not have any infection. ON Day 253 he recovered from neutropenia. Study treatment was ongoing. <i>Neutropenia with ANC between 0.5 and 1 Giga/L probably related to teriflunomide.</i>
Teri 7				
010531-804-0121-0004	Mild	N	R	30 yo M, on Teri 7 . Hx of mononucleosis and bronchitis. Treated with tacrine, cyclophosphamide, methylprednis., pentoxifylline in the past. No concom meds reported. On Day 15, ANC 1.68 Giga/L. On Day 56, ANC 1 Giga/L . WBC was also decreased (2.81 Giga/L). After Day 56 the neutrophil count increased and returned to normal on Day 85. Drug continued. <i>Event is probably related to drug.</i>
010531-112-0102-0014	Mod	N	Y	25 yo M, on Teri 7 . Past hx of pneumonia. On Day 113, WBC 2.48 Giga/L and ANC at 1.31 Giga/L. He had an upper respiratory infection the previous week, without fever. He recovered on Day 119. On Day 155 another episode of neutropenia with ANC 0.59 Giga/L, recovered on Day 161. <i>The first episode could be due to a viral infection but recurrence of the event makes it more likely to be drug related.</i>
010531-804-0121-0003	Mild	N	Y	40 yo F, on Teri 7 . hx of HTN, myocardial fibrosis, pyelonephritis She was previously treated with multiple medications/herbal supplements. Concomitant therapies included lisinopril. On Day 127, labs showed neutropenia with ANC of 0.99 Giga/L. She had no complaints. Other cell lines were WNL. Drug was stopped for 9 days. On Day 141 event resolved, with ANC 4.51 Giga/L. Drug was re-started.
Placebo				
010531-112-	Mod	N	Y	25 yo M on PLACEBO . Concomitant therapies ibuprofen

0103-0003				and paracetamol. On day 132 labs showed neutropenia with WBC 3.38 Giga/L and ANC 0.88 Giga/L , with fever, myalgia and weakness. Diagnosed with acute respiratory viral infection. Resolved on Day 140. <i>Neutropenia may have been related to respiratory viral infection.</i>
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Source: TOWER study datasets and narratives in original submission.

Additionally, there was one case of thrombocytopenia as follows.

- **010531/840/0036/0006**, 47 you F on **Teri 7 mg**. No concom Meds. On Day 294 presented platelet count 76 Giga/L (range 140-400 Giga/L). On Day 300 platelet count 44 Giga/L, On Day 305 < 10 Giga/L. Diagnosed as autoimmune thrombocytopenia. Treated with pulse decadron. Day 318 platelet count still <10 Giga/L, treated with another course of decadron and was given 1000 mg/K IV immunoglobulin. Transient mild vaginal spotting, no major bleeding. Rituxan added to treatment. Bone marrow biopsy and peripheral smear showed hypocellular marrow with trilineage hematopoiesis with full range of maturation; no dysplasia, no increase in blasts. Patient recovered on Day 554; investigator attributed to drug. Last dose of Teri was taken Day 299; cholestyramine given Day 301 to 311.

There was severe thrombocytopenia with platelet count <10 Giga/L, without major bleeding. It was diagnosed as “autoimmune” but it is unclear how the diagnosis was made. The reporting term was “immune mediated thrombocytopenia” It is possible that this event was drug induced thrombocytopenia.

AE in the Blood and lymphatic system disorders SOC in TOWER are consistent with known leflunomide effects of bone marrow suppression. There is one case of profound thrombocytopenia (<10 Giga/L) and several cases of neutropenia, including three with ANC between 0.5 and 1 Giga/L (one on placebo). Cases were not complicated by either major bleeding or infection and they recovered without specific treatment or drug discontinuation. The case of neutropenia on placebo was likely related to a viral infection. The case of thrombocytopenia was diagnosed as “autoimmune” but the evidence of this being an autoimmune process is missing. It could be drug induced-immune mediated thrombocytopenia.

In addition to these cases, some cases were non-serious but led to study discontinuation.

- SAE in Cardiac SOC, TOWER

In the Cardiac disorders SOC, there was one SAE **case of atrial fibrillation (on Teri 14) and one case of pericardial effusion (on placebo)**. Additionally, one case was reported as “renal artery stenosis” but the coding should have been chest pain/unstable angina. The narratives are as follows:

- **840/086/007**, 48 Black female, on Day 67 of Teriflunomide 7 developed SAE of **Renal artery stenosis**. She had history of diabetes mellitus, hyperlipidemia, obesity, dysphagia, GERD, hematuria, urinary incontinence, hypothyroidism, anemia, DVT, drug hypersensitivity, depression, pain, dysarthria, and benign pituitary tumor and angina pectoris. Previous treatment for MS included methylprednisolone and glatiramer. Concomitant meds included baclofen, amlodipine, olmesartan, clopidogrel, hydrochlorothiazide, escitalopram, zolpidem, labetalol, spironolactone, clonidine,

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metformin, rosuvastatin, fexofenadine and levothyroxine. As per clarification submitted on 4/12/12 at FDA request, the patient had seen a cardiologist approximately one year before entering the TOWER study. At that time an echo had suggested possible ischemia in the high lateral wall; she was advised to better control her BP and heart catheterization was deferred until she presented symptoms. On Day 64 of the TOWER study she went to the ER with chest pain radiating to left arm, diaphoretic and short of breath. ECG showed lateral T wave inversion, consistent with unstable angina. During cardiac catheterization (Day 67) she was diagnosed with left renal artery stenosis, requiring a stent. After stenting her BP was better controlled. Subsequently she withdrew consent.

- **276001/012** Teri 14. 24 yo F medical hx of epilepsy and brain injury, migraine, asthma, diagnosed with MS one year prior to entering the study developed **atrial fibrillation** on Day 73 of Teri 14 treatment. Concomitant meds included sumatriptan. She had tachycardia, vertigo, nausea and diarrhea and felt chest tightness. She was hospitalized and treated with metoprolol and enoxaparin. Spontaneous conversion to sinus rhythm occurred. She persisted with position dependent vertigo and nystagmus. Brain MRI showed new inflammatory foci consistent with MS lesion. Echocardiogram showed no atrial enlargement. The reason for the atrial fibrillation was not identified. Urinalysis showed a urinary infection that was treated with oral antibiotic (cotrim forte) for 5 days. She was discharged on Day 78 on stable condition and continued in the study. Event was not considered related to study drug by the investigator.

It is unclear how the diagnosis of atrial fibrillation was made. There is no information on laboratory measurements at the time of the Afib.

- SAE Infections and infestations SOC, TOWER

Overall, the risk of serious infections and infestations was similar between placebo and teriflunomide groups (1.4%, 2.1% and 1.7% for placebo, Teri 7 and Teri 14, respectively). Most events occurred in only one patient in each treatment group, except for two urinary tract infections on Teri 14. Of note, there was a case of gastrointestinal tuberculosis **and a case of osteomyelitis by prevotella species** in the Teri 14 group. These cases have been discussed in section 7.3.2.3.

- SAEs Psychiatric system disorders SOC, TOWER.

Table 4.5. Serious adverse events n Psychiatric system disorders SOC (TOWER)

Primary System Organ Class Preferred Term n(%)	Placebo (N=363)	teriflunomide	
		7 mg (N=379)	14 mg (N=350)
Psychiatric disorders	1 (0.3%)	3 (0.8%)	2 (0.6%)
Depression	1 (0.3%)	1 (0.3%)	0
Completed suicide	0	0	1 (0.3%)
Suicide attempt	0	1 (0.3%)	1 (0.3%)
Schizophrenia	0	1 (0.3%)	0

Source: Table 14.2.7.2.3, TOWER interim report

One completed suicide and two suicide attempts occurred during this study, all on teriflunomide.

- **156012005**, 19 yo F committed suicide by carbon monoxide poisoning on Day 71 of Teri 14 treatment (described under Deaths). She had a history of depression. No concomitant therapies were reported. The event was not considered related to study drug by the investigator.
- **00330001**, 25 yo M. On Day 17 of Teri 14 he developed moderate affective disorder; on Day 18, after fighting with spouse had had a suicide attempt stabbing himself with a knife in the abdomen and

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wrist. Hospitalized, underwent abdominal surgery. During surgery he developed hemorrhagic shock. He recovered. The patient never had experienced depression, suicidal ideation or suicide attempt. Psychiatrist who evaluated him considered the patient’s anxiety had been caused by environmental factors but could not exclude relationship to study drug. Drug was discontinued.

- **276001011**, 40 yo M with a medical history of depression. Concomitant therapies included trimipramine maleate, carbamazepine, baclofen, perazine, venlafaxine hydrochloride and ibuprofen. On day 40 of Teri 7 treatment, he made a suicide attempt by ingesting 70-100 tablets of perazin and lorazepam, leading to hospitalization. He was diagnosed with a strong depressive syndrome. He was treated and stabilized and discharged home on Day 47. Therapy with study drug continued.

- SAEs, Nervous system disorders SOC, TOWER

Table 4.6. Serious adverse events in Nervous system disorders SOC (TOWER)

Primary System Organ Class Preferred Term n(%)	Placebo (N=363)	teriflunomide	
		7 mg (N=379)	14 mg (N=350)
Nervous system disorders	3 (0.8%)	1 (0.3%)	5 (1.4%)
Headache	2 (0.6%)	0	1 (0.3%)
Sensory disturbance	1 (0.3%)	0	0
Optic neuritis	0	0	1 (0.3%)
Syncope	0	1 (0.3%)	1 (0.3%)
Multiple sclerosis relapse	0	0	1 (0.3%)
Polyneuropathy	0	0	1 (0.3%)

Source: Table 14.2.7.2.3, TOWER interim report

There were more events in the Teri 14 group as compared to placebo, but the total number of events is small. Events occurred only once in each treatment group. There was one case of syncope on Teri 7 and one on Teri 14.

- **84000150009**, 52 yo F with history of hypertension, mitral valve prolapse, depression and drug hypersensitivity. She was taking multiple concomitant medications. On Day 20 of Teri 14 treatment she was diagnosed with urinary tract infection. The infection was resistant to oral medications. On Day 35 the patient passed out without warning sings at her daughter’s house. She was hospitalized and placed on telemetry for continuous cardiac monitoring. There is no mention of abnormal ECG during monitoring. On Day 123 she experienced **intermittent atrial fibrillation**. No vital signs are available at that time. She recovered on Day 134 without corrective treatment. The events of syncope and AFIB were considered not related to study drug. It is unclear how long was the patient in the hospital and whether the episode of atrial fibrillation was diagnosed under monitoring. *It is unclear if the syncope was related to intermittent AFIB and whether these events were related to teriflunomide.*
- **61600020005**, 53 yo M presented syncope on Day 474 of Teri 7 treatment. This was secondary to an accidental head contusion. *Not related to Teriflunomide.*

There was one case of SAE of polyneuropathy in the Teri 14 group.

- **6160030011**, 26 yo M, diagnosed with MS one year prior to entry. Concomitant meds included amoxicillin/clavulanic acid, potassium and omeprazole. On Day 425 polyneuropathy was suspected. The diagnosis was confirmed by NCS. Event worsened in intensity from mild to moderate on Day 569. He was treated with methylprednisolone. Drug was discontinued on Day 577 and he underwent cholestyramine washout from Day 586 to 596. On Day 603 he was hospitalized with shortening of

walking distance with feeling of burning and numbness of feet and fingers. On physical examination he had distal paresis of upper and lower limbs, lack of knee, ankle, and Achilles tendon reflexes bilaterally. EMG revealed features of sensory axonal polyneuropathy. He had no prior history of similar events, no diabetes or alcohol abuse, no nutritional deficiencies. The event was considered related to study drug by the investigator. At the last report the patient was recovering.

Typical polyneuropathy with sock and glove distribution during teriflunomide treatment. He improved after drug discontinuation, although at time of last report he was not fully recovered yet.

In the Vascular disorders SOC, there was a SAE case of hemorrhagic shock in the Teri 14 group in a patient who had a suicide attempt.

In the Respiratory disorders SOC, there were two SAE cases of asthma on placebo and one in the Teri 14 group.

Table 4.7. Serious adverse events in Hepatobiliary SOC (TOWER)

Primary System Organ Class Preferred Term n(%)	Placebo (N=363)	teriflunomide	
		7 mg (N=379)	14 mg (N=350)
Hepatobiliary disorders	1 (0.3%)	1 (0.3%)	4 (1.1%)
Cholelithiasis	0	0	1 (0.3%)
Cholecystitis	1 (0.3%)	0	1 (0.3%)
Cholecystitis acute	0	0	1 (0.3%)
Hepatitis toxic	0	0	1 (0.3%)
Gallbladder perforation	0	1 (0.3%)	0

The percentage of hepatobiliary disorders is higher on teriflunomide 14, but the number of events is small.

- **804111008.** 32 yo F diagnosed with **Hepatitis toxic** on Day 15 of Teri 14 treatment. Concomitant meds included citrargine. At screening, ALT was 14 U/L (nl 6-34) with total BR 27 UMOL/L (nl 3-21). On Day 15 ALT increased 2.4 x ULN and AST 1.2 xULN. Total BR was 1.7 x ULN on Day 15 and 43, and intermittently mildly elevated at other timepoints. Alk P was normal. Patient also had neutropenia 0.8 Giga/L (nl > 1.96) on Day 76. Drug was discontinued on Day 79 due to transaminase increase and neutropenia. The patient followed the washout procedure with cholestyramine as per protocol given from Day 83 to Day 93. ALT value on Day 97 was ALT 453 (13.3 xULN) and AST 360 (10.6 xULN). ALT values returned to normal on Day 140.

Events of ALT elevated and neutropenia appear related to teriflunomide. The patient had a baseline increase in BR (perhaps underlying Gilbert's disease). The maximum ALT/AST values occurred while on cholestyramine. There is no mention of hepatitis serology.

In the Investigations SOC, there was a higher number of SAE in the placebo group as compared to teriflunomide groups. Except for one case of neutrophil count decreased and one APTT prolonged (both in the placebo group), all other events were in the Hepatobiliary Investigations HLGT.

Table 4.8. Serious adverse events in Investigations SOC (TOWER)

Primary System Organ Class Preferred Term n(%)	Placebo (N=363)	teriflunomide	
		7 mg (N=379)	14 mg (N=350)
Investigations	7 (1.9%)	6 (1.6%)	3 (0.9%)
Alanine aminotransferase increased	3 (0.8%)	5 (1.3%)	1 (0.3%)
Neutrophil count decreased	1 (0.3%)	0	0
Aspartate aminotransferase increased	0	1 (0.3%)	0
Gamma-glutamyltransferase increased	0	0	1 (0.3%)
Transaminases increased	0	0	1 (0.3%)
Activated partial thromboplastin time prolonged	1 (0.3%)	0	0
Hepatic enzyme increased	2 (0.6%)	0	0
Liver function test abnormal	0	1 (0.3%)	1 (0.3%)

Source: ISS interim analysis of TOWER.

Selected narratives are as follows.

On Teri 14

- 156018004**, 33 yo F on Teri 14. Prior treatment with dexamethasone and prednisone. No concomitant therapies. On Day 43 labs showed ALT increased 2.6xULN. Total BR, AlkP and GGT normal. The patient was asymptomatic. She had no known hepatobiliary disorder, respiratory or heart disease, she had no cancer and had not recently undergone surgery or blood transfusion. She denied alcohol consumption, acupuncture, drug abuse and had no known occupational toxic agent exposure. No liver orientated serology or abdominal ultrasound was performed. On Day 64 laboratory done at local lab showed further increase in ALT. On Day 71 **ALT was 9.5 xULN**, AST 4.3 xULN and GGT 1.5 xULN. Normal BR. Drug was discontinued (last dose Day 70). On day 78 and abdominal US showed small hepatic cysts (*probably incidental findings not related to increase in ALT and not related to study drug*). No washout was given. The patient recovered from elevated ALT on Day 127. *In the absence of evidence of an alternative etiology, the event of ALT increased appears to be drug-related, however, the work up was incomplete.*
- 276009003**, 44 y F on Teri 14. hx of goiter, recurrent herpes zoster and synovitis. On day 127 labs showed ALT increased 8.7 xULN, AST 2xULN with normal TBili. This occurred 2 days after IV methylprednisolone for MS relapse. Patient was asymptomatic. Drug was continued. Serologies and abdominal US not done. *IM methylprednisolone is the likely explanation to this event.*

On Teri 7

- 112105002**, on Teri 7, 33 yo M, no concomitant therapies were reported. On day 55, labs showed **ALT 6.7x ULN** and AST 1,8xULN. TBili was normal. The event led to study drug discontinuation. Last dose taken on Day 65. On Day 61, levels of ALT were at 3.7 ULN (157 IU/L) and AST at 2.4 ULN (88 IU/L). The last abdominal ultrasound before the event (Day -13) was normal. He was asymptomatic. On Day 68, serologies were negative or revealed past infection. The patient received phospholipids (Essentiale Forte N) as corrective treatment. On Day 75, the patient recovered from the ALT increased and the event was considered as related to the IP by the Investigator. Pt underwent cholestyramine washout from Day 68 to 80. *Increased ALT up to 6.7 xULN with normal BR with negative serologies. Abdominal ultrasound normal at screening but not repeated at time of event. No testing for Hepatitis E.. In the absence of evidence, the event appears to be drug related.*
- 840033008** 37 yo F, on Teri 7. Hx of drug hypersensitivity, migraine and headache. Concomitant therapies included ibuprofen, exedrin, naproxen, oxycodone, ciprofloxacin hydrochloride, tamsulosin,

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prochlorperazine, penicillin, etofylline/bromhexine hydrochloride/salbutamol and codeine phosphate/paracetamol. On Day 78 labs showed **ALT 11.4x ULN** and AST 4.8 xULN, GGT 2.6 xULN, normal Total Bili. Baseline and repeated abdominal US showed mild focal fatty liver in the region of the porta hepatis unchanged. Last dose of drug was taken on Day 80. She recovered on Day 103 from ALT increased. She received cholestyramine washout from Day 84 to 88.

Again, event may be drug related, although there is no mention of hepatitis serologies. Case confounded by use of multiple medications that could cause hepatotoxicity.

On placebo, four cases presented significant increase in ALT (ALT >9x ULN) including one with increased BR. Of these, two had an alternative explanation (IV corticosteroids and hepatitis C), and two did not.

- **276002005** hepatic enzyme increased. 49 yo F with prior hx of hepatitis. On Day 353, the patient was hospitalized due to suspicion of a new MS episode and treated with 1000 mg methylprednisolone IV, and a urinary-tract infection treated with antibiotics. On Day 379, laboratory results showed **ALT at 20.4 xULN** (693 IU/L) and AST at 13.6 ULN (461 IU/L). Total BR normal. US and serology negative for acute infection. Drug discontinued. *Increase in ALT probably related to high dose corticosteroids.*
- **840015007** 44 yo F, Hx of Crohn's disease and drug hypersensitivity and headaches. On Day 174 of placebo treatment a benign, asymptomatic hepatic lesion was detected by abdominal US, considered not related to drug. On day 444 labs showed hepatic enzyme increased with **ALT 11.4 xULN**, AST 11.2xULN and GGT 28.3 xULN with normal BR. On Day 445 she was diagnosed with hepatitis C, reported as non-serious. *Not drug related.*
- **276003001**. 18 yo F on placebo, on Day 15 **ALT 9.4x ULN**, with AST 3.8xULN. ALT decreased to 4.1 x ULN on Day 43, and increased to 14.3xULN on Day 75. Normal TBili and ALkP. The patient was asymptomatic. Concomitant therapies included oral contraceptive. Antibody test were all negative for acute viral hepatitis. The patient had a consultation with a hepatologist who suspected toxic hepatitis. Drug discontinued on Day 29. Washout given from day 33 to 43. As of Day 102, ALT was still 4xULN and AST 1.9xULN. Patient recovered from increased liver enzymes on Day 118. *It is unclear what the cause of increased liver enzymes was. There was no testing for Hepatitis E.*
- **642006004** ALT increased. 41 yo F on placebo. She was previously treated with methylprednisolone for MS. Concomitant therapies included methylprednisolone and thioctic acid. On day 127 ALT at 7.2 ULN (244 IU/L) and AST at 1.6 ULN (56 IU/L). On day 137 ALT was 9.1xULN with normal BR and AlkP. Patient was asymptomatic. Abd US normal. Liver oriented serology was negative for acute infection with hepatitis A, B, C and CMV and positive for previous infection with EBV, mumps, rubella, measles and toxoplasma. Drug discontinued on Day 132. Patient recovered from ALT increased on Day 149. Washout procedure was done day 142 to Day 152. *I would have thought this was drug related. Again, no testing for Hepatitis E.*

Evaluation of eDISH plot for TOWER (uploaded to FDA intranet by Dr. Ted Guo) identified 3 patients with liver enzymes in the Hy's law range as follows: patient #276 002 005 [on placebo, post high dose corticosteroid treatment], #840 0015 0007 [on placebo, found to have Hepatitis C, reported as non serious], and #250 0001 0003 on Teri 7, but the patient had Gilbert's syndrome. Maximum BR in this patient was 2.4x ULN. However, at the time of maximum ALT (7.7x ULN) on Day 334, total BR was normal.

- SAEs in renal and urinary disorders SOC, TOWER

In the Renal and urinary disorders SOC there was one case of renal failure (on Teri 14) and one case of renal artery stenosis on Teri 7 (the latter was discussed in the Cardiac SOC section).

- **804117008**, 33 yo F from Ukraine, had medical hx of autonomic nerve system imbalance, chronic glomerulonephritis, optic neuritis, and ischemic neuropathy. Urinalysis performed in the year the patient started study drug showed “minimal proteinuria, erythrocyturia and leukocyturia.” On Day 18 of Teri 14 the patient was diagnosed with chronic disease of the kidney, stage 1 glomerulonephritis, isolated urinary syndrome in combination with pyelonephritis (coded as chronic renal failure). The patient was examined by a nephrologist and hospitalized. On day 31 the patient recovered from the chronic renal failure and the event was considered not related to study drug by the investigator. Drug was not discontinued. Treatment is still ongoing.
Additional information was submitted at the FDA request on April 12, 2012. As per this submission, the patient had preexistent renal disease. She was admitted to the hospital with complaints of lumbar region discomfort and evaluated by a nephrologist. Creatinine clearance was 131 ml/min. A renal ultrasound showed normal size of the kidneys with hyperechogenic inclusions up to 0.2 cm. Conclusion was “moderate evidence of salt diathesis with decrease of corticomedullary differentiation”. The patient was discharged with a diagnosis of chronic disease of the kidneys.

- SAEs Injury, poison and procedural complications SOC, TOWER

There were no excess of fractures in TOWER at the time of the interim analysis (mostly 1-year exposure).

Additional SAEs from TOWER submitted with 120-day report:

Two suspected unexpected serious adverse reactions (SUSAR) were submitted from TOWER at the time of the SUR.⁵³

- A 26-year-old male patient (10531/616003011) receiving Teri 14 mg for 10 weeks, experienced an SAE of **polyneuropathy** (2 limbs and face, sensory disorder).
- A 24-year-old female patient (10531/276001012) receiving Teri 14 mg experienced 2 SAEs of atrial fibrillation from Day 73 to Day 75 and from Day 160 to Day 165. The patient received corrective therapy and recovered. The patient discontinued the study due to the second episode of **atrial fibrillation**.

Selected, additional SAEs from TOWER submitted as IND safety reports

- MFR# 2011SA081991. **Enterococcal endocarditis** (Teri 7). Investigator 792012, patient 003. Turkey). Discussed in section 7.3.2 of this review.

⁵³ SUSAR “suspected” reactions (suspected to be related to study drug by the applicant), and “unexpected” (not listed in the Investigator Brochure). These are reportable IND events but do not include events that may have been serious but are not suspected to be related to drug or listed in the IB. In addition to these cases, the applicant submitted 3 cases that occurred in patients taking placebo (one case of cervical dysplasia, one pancreatitis and one ALT elevation 25xULN in a patient with cholelithiasis and negative hepatitis serology).

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- 36 yo F. (Investigator 703001, patient 007, Slovakia). 1.5 years into Teri 14 treatment she experienced severe abdominal pain and vomiting requiring hospitalization. US of abdomen showed no pathological findings. Chest Xray was negative. WBC was normal. Neutrophil count was mildly elevated. Other white blood cells counts were normal, as well as hemoglobin and platelet count. She was diagnosed with **mesenteric lymphadenitis**. She improved with symptomatic treatment.
- A 53-year-old male patient (840/024/004) with medical history of gastritis, perforated bowel, and Crohn’s disease experienced a **hematochezia** 2 days after starting the study drug. He had syncope in the following day leading to hospitalization. He was found with anemia and he was taking acetaminophen and aspirin for a long time. He was also receiving a course of IV methylprednisolone 1 g daily, 5 days before the event onset for a relapse. The study medication was continued as planned. At the time of report, the patient had not yet recovered. The patient was treated with teriflunomide.
- A 50-year-old female patient (724/002/003) with medical history of fibromyalgia treated with the study drug for 1.6 years when she experienced **heart attack/myocardial infarction** while she was swimming. Enzymatic alteration was shown with troponin values of 0.35 and creatine phosphokinase (CPK) of 190. She developed hypotension and bradycardia. She was treated and recovered two days later. She was on Teri 7.

7.3.2.4.2 SAE in other ongoing phase 2/3 studies (TOPIC, TENERE, TERACLES)

At the time of the original NDA submission, TENERE, TOPIC and TERACLES were ongoing. A summary of blinded SAE were provided for these studies. The unblinded analysis of SAEs was submitted for TENERE as part of the 120-day SUR.

- TENERE

TENERE was a controlled study of two doses of teriflunomide and subcutaneous INF beta (Rebif). Teriflunomide dose was blinded, and assessments were done by a blinded rater.

SAE in TENERE are presented in the following table.

Table 4.9. SAE in study EFC10891/TENERE (as per 120-day SUR)

Primary system organ class Preferred term	Teri 7 (N=110) n(%)	Teri 14 (N=110) n(%)	Rebif (N=101) n(%)
Any class	12 (10.9)	6 (5.5)	7 (6.9)
Blood and lymphatic system disorders	1 (0.9)	1 (0.9)	0
Haemolysis	1 (0.9)	0	0
Neutropenia	0	1 (0.9)	0
Eye disorders	1 (0.9)	0	0
Eye edema	1 (0.9)	0	0
Optic ischemic neuropathy	1 (0.9)	0	0
Cardiac disorders	1 (0.9)	0	0
Supraventricular tachycardia	1 (0.9)	0	0
Gastrointestinal disorders	1 (0.9)	0	0
Diarrhea	1 (0.9)	0	0
Hepatobiliary disorders	0	0	1 (1.0)
Cholecystitis	0	0	1 (1.0)

Infections and infestations	2 (1.8)	2 (1.8)	1 (1.0)
Cellulitis	1 (0.9)	0	0
Cervicitis	1 (0.9)	0	0
Chronic sinusitis	0	1 (0.9)	0
Tuberculosis	0	1 (0.9)	0
Anal abscess	0	0	1 (1.0)
Injury, poisoning and procedural complications	1 (0.9)	0	1 (1.0)
Tibia fracture	1 (0.9)	0	0
Forearm fracture	0	0	1 (1.0)
Investigations	3 (2.7)	1 (0.9)	1 (1.0)
Alanine aminotransferase increased	3 (2.7)	1 (0.9)	1 (1.0)
Musculoskeletal and connective tissue disorders	0	1 (0.9)	1 (1.0)
Intervertebral disc disorder/protrusion	0	1 (0.9)	1 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.9)	0	0
Uterine leiomyoma	1 (0.9)	0	0
Nervous system disorders	1 (0.9)	0	0
Optic neuritis	1 (0.9)	0	0
Reproductive system and breast disorders	0	0	1 (1.0)
Cervical polyp	0	0	1 (1.0)
Vascular disorders	0	0	1 (0.9)
Venous stenosis	0	0	1

In this table, events are presented by SOC in alphabetical order. MedDRA version 14.0.

Comment: this is a very small study, not adequate to evaluate differences in safety between teriflunomide and interferon beta or between teriflunomide doses. The safety profile of teriflunomide in this study is consistent with other studies. Of note, there was one case of tuberculosis on Teri 14, as follows:

Patient #006, Investigator 348004 (MFR report 2011SA047846) was a 38 year-old female from Hungary, treated with Teri 14 for 1.3 years. Discussed in section 7.3.2. of this review.

There was a case of hemolysis in the Teri 7 group (patient 276002002). One of the manifestations of hypophosphatemia is hemolysis. As per a response to an FDA request for information, this case was associated with a viral respiratory infection. Phosphorus levels were normal in this patient.

Within the investigations SOC, SAEs of ALT increase were reported in 3 patients treated with teriflunomide 7 mg, 1 patient treated with teriflunomide 14 mg, and 1 patient treated with Rebif®. All cases of ALT increase were asymptomatic and reversible. No patient experienced an increase of ALT above 3 x ULN concomitantly with an increase in bilirubin above 2 x ULN. Short patient narratives of SAE of ALT elevation in TENERE are given below:

On teriflunomide:

- A 29-year-old female patient (10891/300002003) had ALT 5.7 x ULN 3 months into **Teri 7** treatment. Normal BR. Liver serologies were negative. The treatment was permanently

discontinued due to this event and the patient underwent the rapid elimination procedure. The patient recovered 2 weeks after the onset.

- A 23-year-old male patient (10891/348005003) had an increase of 4.1 x ULN in ALT (with AST 1.5 ULN, and total bilirubin up to 1.2 ULN) 9 months into **Teri 7** treatment. The treatment was temporarily discontinued and then resumed after the patient recovery, 2 weeks after the onset.
- A 32-year-old male patient (10891/616004013) had an increase of 8.7 x ULN in ALT, 3.3 x ULN in AST, and 1.8 x ULN in GGT, and with normal bilirubin 4 months into **Teri 7**. Liver serologies were not tested and liver ultrasound was normal at the time of this serious hepatic event. The treatment was permanently discontinued due to this event and the patient underwent the rapid elimination procedure. The patient recovered 2 weeks after the onset.
- A 48-year-old male patient **10891/616002001** experienced, 6 months after the first intake of teriflunomide 14 mg, an increase of 8.5 x ULN in ALT, 2.6 x ULN in AST, and a slight elevation in GGT. Bilirubin levels were normal. Liver serologies were not tested, and liver ultrasound was normal at the time of this serious hepatic event. The treatment was permanently discontinued due to this event and the patient underwent the rapid elimination. The patient recovered 5 weeks after the onset of this SAE.

On Rebif®: There was only one SAE of ALT elevation in this group.

- A 57-year-old female patient (10891/826002003) had an increase in ALT of 2.4 x ULN, 1.5 x ULN in AST with normal bilirubin levels, 3 months after the first intake of Rebif®. The treatment was continued as planned and the patient recovered 4 months after the onset of this AE, while on treatment. The event was reported as an SAE by the Investigator.

A case of ALT elevation up to 12.5x ULN with normal BR was reported from TENERE extension study as an IND safety report, on February 2012, as follows:

- EFC10891ext-616001011 presented asymptomatic elevation of **ALT up to 12.5 x ULN** (425 U/L) and **AST up to 5.6 x ULN** (191 U/L) about 5 months after starting teriflunomide 14 mg treatment in the extension study. She was previously receiving teriflunomide 7 mg for about 2 years in the core study with normal ALT and AST values. GGT, alkaline phosphatase (AP), total bilirubin, amylase, and lipase remained normal during the core and the extension study. Concomitant medications included oral contraceptive. Serology was not performed on this patient and imaging results were unremarkable (pancreatic enlargement at abdominal ultrasound with normal subsequent CT-scan). The causal relationship to teriflunomide 14 mg dose remains possible. However the start of the increase after the corticosteroid pulse therapy given for MS relapse may suggest that this corticosteroid use could be a potential confounding factor. No jaundice was reported. Patient underwent rapid elimination procedure. One month after drug discontinuation ALT was 2.6xULN with normal total BR and ALK phosphatase.

This case appears to be drug related but confounded by high dose corticosteroids.

- TOPIC Study

The number of patients with serious treatment emergent AEs in TOPIC are presented in the following table (cut off date of January 10, 2011)

Table 4.10. Serious AE in ongoing studies TOPIC (original application)

Primary system organ class Preferred term	TOPIC Blinded (N=404)
Any class	35 (8.7%)
Blood and lymphatic system disorders	3 (0.7%)
Haemolysis	0
Neutropenia	2 (0.5%)
Lymphadenitis	1 (0.2%)
Eye disorders	1 (0.2%)
Conjunctivitis allergic	1 (0.2%)
Gastrointestinal disorders	3 (0.7%)
Pancreatitis	1 (0.2%)
Pancreatitis acute	1 (0.2%)
Radicular cyst	1 (0.2%)
Hepatobiliary disorders	3 (0.7%)
Bile duct stone	1 (0.2%)
Cholecystitis	1 (0.2%)
Cholecystitis acute	1 (0.2%)
Cytolytic hepatitis	1 (0.2%)
Infections and infestations	8 (1.6%)
Appendicitis	2 (0.5%)
Abdominal abscess	2 (0.5%)
Bronchitis	2 (0.5%)
Cystitis	1 (0.2%)
Pulmonary tuberculosis	1 (0.2%)
Sinusitis	1 (0.2%)
Injury, poisoning and procedural complications	3 (0.7%)
Ankle fracture	1 (0.2%)
Joint sprain	1 (0.2%)
Overdose	1 (0.2%)
Investigations	
Alanine aminotransferase increased	7 (1.7%)
Lipase increased	2 (0.5%)
Neck pain	1 (0.2%)
Rheumatoid arthritis	1 (0.2%)
Neoplasms benign, malignant and unspecified	3 (0.7%)
Breast cancer	1 (0.2%)
Thyroid cancer	1 (0.2%)
Uterine leiomyoma	1 (0.2%)
Nervous system disorders	1 (0.2%)
Loss of consciousness	1 (0.2%)
Pregnancy, puerperium and perinatal conditions	1 (0.2%)
Abortion spontaneous	1 (0.2%)
Psychiatric disorders	2 (0.5%)

Completed suicide	1 (0.2%)
Psychiatric decompensation	1 (0.2%)
Reproductive system and breast disorders	3 (0.7%)
Fallopian tube cyst	2 (0.5%)
Testicular torsion	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	1 (0.2%)
Dyspnoea	1 (0.2%)
Vascular disorders	1 (0.2%)
Subclavian vein thrombosis	1 (0.2%)

Cut-off January 11, 2011. Source: ISS Table 59 and 65.

Selected narratives are discussed below.

- **6607/0016** – (France) This 36-year-old female with a medical history of hypertension and lipase increased. On Day 337, the patient experienced **hepatic cytolysis**. Maximum ALT was at 3.7 xULN [113 IU/L] and AST at 4.3x ULN [137 IU/L] on Day 365. GGT, amylase, lipase, and total bilirubin remained within normal range. US performed on Day 176 and on Day 340 were normal. Due to the event, drug was discontinued on Day 358. No liver oriented serologies were performed. On Day 393, the patient recovered from the event without sequelae and the event was considered as related to the IP by the Investigator.

Again, the use of cytolytic hepatitis appears inappropriate. Maximum ALT/AST was <5x ULN. This may be related to study drug although there were no “liver oriented serologies” therefore an infectious cause can not be ruled out.

- **5401/0004** - (Canada). This 36-year-old female patient with no significant medical history. No history of DVT. On Teri 14. Discussed in section 7.3.2 of this review.
- **8510/0005** – (Ukraine). This 34-year-old female patient had a medical history of ear and sinus operation. Randomized to Teri 7. Discussed in section 7.3.2 of this review.

The following are SAE reported as IND safety reports submitted after the 120-day SUR (Still blinded).

- **6201/005** (MFR# 2012SA002518). 27 yo F randomized to Teri 7 was diagnosed with **asthma, infectious mononucleosis and clostridium difficile enterocolitis**. She had no history of asthma. Allergic to cat, dogs and eggs and allergic rhinitis. Non-smoker. On Day 138 she had mild upper resp infection, on Day 330 developed cough for 3 weeks (initially with sputum, followed by dry cough), treated with salbutamol. She improved. No Xray or PFT done. On Day 406 she developed shortness of breath and nightly cough. A spirometry was normal and methacoline test was negative. Xray was normal. Atypical lung infection was not confirmed. Symptoms remained. Bronchial asthma was suspected. She was treated with budesonide and referred to asthmatic patient education. On (b) (6) Day 463 (1 year and 2 months into treatment) she developed low grade fever (37.7°C) followed by minor rash on hands and legs for 1 day and watery stools. At that time she was found to have ALT 4.7 xULN and AST 3x ULN. Total BR and ALKP were normal. Abdominal US was normal. She was diagnosed with mononucleosis due to EBV and CDifficile enterocolitis. Drug was discontinued on Day 467 and she was hospitalized on Day 469. Tests for HIV, syphilis, hepatitis A, B and C were negative. A stool sample was positive for Clostridium A and B

toxins. She was treated with metronidazol and improved. Cholestyramine washout was done Day 482 to 492. She recovered from ALT increase on Day 493.

It is unusual for a young, healthy patient (other than MS) to develop diseases affecting three different organ systems: lung, liver and GI. Laboratory evaluation also showed neutropenia (down to 0.67 [normal 2.1 to 6.7 GG/L]). There was no eosinophilia. Hemoglobin and platelet were within normal values. FDA requested additional information about the diagnoses of asthma, EBV hepatitis and C difficile enterocolitis. Sanofi clarified that a pneumologist consult did not confirm the diagnosis of asthma. However, C diff toxin A and B were positive in stool samples and EBV serology showed positive IgM, confirming the diagnosis of mononucleosis.

- TOPIC study, center 3005, Investigator 6802, Patient 0003. (MFR # 2011SA081324) 31 yo male patient with known history of HTN, treated with ramipril for two years prior to study entry, developed **impaired speech** 13 days into blinded treatment. The event resolved after one hour. No vital signs were provided at the time of the event. Therapy was continued.
This could have been a TIA. No additional information is available at this time.
- TOPIC, patient 68002/0004. A 47 yo male treated with teriflunomide for 1.5 years developed serious **axonal polyneuropathy** of mild intensity consisting of paresthesias and numbness of on ball of both feet, with loss of sensation and tingling. Results of EMG and NCS were not reported. Study continued. Event continued.

- TERACLES

One SAE of spinal fracture following a car accident (still blinded) was reported in Study EFC6058/TERACLES study as of June 1, 2011.

A SAE of ALT increased was reported in the 120 day SUR. The patient (840033003) a 19 yo female developed elevated ALT up to 10x ULN and AST 5xULN with normal TBR. All virology tests were negative except EBV, post exposure positive. The blinded drug was discontinued on Day 57 and she received cholestyramine treatment. The patient recovered from the event on Day 66.

The overall pattern of serious TEAEs in TOPIC and TERACLES (both still blinded) is consistent with that of the ISS population.

Appendix 5. Adverse events leading to drug discontinuation in clinical pharmacology studies and ongoing phase 3 studies.

- Dropouts due to AE in Clinical pharmacology studies

Number of subjects with AE leading to discontinuation in Clin Pharm studies (single dose and repeated dose) are summarized as follows:

Table 5.1. AE leading to discontinuation in Clinical pharmacology studies (single and repeated dose)

Preferred Term	Placebo (N=136) n (%)	Teriflunomide		
		7 mg ^a (N=69) n (%)	14 mg (N=104) n (%)	>14 mg ^b (N=241) n (%)
Any TEAE related with study discontinuation	0	5 (7.2%)	4 (3.8%)	5 (2.1%)
Urticaria	0	0	0	2 (0.8%)
Contusion	0	0	0	1 (0.4%)
Excoriation	0	0	0	1 (0.4%)
Neutropenia	0	0	0	1 (0.4%)
Pancreatic enzymes increased	0	0	0	1 (0.4%)
Appendicitis	0	0	1 (1.0%)	0
Headache	0	0	1 (1.0%)	0
Tonsillitis	0	0	1 (1.0%)	0
Transaminases increased	0	1 (1.4%)	1 (1.0%)	0
Alanine aminotransferase increased	0	2 (2.9%)	0	0
Atrial fibrillation	0	1 (1.4%)	0	0
Hepatic enzyme increased	0	1 (1.4%)	0	0

^a The 7 mg dose pool includes the 10 mg/mL IV dose. ^b The "70 mg ± 14 mg" group from the RD pool dose group is included in the ">14 mg" group. TEAE: Treatment Emergent Adverse Event. N = Number of subjects treated within each group, n (%) = Number and % of subjects with at least one TEAE in each category. Source Table 23, ISS.

In general the AE profile resulting in dropouts in the clinical pharmacology studies is consistent with that of Pool 1.

- Dropouts in ongoing phase 3 studies

Dropouts due to AE in TOWER (interim analysis)

TEAEs leading to treatment discontinuation occurred with a higher frequency in the teriflunomide groups compared with the placebo group (placebo: 4.4%; teriflunomide 7 mg: 11.3%; and teriflunomide 14 mg: 12.0%). A summary by SOC is shown below.

Table 5.2 Patients who discontinue due to AE in TOWER, interim report

Primary System Organ Class	Placebo N=363 n (%)	7 mg N=379 n (%)	14 mg N=350 n (%)
Any class	16 (4.4)	43 (11.3)	42 (12.0)
Infections and infestations	2 (0.6)	3 (0.8)	3 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.3)	0
Blood and lymphatic system disorders	0	6 (1.6)	9 (2.6)
Immune system disorders	0	1 (0.3)	0
Psychiatric disorders	0	2 (0.5)	3 (0.9)
Nervous system disorder	2 (0.6)	4 (1.1)	2 (0.6)
Ear and labyrinth disorders	0	1(0.3)	0
Cardiac disorders	0	0	1 (0.3)
Vascular disorders	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.3)
Gastrointestinal disorders	1 (0.3)	6 (1.6)	9 (2.6)
Hepatobiliary disorder	0	0	3 (0.9)
Skin and subcutaneous tissue disorders	2 (0.6)	2 (0.5)	8 (2.3)
Musculoskeletal and connective tissue disorders	0	2 (0.5)	0
Renal and urinary disorders	0	0	1 (0.3)
Pregnancy, puerperium and perinatal conditions	0	3 (0.8)	0
General disorders and administration site conditions	0	2 (0.5)	1 (0.3)
Investigations	8 (2.2)	12 (3.2)	13 (3.7)
Injury, poisoning and procedural complications	1 (0.3)	2 (0.5)	1 (0.3)

n (%) = number and percentage of patients with at least one TEAE leading to permanent treatment discontinuation
 Note: Table sorted by SOC internationally agreed order. Source: Table 14.2.7.3.1, interim analysis.

In general, the pattern of AE leading to drug discontinuation in TOWER was similar to that of Pool 1. Most AEs leading to drug discontinuation were serious and therefore already described in the SAE section of this review. AE leading to drug discontinuation in selected SOCs are discussed below.

- Dropouts due to AE in Blood and lymphatic system disorders SOC, TOWER

Table 5.3 AE leading to drug discontinuation in Blood and lymphatic system disorders SOC, TOWER

Primary System Organ Class Preferred Term n(%)	Placebo (N=363)	teriflunomide	
		7 mg (N=379)	14 mg (N=350)
Blood and lymphatic system disorders	0	6 (1.6%)	9 (2.6%)
Neutropenia	0	5 (1.3%)	8 (2.3%)
Leukopenia	0	0	1 (0.3%)
Autoimmune thrombocytopenia	0	1 (0.3%)	0

Source: Appendix 14.2.7.3.2 Tower interim report

There is a dose-related bone marrow effect in the Blood and Lymphatic system disorders SOC, driven by neutropenia. In addition to patients in this SOC, three patients in the Investigations SOC had hematologic events that led to discontinuation: 3 neutrophil count decreased (1 on placebo, 2 on Teri 14), and one platelet count decreased (on Teri 7).

Among the non-serious AE leading to study drug discontinuation in the Blood and lymphatic system and Investigations (bone marrow related) SOC, five had an ANC < 1 Giga/L (3 on Teri 7, 2 on Teri 14 and none on placebo)(See table).

Table 5.4. Listing of patients with neutropenia that were non-serious but led to drug discontinuation in Blood and lymphatic system disorders SOC (ANC ≤ 1 Giga/L). TOWER.

	Day	Comment
010531-840-0071-0004	29 & 338	45 yo F, on Teri 7. Concomitant therapy: fluoxetine and etodolac. Low ANC started on Day 29 (ANC 1.47 Giga/L) . ANC decreased over time. On Day 346 ANC 0.87 Giga/L . Drug was discontinued . Washout from Day 361 to 371. On Day 388 she recovered from neutropenia.
010531-840-0073-0009	37 & 58	41 yo F on Teri 14 . Concomitant therapy seretide and ranitidine. On Day 37 ANC 0.95 GI/L. Nadir ANC 0.84 GI/L on Day 58. Asymptomatic. Drug discontinued on Day 61. Washout given from Day 64 to 74. The neutropenia resolved 4 months later.
010531-156-0009-0009	99 & 105	38 yo F on Teri 14 . No concom med reported. On Day 55 she had ANC 1.38 Giga/L other blood cells were normal. She recovered spontaneously. On Day 99 another episode of neutropenia with ANC 1.44 Giga/L. On Day 105 labs showed ANC 0.84 Giga/L, leading to drug discontinuation. No washout treatment given. Patient recovered to normal ANC on Day 133. Event of neutropenia, ANC <1.0 Giga/L, probably drug related.
010531-804-0105-0008	15	28 yo F, on Teri 7 . Concomitant medications included Eugynon (oral contraceptive). On Day 15, ANC 0.9 Giga/L ; On Day 27 ANC was 1.4 Giga/L. Hb was 108 g/L (normal range 116-164) and normal platelets. On Day 36, ANC 1.52 Giga/L, Hb 100 g/L and normal platelets. Drug was discontinued, with last dose taken on Day 29. She recovered. <i>Patient was asymptomatic, Investigator did not think it was drug related.</i>
010531-156-0032-0002	15 & 58	19 yo F on Teri 7 . On day 15 ANC was 1.8 Giga/L; it worsen on day 58 with ANC 0.94 Giga/L . Discontinued on day 61. Washout on Day 81-91. Recovered on Day 79.

I believe that all these cases are consistent with a drug-induced a bone marrow suppression effect because of the temporal relationship with starting study drug. All patients were asymptomatic. Low neutrophil counts were not associated with low platelets or anemia (except for one case with low Hb). No infections were reported in these patients.

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- Dropouts due to AE from the Investigations SOC are presented below.

Table 5.5. AE leading to drug discontinuation. Investigations SOC, TOWER.

Primary System Organ Class Preferred Term n(%)	Placebo (N=363)	teriflunomide	
		7 mg (N=379)	14 mg (N=350)
Investigations	8 (2.2%)	12 (3.2%)	13 (3.7%)
Alanine aminotransferase increased	4 (1.1%)	8 (2.1%)	5 (1.4%)
Blood creatine phosphokinase increased	0	0	1 (0.3%)
Neutrophil count decreased	1 (0.3%)	0	2 (0.6%)
Aspartate aminotransferase increased	2 (0.6%)	4 (1.1%)	3 (0.9%)
Gamma-glutamyltransferase increased	0	1 (0.3%)	1 (0.3%)
Transaminases increased	0	0	2 (0.6%)
Lipase increased	0	1 (0.3%)	0
Blood amylase increased	0	1 (0.3%)	0
Blood pressure increased	0	1 (0.3%)	0
Body temperature increased	0	0	1 (0.3%)
Hepatic enzyme increased	3 (0.8%)	1 (0.3%)	1 (0.3%)
Liver function test abnormal	0	1 (0.3%)	1 (0.3%)
Platelet count decreased	0	1 (0.3%)	0

Source: Table 14.2.7.3.2. TOWER interim report.

Events are consistent with findings in Pool 1 and 2. The most common events leading to drug discontinuation were hepatic-related investigations.

- Dropouts due to AE in Nervous system disorders SOC, TOWER:

Patients with events leading to drug discontinuation in the Nervous system SOC are presented below.

Table 5.6. Adverse events leading to discontinuation, Nervous system disorders SOC, TOWER.

Primary System Organ Class Preferred Term n(%)	Placebo (N=363)	teriflunomide	
		7 mg (N=379)	14 mg (N=350)
Nervous system disorders	2 (0.6%)	4 (1.1%)	2 (0.6%)
Paraesthesia	1 (0.3%)	1 (0.3%)	0
Multiple sclerosis relapse	0	0	1 (0.3%)
Neuropathy peripheral	0	1 (0.3%)	0
Multiple sclerosis	1 (0.3%)	0	0
Polyneuropathy	0	1 (0.3%)	1 (0.3%)
Hemiparesis	0	1 (0.3%)	0

Source: Table 14.2.7.3.2, TOWER interim report.

Paresthesia, polyneuropathy and peripheral neuropathy were reported in 4 patients on teriflunomide (7 and 14 mg) and none on placebo. Several cases of neuropathy were reported as IND Safety reports after the cut-off date of the NDA analysis.

- Dropouts due to AE in the Skin and subcutaneous tissue disorders SOC are shown below.

Table 5.7. AE leading to discontinuation. Skin and subcutaneous tissue disorders SOC.
 TOWER

Primary System Organ Class Preferred Term n(%)	Placebo (N=363)	teriflunomide	
		7 mg (N=379)	14 mg (N=350)
Skin and subcutaneous tissue disorders	2 (0.6%)	2 (0.5%)	8 (2.3%)
Alopecia	1 (0.3%)	0	5 (1.4%)
Rash	1 (0.3%)	0	0
Pruritus	0	0	1 (0.3%)
Eczema	0	1 (0.3%)	0
Dry skin	0	1 (0.3%)	0
Eczema nummular	0	0	1 (0.3%)
Rash pruritic	0	0	1 (0.3%)

Source: Table 14.2.7.3.2, TOWER interim report.

Consistent with the analysis of SAEs, the most common event leading to drug discontinuation in this SOC was alopecia. There were no cases of SJS or TEN.

- Dropouts in other SOCS, TOWER

In the Psychiatric disorders SOC, there was one suicide and one attempted suicide in the Teri 14 group (described in the SAE section). There were no such cases on placebo or Teri 7.

One case of hypersensitivity was reported in one patient on Teri 14. One case of atrial fibrillation and one of hemorrhagic shock were reported in patients on Teri 14, both described in the SAE section.

- Dropouts due to AE in ongoing studies: TOPIC and TENERE

In Study EFC10891/TENERE, at the cut-off date of the original application, 13.3% (43 of 324) of patients had AEs leading to discontinuation. The most frequent AEs leading to discontinuation were ALT increased (3.7% of patients) and gastrointestinal disorders (2.5% of patients).

At the time of the 4-month safety update report, a total of 15 patients discontinued because of ALT elevation (2 in the 7 mg teriflunomide group, 4 in the 14 mg teriflunomide group, and 9 in the Rebif® group). In all cases ALT normalized after treatment discontinuation. These discontinuations were consistent with the mandatory threshold of ALT > 3 x ULN for patient withdrawal required by the study protocol. Two patients (10891/300002003) and (10891/616004013) with SAE while on Teri 7 are described in the SAE section of this review. Four patients (10891/124004002), (10891/250002002), (10891/616004011), (10891/616002001) discontinued because of ALT elevation from the Teri 14 group. The latter patient had a SAE described in the SAE section of this review. The first three patients are as follows:

- Patient 10891/124004002 had a peak ALT increase of 4.2 x ULN (with AST increase of 4.2 x ULN), which occurred 8 months after the first study drug intake and normalized in 1 month.

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- Patient (10891/250002002) had a peak ALT increase of 7.3 x ULN (with AST increase of 3.8 x ULN) which occurred 6 months after first study drug intake and normalized in 3 months.
- Patient (10891/616004011) had a peak ALT increase of 3.3 x ULN (with AST increase of 2 x ULN) which occurred 2 months after the first study drug intake and normalized in 2 months.

- ALT increase leading to drug discontinuation in the Rebif® group:

9 patients in the Rebif® group experienced ALT increases leading to permanent study drug discontinuation. Three patients experienced ALT increases between 5 and 6 x ULN, the 6 other patients had ALT level below 5 x ULN. It is unclear what kind of work up these patients had. All had normal BR.

In Study EFC6260/TOPIC, at the cut-off date, 9.7% (39 of 404) of patients had AEs leading to Discontinuation. The main reason for discontinuation was ALT increased (4.2%).

Appendix 6. Laboratory evaluations and concomitant meds in patient 3201/0009 (TOXIC HEPATITIS)

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Table 6.1. Liver related chemistries

1 Patient ID: 3201/0009 (EFC6049, 14mg teri)
 1.6 Listing of clinical chemistry data (Liver function)

Visit	Sample		Lab name (b) (4)	AST	ALT	Total bilirubin	ALP	SGGT	LDH	Direct bilirubin	Indirect bilirubin
	Date (b) (6)	Time		(9.00 - 34.00 U/L)	(6.00 - 34.00 U/L)	(3.00 - 21.00 UMOL/L)	(31.00 - 106.00 U/L)	(4.00 - 49.00 U/L)	(53.00 - 234.00 U/L)	(0.00 - 7.00 UMOL/L)	(0.00 - 21.00 UMOL/L)
Visit 1/Screening		9:20		23	33	11	66	13	148	3	8
Visit 2		9:35		19	23	7	69	13	148	2	5
Visit 3A/Week 2		10:25		27	37	9		11		2	
Visit 4		9:30		33	45	8	73	9	156	2	6
Visit 4A/Week 6		9:30						10			
Unscheduled		8:59		23	27	10	67	9	148		
Visit 5		9:23		31	38	7	62	9	143	2	5
Visit 5A/Week 10		9:40		17	22	7		10		2	
Visit 6		9:39		23	30	7	75	11	166	2	5
Visit 6A/Week 14		9:38		14	24	9		13		2	
Visit 7		9:49		27	39	6	68	10	175	1	3
Unscheduled		9:40		17	21	7	70	10	156	2	5
Visit 7A/Week 18		9:59		18	21	7		7		2	
Visit 8		9:15		31	43	7	73	10	160	2	5
Unscheduled		9:41		691	1101	36	326	232	383	20	16
UNSCHEDULED LAB		.			17	10					
UNSCHEDULED LAB		.			28	7					

Table 6.2. Hematology (WBC)

1 Patient ID: 3201/0009 (EFC6049, 14mg teri)
 1.2 Listing of hematology data (White blood cells)

Visit	Sample		Lab name (b) (4)	WBC count	Neutrophils	Lymphocytes	Basophils	Monocytes	Eosinophils
	Date (b) (6)	Time		(3.80 - 10.70 GG/L)	(1.96 - 7.23 GG/L)	(0.91 - 4.28 GG/L)	(0.00 - 0.20 GG/L)	(0.12 - 0.92 GG/L)	(0.00 - 0.57 GG/L)
Visit 1/Screening		9:20		4.39	2.94	0.98	0.05	0.34	0.08
Visit 2		9:35		4.39	2.68	1.21	0.04	0.38	0.08
Visit 3A/Week 2		10:25		4.36	2.39	1.46	0.03	0.4	0.09
Visit 4		9:30		4.01	2.14	1.22	0.07	0.45	0.14
Visit 4A/Week 6		9:30							
Unscheduled		8:59							
Visit 5		9:23		3.16	1.62	1.13	0.04	0.29	0.08
Visit 5A/Week 10		9:40		3.04	1.67	0.91	0	0.3	0.15
Visit 6		9:39		4.74	2.28	1.09	0.12	0.47	0.78
Visit 6A/Week 14		9:38		11.45	9.74	0.83	0.02	0.82	0.05
Visit 7		9:40							
Unscheduled		9:40		3.15	1.45	1.23	0	0.35	0.13
Visit 7A/Week 18		9:59		3.97	2.19	1.16	0.04	0.49	0.09
Visit 8		9:15		4.58	2.8	0.76	0.08	0.53	0.41
Unscheduled		9:41		6.29	3.42	1.27	0.08	0.49	1.03
UNSCHEDULED LAB		.		6.5					
UNSCHEDULED LAB		.		11					

Table 6.3. Hematology: Hb and platelets

1 Patient ID: 3201/0009 (EFC6049, 14mg teri)
 1.1 Listing of hematology data (Red blood cells, platelets and coagulation)

Visit	Date	Time	Lab name	Hemoglobin		RBC count (TL)	Platelet count (GG/L)	MCH (PG)	INR (SEC)	aPTT (SEC)
				(116.00 - 164.00 G/L)	Hematocrit (0.34 - 0.48 l)					
Visit 1/Screening	(b) (6)	9:20	(b) (4)	117	0.39	5.2	280	23	11.6	26.5
Visit 2		9:35		113	0.39	5.2	338	22	11.8	25.7
Visit 3A/Week 2		10:25		117	0.37	5.2	314	22		
Visit 4		9:30		110	0.35	5	276	22	11.9	26
Visit 4A/Week 6		9:30								
Unscheduled		8:59								
Visit 5		9:23		112	0.38	5.3	228	21	11.9	24.8
Visit 5A/Week 10		9:40		108	0.37	5.2	213	21		
Visit 6		9:39		113	0.36	5.4	286	21	12	23.8
Visit 6A/Week 14		9:38		116	0.37	5.3	284	22		
Visit 7		9:49							11.4	23.2
Unscheduled		9:40		113	0.36	5.1		22		
Visit 7A/Week 18		9:59		109	0.33	4.8	248	23		
Visit 8		9:15		109	0.36	5.1	271	21	12.2	25.5
Unscheduled		9:41		105	0.34	4.9	193	21		
UNSCHEDULED LAB				144		4.4				

Table 6.4. Concomitant medications

1.139 Patient ID: 3201/0009 (EFC6049, 14mg teri, first dose date of study drug in EFC6049: (b) (6)
 1.139.1 Listing of concomitant medication taken during the study

Concomitant medication standardized (reported)	Reason	Concom med start date	Concom med start relative study day	Concom med stop date	Concom med stop relative study day	Continues
CALCIUM (CALCIUM-ACTIV)	PROPHYLAXIS	2005-10-XX	-38	2005-12-18	41	No
IODINE (IODINE-ACTIV)	PROPHYLAXIS	2005-10-XX	-38	2005-12-18	41	No
ESSENTIALE /02318601/ (ESSENTIALE)	PROPHYLAXIS	2005-12-20	43	2006-01-19	73	No
ALUDROX /00082501/ (MAALOX)	PROPHYLAXIS	2006-01-24	78	2006-01-31	85	No
METHYLPREDNISOLONE SODIUM SUCCINATE (SOLUMEDROL)	STUDY INDICATION	2006-01-24	78	2006-01-25	79	No
MILGAMMA NA (MILGAMMA)	STUDY INDICATION	2006-01-25	79	2006-02-03	88	No
RANITIDINE (RANITIDINE)	PROPHYLAXIS	2006-01-25	79	2006-01-30	84	No
PROPRANOLOL HYDROCHLORIDE (ANAPRILIN)	CURATIVE	2006-01-27	81	2006-01-27	81	No
TRIOVIT /02384401/ (TRIOVIT)	STUDY INDICATION	2006-02-04	89	2006-02-27	112	No
METHYLPREDNISOLONE SODIUM SUCCINATE (SOLUMEDROL)	STUDY INDICATION	2006-02-09	94	2006-02-10	95	No
ACETYLCYSTEINE (ACC-LONG)	STUDY INDICATION	2006-02-13	98	2006-02-17	102	No
METHYLPREDNISOLONE SODIUM SUCCINATE (SOLUMEDROL)	STUDY INDICATION	2006-02-13	98	2006-02-15	100	No
CEREBROLYSIN /02156801/ (CEREBROLYSINE)	STUDY INDICATION	2006-02-17	102	2006-02-26	111	No
GLYCINE (GLYCINE)	STUDY INDICATION	2006-02-22	107	2006-03-21	134	No
HOPANTENATE CALCIUM (PANTOGAME)	STUDY INDICATION	2006-02-22	107	2006-03-12	125	No
TROPICARD (PANANGINE)	STUDY INDICATION	2006-02-22	107	2006-03-13	126	No
ASCORUTIN (ASCORUTUNUM)	PROPHYLAXIS	2006-03-17	130	2006-03-26	139	No
HYMECROMONE (ODESTON)	ADVERSE EVENT/PREEXISTING CONDITION	2006-04-04	148	2006-05-15	189	No
METOCLOPRAMIDE HYDROCHLORIDE (CERUCAL)	ADVERSE EVENT/PREEXISTING CONDITION	2006-04-04	148	2006-05-15	189	No

Appendix 7. Hepatic Injury with Beta-Interferons for Multiple Sclerosis

The first beta-interferon for use in MS in the USA was approved in 1993. Liver injury with beta-interferons is listed as a Warning in the prescribing information for each of the four beta-interferons currently approved for treatment of MS; this information is briefly summarized in the table below.

Table 7.1. Interferons Indicated for Multiple Sclerosis: Liver Injury Prescribing Information

Brand Name/ Generic Name	Prescribing Information
Avonex/ Interferon beta-1a	Warnings: <ul style="list-style-type: none"> Severe hepatic injury (rare), including hepatic failure, and asymptomatic transaminase elevation Precautions: <ul style="list-style-type: none"> Autoimmune disorders – post-marketing cases of disorders including autoimmune hepatitis have been reported
Betaseron/ Interferon beta-1b	Warnings: <ul style="list-style-type: none"> Increased transaminases and rare severe hepatic injury, including hepatic failure
Extavia/ Interferon beta-1b	Warnings and Precautions: <ul style="list-style-type: none"> Hepatic enzyme elevation
Rebif/ Interferon beta-1a	Warnings: <ul style="list-style-type: none"> Severe hepatic injury (rare), including hepatic failure, and asymptomatic transaminase elevation

Four cases of liver failure requiring transplantation with beta-interferons^{54 55 56 57} have been mentioned in the published literature. In a review article written by the manufacturer of Rebif,² 30 postmarketing cases of serious liver dysfunction⁵⁸ were reported over 5 years (patient population reported to be approximately 70,000 patients).

The review by Tremlett⁵⁹ summarizes information on hepatic injury in pre- and post-marketing studies of beta-interferons for MS (see Table 2 from the Tremlett review below).

54 Yoshida EM, Rasmussen SL, Steinbrecher UP, Erb SR, et al (2001) Fulminant liver failure during interferon beta treatment of multiple sclerosis. *Neurology* 56:1416

55 Francis GS, Grumser Y, Alteri E, et al (2003) Hepatic Reactions during treatment of Multiple Sclerosis with Interferon-beta-1a. *Drug Safety* 26:815–827 (liver failure case mentioned on p. 824)

56 Montero JL, Cerezo A, Fraga E, et al (2007) Acute liver failure in a patient with multiple sclerosis treated with interferon-β. *Multiple Sclerosis* 13:820

57 Duchini A (2002) Autoimmune hepatitis and interferon beta-1a for multiple sclerosis. *Am J Gastroenterol* 97:767–768

58 Cases of serious liver dysfunction, defined by ICH E2A as causing death or life-threatening

59 Tremlett H, Oger J. (2004) Hepatic injury, liver monitoring, and the beta-interferons for multiple sclerosis. *J Neurol* 251:1297-1303

Table 7.2. Tremlett Review ALT elevations reported in pre- and post-marketing studies

Table 2 ALT elevations reported in pre- and post-marketing studies

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In the PRISMS trial,⁶⁰ 27% of patients who received interferon beta-1a (44 mcg 3x/week sc) developed “increased” ALT, compared to 1.1% of placebo-treated patients. “Mild or moderate” increases in ALT occurred in 11% of patients treated with interferon beta-1b (250 mcg sc on alternate days), compared to 4% of placebo-treated subjects.⁶¹ Rates of increased ALT (> upper normal limit) in post-marketing studies (or re-analysis of clinical trial data) which ranged from 23 %⁶² to 67 %.⁶³

⁶⁰ PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group (1998) Randomised doubleblind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 352: 1498–1504

⁶¹ The IFNB Multiple Sclerosis Study Group (1993) Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 43:655–661

⁶² Tremlett H, Yoshida EM, Oger J (2004) Liver injury associated with the Beta-Interferons for MS: a comparison between the three products. *Neurology* 62:628–631

⁶³ Francis GS, Grumser Y, Alteri E, Micaleff A, O’Brien F, Alsop J, Moraga MS, Kaplowitz N (2003) Hepatic Reactions during treatment of Multiple Sclerosis with Interferon-beta-1a. *Drug Safety* 26:815–827

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/s/

MARIA L VILLALBA
07/12/2012

EVELYN K MENTARI
07/12/2012

Note: I (Dr. Mentari) wrote the sections listed below. My signature applies to these sections.

- Section 2.2 Tables of Currently Available Treatments for Proposed Indications
- Section 7.2.1.2 Selection Criteria
- Section 7.3.3.4 Discontinuations likely due to adverse events but not categorized as such
- Section 7.7.1 Newly identified adverse event: acute renal failure
- Appendix 7 Hepatic Injury with Beta-Interferons for Multiple Sclerosis
- I contributed to the evaluation and discussion of electrolytes and renal function in Section 7.4.2.1.

SALLY U YASUDA
07/12/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 EFC6049 Indication: relapsing multiple sclerosis Pivotal Study #2- not applicable Indication:				have robust results for the primary endpoint
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		Not deemed necessary
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?				See safety assessment for all of questions in this section 18-25
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?				
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?				
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			The language for the deferral will be written by the pediatric maternal health care team
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	x			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		Not deemed necessary
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? yes

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical 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.

Jody E. Green, M.D.	10/3/2011
Reviewing Medical Officer	Date
Billy Dunn, M.D.	10/3/2011
Clinical Team Leader	Date

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

/s/

JODY E GREEN
10/16/2011

WILLIAM H Dunn
10/18/2011