CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202992Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template for Teriflunomide
PMR # 1924-1

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Prospective, randomized, controlled, double-blind, efficacy and safety study of teriflunomide in children ages 10-17.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	05/2013
Study/Clinical trial Completion Date:	07/2017
Final Report Submission Date:	12/2017
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is a PREA requirement. A waiver has been given for children under the age of 10 due to the impractical nature of studying a population that is very small in number world-wide. A deferral has been given for those ages 10 up to 17; it is appropriate for a PMR because the drug is about to be approved and the pediatric study has not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this study is to evaluate the safety and efficacy of teriflunomide in those ages 10 to up to 17. In addition, a PK study would be incorporated into the run-in phase to provide individual PK parameters to study single and multiple dose pharmacokinetics of teriflunomide and allow for dose adjustment to the adult-equivalent dose. This would subsequently be used to establish a pediatric dose.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Deferred pediatric trial under PREA: A randomized, controlled, parallel group superiority trial to evaluate the single and multiple dose pharmacokinetics of teriflunomide, and the safety and efficacy of teriflunomide compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
A prospective study in children ages 10-17 that is a randomized, placebo-controlled, double-blind efficacy and safety study.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template for Teriflunomide
PMR # 1924-2

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Teriflunomide Pregnancy Registry

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	12/12
	Study Completion Date:	06/19
	Final Report Submission Date:	12/19
	Other: 1st interim report	9/14
	2nd interim report	9/15
	3rd interim report	09/16
	4th interim report	09/17
	5th interim report	09/18

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Pregnancy registries are conducted post-marketing to obtain safety data on drug use during pregnancy including maternal and infant outcomes. Historically, pregnancy registries are not conducted during the pre-marketing period, because except in unusual circumstances, it is ethically and medically important to demonstrate safety and efficacy in nonpregnant women before studying the drug in pregnant women.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

When teriflunomide or the prodrug leflunomide were administered to pregnant rats and rabbits throughout the period of organogenesis, high incidences of fetal malformation and embryofetal death were observed. However, while adverse developmental outcomes in other species raise the likelihood of adverse developmental outcomes in human pregnancy, these data can not reliably predict the type or frequency of adverse developmental outcomes in humans. Therefore, the goal of the pregnancy registry is to obtain data on teriflunomide exposure during pregnancy including infant outcomes to inform prescribing for and counseling with women affected by multiple sclerosis who are pregnant and of childbearing potential.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective, observational exposure cohort study conducted in the United States that compares the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to teriflunomide during pregnancy to unexposed control populations (one with women with multiple sclerosis who have not been exposed to teriflunomide in pregnancy and the other in women without multiple sclerosis). The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes will be assessed through at least the first year of life. Annual interim reports are to be submitted to the Agency

Required

☐ Observational pharmacoepidemiologic study
☒ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

PMR/PMC Development Template for Teriflunomide
PMR # 1924-3

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Summary analysis of pooled safety results of TOWER and Study 6049

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	
Study Completion Date:	
Final Report Submission Date:	12/12
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The safety database available in the NDA was sufficient to support approval. The data from the TOWER study will provide additional and confirmatory data.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The TOWER study is a clinical trial completed subsequent to submission of the NDA that will provide additional safety information. The PMR is to provide an integrated summary analysis of the pooled sfaty results of TOWER with the NDA Study 6049. It will provide confirmatory support for safety and will allow for further evaluation of specific areas of potential concern.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A summary analysis of the pooled safety results of the TOWER and Study 6049 clinical trials. The summary should include information on the effect of teriflunomide on bicarbonate, magnesium, and calcium levels and acute renal failure, as measured and evaluated in these trials.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Additional safety data from pooled analysis of the recently completed TOWER study with Study 6049

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template for Teriflunomide
PMR # 1924-4

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A clinical trial to evaluate the effects of teriflunomide on plasma concentrations of rosuvastatin, a substrate of both OATP1B1 and BCRP.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	
Study/Clinical trial Completion Date:	
Final Report Submission Date:	10/12
Other:	MM//YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

This PMR is for a clinical trial to investigate the effect of teriflunomide on plasma concentrations of rosuvastatin. This can be done post marketing, as teriflunomide was shown to be an inhibitor of OATP1B1 and BCRP in vitro and potential for drug-drug interactions with concomitant administration of with medications that are substrates of these transporters, is described in the label based on the results of the in vitro study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Based on an in vitro study teriflunomide was found to be an inhibitor of OATP1B1 and BCRP. Rosuvastatin is a substrate of OATP1B1 and BCRP. Inhibition of both transporters could results in an increase in systemic exposure of the substrates of these transporters. Statins are widely used, hence there is a potential of an increase in statin related adverse events with the increase in exposure of these statins. Rosuvastatin was chosen as it is a substrate of these two transporters and would give an estimate of the worst case by inhibiting the two together, although it will not be able to differentiate the inhibition potential between the two transporters. Therefore, the goal of the trial is to evaluate the impact of the inhibition of both OATP1B1 and BCRP by teriflunomide on plasma concentrations of rosuvastain.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial to evaluate the effects of teriflunomide on plasma concentrations of rosuvastatin, a substrate of both OATP1B1 and BCRP.
Refer to the Agency's Guidance
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf
for more detailed recommendations regarding transporter-based drug-drug interactions.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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

/s/

SALLY U YASUDA
09/12/2012
PMR/PMC Development Template

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: September 12, 2012

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 202-992 (Aubagio, teriflunomide)

This memo provides labeling recommendations for teriflunomide for treatment of patients with relapsing forms of multiple sclerosis. All other comments and recommendations regarding this NDA were provided in a previous memo (*cf. Memorandum NDA 202-992, Lois M. Freed, Ph.D., July 20, 2012*). Labeling recommendations are made using the sponsor's original proposed labeling as a base, and taking into consideration internal discussions, including comments provided by Dr. J. Edward Fisher (DNP) on the pregnancy data. Safety margins were calculated based on body surface area or, when sufficient data were available, plasma exposures (AUC) for teriflunomide, using 14 mg/day for the maximum recommended human dose (MRHD) and plasma teriflunomide AUC at the MRHD. These labeling recommendations do not reflect the most recent internal discussions or labeling negotiations with the sponsor.

ARAVA (LEFLUNOMIDE) - APPROVED	TERIFLUNOMIDE - SPONSOR'S	TERIFLUNOMIDE - RECOMMENDATIONS
HIGHLIGHTS OF PRESCRIBING INFORMATION		
		Box **WARNING: RISK OF TERATOGENICITY** Based on animal data, TRADENAME may cause major birth defects if used during pregnancy. TRADENAME is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during TRADENAME treatment. (4.2, 5.2)
n/a	**----------INDICATIONS AND USAGE----------** TRADENAME is indicated for the treatment of patients with relapsing forms of multiple sclerosis (b) (4)	**----------INDICATIONS AND USAGE----------** TRADENAME is a pyrimidine synthesis inhibitor indicated for the treatment of patients with relapsing forms of multiple sclerosis (1).
		-----------CONTRAINDICATIONS----------- • Pregnancy (4.2)
	-------USE IN SPECIFIC POPULATIONS----- (b) (4)	**-------USE IN SPECIFIC POPULATIONS-----** • Contraindicated in pregnancy; pregnancy registry available (4.2, 8.1)
FULL PRESCRIBING INFORMATION		
CONTRAINDICATIONS		
ARAVA is contraindicated in patients with known hypersensitivity to leflunomide or any of the other components of ARAVA. ARAVA can cause fetal harm when administered to a pregnant woman. Leflunomide, when		**4.2 Patients who are pregnant or** (b) (4) TRADENAME may cause fetal harm when administered to a pregnant woman.

ARAVA (LEFLUNOMIDE) - APPROVED	TERIFLUNOMIDE - SPONSOR'S	TERIFLUNOMIDE - RECOMMENDATIONS
administered orally to rats during organogenesis at a dose of 15 mg/kg, was teratogenic (most notably anophthalmia or microphthalmia and internal hydrocephalus). The systemic exposure of rats at this dose was approximately 1/10 the human exposure level based on AUC. Under these exposure conditions, leflunomide also caused a decrease in the maternal body weight and an increase in embryolethality with a decrease in fetal body weight for surviving fetuses. In rabbits, oral treatment with 10 mg/kg of leflunomide during organogenesis resulted in fused, dysplastic sternebrae. The exposure level at this dose was essentially equivalent to the maximum human exposure level based on AUC. At a 1 mg/kg/ dose, leflunomide was not teratogenic in rats and rabbits. When female rats were treated with 1.25 mg/kg of leflunomide beginning 14 days before mating and continuing until the end of lactation, the offspring exhibited marked (greater than 90%) decreases in postnatal survival. The systemic exposure level at 1.25 mg/kg was approximately 1/100 the human exposure level based on AUC. ARAVA is contraindicated in 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.		In animal studies, teriflunomide has been shown to be selectively teratogenic and embryolethal in multiple species when administered during pregnancy at doses less than those used clinically. Nonclinical studies indicate further that the intended pharmacologic action of the drug is involved in the mechanism of developmental toxicity *[see Use in Specific Populations (8.1)]*. TRADENAME is contraindicated in women who are (b) (4) 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 a fetus. If pregnancy does occur during treatment, the drug should be immediately discontinued and an accelerated elimination procedure should be initiated *[see Warnings and Precautions 5.3]*. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling *[see Warnings and Precautions (5.2)]*.
WARNINGS		
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		**5.2 Use in Women of Childbearing Potential** There are no adequate and well-controlled studies evaluating TRADENAME in pregnant women. However, based on animal studies, teriflunomide may increase the risk of teratogenic effects or fetal

ARAVA (LEFLUNOMIDE) - APPROVED	TERIFLUNOMIDE - SPONSOR'S	TERIFLUNOMIDE - RECOMMENDATIONS
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.		death when administered to a pregnant woman *[see Contraindications (4.2)]*. Women of childbearing potential must not be started on TRADENAME until pregnancy is excluded and it has been confirmed that they are using reliable contraception. Before starting treatment with TRADENAME, 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 fetus. It is possible that rapidly lowering the (b) (4) of teriflunomide by instituting an accelerated drug elimination procedure may decrease the risk to the fetus from TRADENAME. *[See Warnings and Precautions (5.3).]* Upon discontinuing TRADENAME, it is recommended that all women of childbearing potential undergo an accelerated drug elimination procedure. Women receiving TRADENAME treatment who wish to become pregnant must discontinue TRADENAME and undergo an accelerated drug elimination procedure, which includes verification of teriflunomide plasma concentrations less than 0.02 mg/L (0.02 µg/mL). Human plasma concentrations of teriflunomide less than 0.02 mg/L (0.02 µg/mL) are expected to have minimal risk. *[See Contraindications (4.2), Warnings and Precautions (5.3), Use in Specific Populations (8.1).]*

ARAVA (LEFLUNOMIDE) - APPROVED	TERIFLUNOMIDE - SPONSOR'S	TERIFLUNOMIDE - RECOMMENDATIONS
PRECAUTIONS	**8. USE IN SPECIFIC POPULATIONS**	
Pregnancy **Pregnancy Category X** (see **CONTRAINDICATIONS** section). Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to leflunomide, health care providers are encouraged to register such patients by calling 1-877-311-8972.	**8.1 Pregnancy** (b) (4)	**8.1 Pregnancy** *Pregnancy Category X [See Contraindications (4.2).]* When teriflunomide (oral doses of 1, 3, or 10 mg/kg/day) was administered to pregnant rats throughout the period of organogenesis, high incidences of fetal malformation (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death were observed at doses not associated with maternal toxicity. Adverse effects on embryofetal development were observed following dosing at various stages throughout organogenesis. Maternal plasma exposure at the no-effect level (1.0 mg/kg/day) for embryofetal developmental toxicity in rats was less than that in humans at the maximum recommended human dose (MRHD, 14 mg/day). Administration of teriflunomide (oral doses of 1, 3.5, or 12 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in high incidences of fetal malformation (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death at doses associated with minimal maternal toxicity. Maternal plasma exposure at the no-effect dose (1.0 mg/kg/day) for embryofetal developmental toxicity in rabbits was less than that in humans at the MRHD. In studies in which teriflunomide (oral doses of

ARAVA (LEFLUNOMIDE) - APPROVED	TERIFLUNOMIDE - SPONSOR'S	TERIFLUNOMIDE - RECOMMENDATIONS
	(b) (4)	0.05, 0.1, 0.3, 0.6, or 1.0 mg/kg/day) was administered to rats during gestation and lactation, decreased growth, eye and skin abnormalities, and high incidences of malformation (limb defects) and postnatal death were observed in the offspring at doses not associated with maternal toxicity. Maternal plasma exposure at the no-effect dose for pre- and postnatal developmental toxicity in rats (0.10 mg/kg/day) was less than that in humans at the MRHD. In animal reproduction studies of leflunomide (b) (4) embryolethality and teratogenic effects were observed in pregnant rat and rabbit at or below clinically relevant plasma exposures (AUC). In published reproduction studies in pregnant mice, leflunomide was embryolethal and increased the incidence of malformations (craniofacial, axial skeletal, heart and great vessel). Supplementation with exogenous uridine reduced the teratogenic effects in pregnant mice, suggesting that the mode of action (inhibition of mitochondrial enzyme dihydroorotate dehydrogenase) is the same for therapeutic efficacy and developmental toxicity. TRADENAME is detected in human semen. Animal studies to specifically evaluate the risk male-mediated fetal toxicity have not been conducted. To minimize any possible risk, men not wishing to father a child and their female partners should use reliable contraception. Men wishing to father a child should discontinue use of TRADENAME and undergo an accelerated (b) (4)

ARAVA (LEFLUNOMIDE) - APPROVED	TERIFLUNOMIDE - SPONSOR'S	TERIFLUNOMIDE - RECOMMENDATIONS
	(b) (4)	elimination procedure to decrease the plasma concentration of teriflunomide to less than 0.02 mg/L (0.02 µg/mL). [*See Warning and Precautions (5.3).*] A pregnancy registry has been established to monitor fetal outcomes of pregnant women exposed to TRADENAME. Physicians are encouraged to enroll pregnant women, or pregnant women may enroll themselves in the TRADENAME pregnancy registry by calling 1-XXX-XXXX.
n/a		omit
Nursing Mothers ARAVA should not be used by nursing mothers. It is not known whether ARAVA is excreted in	**8.3 Nursing Mothers** (b) (4) It is not known	**8.3 Nursing Mothers** Teriflunomide was detected in rat milk following a single oral dose of teriflunomide. It is not known

ARAVA (LEFLUNOMIDE) - APPROVED	TERIFLUNOMIDE - SPONSOR'S	TERIFLUNOMIDE - RECOMMENDATIONS
human milk. Many drugs are excreted in human milk, and there is a potential for serious adverse reactions in nursing infants from ARAVA. Therefore, a decision should be made whether to proceed with nursing or to initiate treatment with ARAVA, taking into account the importance of the drug to the mother.	whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TRADENAME a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the important of the drug to the mother *[sic]*	whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TRADENAME, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Use in Males Available information does not suggest that ARAVA would be associated with an increased risk of male-mediated fetal toxicity. However, animal studies to evaluate this specific risk have not been conducted. To minimize any possible risk, men wishing to father a child should consider discontinuing use of ARAVA and taking cholestyramine 8 grams 3 times daily for 11 days.		
Pediatric Use The safety and effectiveness of ARAVA in pediatric patients with polyarticular course juvenile rheumatoid arthritis (JRA) have not been fully evaluated. (See **CLINICAL STUDIES** and **ADVERSE REACTIONS**).	**8.4 Pediatric Use** [redacted] (b) (4)	**8.4 Pediatric Use** Safety and effectiveness in pediatric patients have not been established.
CLINICAL PHARMCOLOGY		
Mechanism of Action Leflunomide is an isoxazole immunomodulatory agent which inhibits dihydroorotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis) and has antiproliferative activity. Several *in vivo* and *in vitro* experimental models have demonstrated an anti-inflammatory effect.	**Mechanism of Action** Teriflunomide is an immunomodulatory agent with anti-inflammatory properties [redacted] (b) (4)	**Mechanism of Action** Teriflunomide, an immunomodulatory agent with anti-inflammatory properties, inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. The exact mechanism by which teriflunomide exerts its therapeutic effect in multiple sclerosis is unknown but may involve a reduction in the number of activated lymphocytes in the CNS.

ARAVA (LEFLUNOMIDE) - APPROVED	TERIFLUNOMIDE - SPONSOR'S	TERIFLUNOMIDE - RECOMMENDATIONS
	(b) (4) [redacted]	
	13 NONCLINICAL TOXICOLOGY	
Carcinogenicity, Mutagenesis, and Impairment of Fertility No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of leflunomide up to the maximally tolerated dose of 6 mg/kg (approximately 1/40 the maximum human M1 systemic exposure based on AUC). However, male mice in a 2-year bioassay exhibited an increased incidence in lymphoma at an oral dose of 15 mg/kg, the highest dose studied (1.7 times the human M1 exposure based on AUC). Female mice, in the same study, exhibited a dose-related increased incidence of bronchoalveolar adenomas and carcinomas combined beginning at 1.5 mg/kg (approximately 1/10 the human M1 exposure based on AUC). The significance of the findings in mice relative to the clinical use of ARAVA is not known. Leflunomide was not mutagenic in the Ames Assay, the Unscheduled DNA Synthesis Assay, or in the HGPRT Gene Mutation Assay. In addition, leflunomide was not clastogenic in the *in vivo* Mouse Micronucleus Assay nor in the *in vivo* Cytogenetic Test in Chinese Hamster Bone Marrow Cells. However, 4-trifluoromethylaniline (TFMA),	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** ***Carcinogenesis***: (b) (4) [redacted] ***Mutagenesis***: (b) (4) [redacted]	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** ***Carcinogenesis***: No evidence of carcinogenicity was observed in lifetime carcinogenicity bioassays in mouse and rat. In mouse, teriflunomide was administered orally at doses up to 12 mg/kg/day for 95-104 weeks; plasma teriflunomide exposures (AUC) at the highest dose tested are approximately 3 times that in humans at the maximum recommended human dose (MRHD, 14 mg/day). In rat, teriflunomide was administered orally at doses up to 4 mg/kg/day for 97-104 weeks; plasma teriflunomide AUCs at the highest doses tested are less than that in humans at the MRHD. ***Mutagenesis***: Teriflunomide was negative in the *in vitro* bacterial reverse mutation (Ames) assay, the *in vitro* HPRT assay, and in *in vivo* micronucleus and chromosomal aberration assays. Teriflunomide was positive in an *in vitro* chromosomal aberration assay in human lymphocytes, with and without metabolic activation. Addition of uridine (to supplement the pyrimidine pool) reduced the

ARAVA (LEFLUNOMIDE) - APPROVED	TERIFLUNOMIDE - SPONSOR'S	TERIFLUNOMIDE - RECOMMENDATIONS
an minor metabolite of leflunomide, was mutagenic in the Ames Assay and in the HGPR Gene Mutation Assay, and was clastogenic in the *in vitro* Assay for Chromosome Aberrations in the Chinese Hamster Cells. TFMA was not clastogenic in the *in vivo* Mouse Micronucleus Assay nor in the *in vivo* Cytogenetic Test in Chinese Hamster Bone Marrow Cells. Leflunomide had no effect on fertility in either male or female rats at oral doses up to 4.0 mg/kg (approximately 1/30 the human M1 exposure based on AUC).	(b) (4)	magnitude of the clastogenic effect; however, teriflunomide was positive in the *in vitro* chromosomal aberration assay, even in the presence of uridine. 4-Trifluoromethylaniline (4-TFMA), a minor metabolite of teriflunomide, was positive in the *in vitro* bacterial reverse mutation (Ames) assay, the *in vitro* HPRT assay, and the *in vitro* chromosomal aberration assay in mammalian cells. 4-TFMA was negative in *in vivo* micronucleus and chromosomal aberration assays.
	Impairment of fertility: (b) (4)	***Impairment of Fertility***: Oral administration of teriflunomide (0, 1, 3, 10 mg/kg/day) to male rats prior to and during mating (to untreated females)

ARAVA (LEFLUNOMIDE) - APPROVED	TERIFLUNOMIDE - SPONSOR'S	TERIFLUNOMIDE - RECOMMENDATIONS
	(b) (4)	resulted in no adverse effects on fertility; however, reduced epididymal sperm count was observed at the mid and high doses tested. The no-effect dose (1 mg/kg) is less than the MRHD on a mg/m^2 basis. Oral administration of teriflunomide (0, 0.84, 2.6, 8.6 mg/kg/day) to female rats, prior to and during mating (to untreated males) and continuing to gestation day 6, resulted in embryolethality, reduced fetal body weight, and/or malformations at all doses tested. Due to marked embryolethality at the highest dose tested, no fetuses were available for evaluation. The lowest dose tested is less than the MRHD on a mg/m^2 basis.

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/s/

LOIS M FREED
09/12/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: September 4, 2012

To: Hamet Toures, PharmD, MBA
LCDR, USPHS
Regulatory Project Manager
Division of Neurology Products (DNP)

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion, Division of Consumer Drug Promotion (formerly known as Division of Drug Marketing, Advertising, and Communications [DDMAC])

Subject: NDA 202992
DCDP Comments for draft MG for TRADENAME (teriflunomide) tablets for oral administration

DCDP has reviewed the proposed Medication Guide (MG) for TRADENAME (teriflunomide) tablets. We have reviewed DMPP's comments from 8/30/12 and agree with those changes. We offer a few additional comments.

Thank you for the opportunity to comment on the proposed MG.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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

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/s/

MEETA N PATEL
09/04/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 9, 2012

TO: Hamet Toure, PharmD., M.P.H, Regulatory Health Project Manager

Jody Green M.D., Medical Officer
Division of Neurology Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202-992

APPLICANT: Sanofi-Aventis

DRUG: Teriflunomide

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review
INDICATION: Treatment of patients with relapsing forms of multiple sclerosis.
CONSULTATION REQUEST DATE: September 30, 2011
DIVISION ACTION GOAL DATE: Extended to September 12, 2012
PDUFA DATE: September 12, 2012

I. BACKGROUND:

Sanofi-Aventis, Inc., the applicant of this NDA, has conducted studies in support of approval for the use of oral teriflunomide in (b) (4) subjects with multiple sclerosis with relapse. One pivotal clinical trial Study EFC6049 (TEMSO) was submitted in support of the application. The study submitted in support of the pending NDA provides for oral tablet formulation in two strengths, 7 mg and 14 mg of teriflunomide or matching placebo once daily for 108 weeks. Randomization was stratified based on a baseline Kurtzke Expanded Disability Status Scale (EDSS) of < 3.5 or >3.5.

Investigational Drug

Teriflunomide is the primary metabolite of leflunomide (Arava®) and is a de novo pyrimidine synthesis inhibitor with antiproliferative activity. The advantage of teriflunomide versus leflunomide as an investigational drug for the treatment of multiple sclerosis (MS) is based largely on the ability to administer the active drug directly. Direct ingestion of only the active metabolite negates the need for formation of the active metabolite and ensures a more consistent delivery and higher bioavailability independent of the enzymatic conversion, which may be impaired in the presence of concomitant drugs or under certain disease conditions. Teriflunomide is not approved in the United States. The applicant submitted data primarily generated in foreign countries to support approval for the treatment of MS, a common neurological disease affecting over one million people worldwide. Despite availability of other medications, more effective and better tolerated treatment options are needed for the population of medically intractable MS subjects.

According to the applicant, teriflunomide may provide an improved safety profile compared to other currently approved medications for the treatment of MS, (b) (4)

Protocol Study EFC6049 entitled "A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Design Study to Evaluate the Efficacy and Safety of Teriflunomide (HMR1726D) in Reducing the Frequency of Relapse and Delaying the Accumulation of Physical Disability in Subjects with Multiple Sclerosis with Relapse" was a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group stratified (baseline EDSS score < 3.5 versus >3.5) study design. After a screening period of up to 4 weeks, subjects were randomized (1:1:1) to one of 3 treatment groups (placebo, 7 mg, or 14 mg teriflunomide daily) and treated for approximately 2 years. Subjects successfully completing the study were offered the opportunity to enter a long-term extension study, which was conducted under a separate protocol. Subjects who were considered to have completed the study had no major protocol violations and completed two years of double-blind treatment.

This protocol has a screening period of approximately four weeks, 1-week of MS Functional Composite practice visits, and a 108-week treatment period.

The primary objective of this study was to determine the efficacy of teriflunomide in reducing the frequency of relapse in subjects with relapsing multiple sclerosis at two dose levels when compared to placebo in subjects with MS. The secondary objectives of this study were to evaluate the effect of teriflunomide on delaying the accumulation of disability as assessed by the Kurtzke EDSS and to evaluate the effects of teriflunomide on the burden of disease (defined as the total volume of all T2 lesions detected by MRI of the brain and other MRI-related variables).

The review division requested inspection of three foreign clinical investigators for the pivotal protocol Study EFC 6049 because data from the protocol are considered essential to the approval process. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects, and 2) the need to determine if sites conducted the trial ethically and were in compliance with GCP and local regulations.

II. RESULTS (by protocol/site):

Name of CI, site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
Paul O'Connor, M.D. St. Michael's Hospital 30 Bond Street M5B W8 Toronto, Ontario Canada	Protocol EFC 6049 Number of subjects: 48	11/7-11/2012	VAI
Christine Lebrun-Frenay, M.D. Hospital Pasteur Service de Neurologie 30, Voie Romaine 06002 Nice Cedx, France	Protocol EFC6049 Number of subjects: 36	1/9-13/2012	VAI
Jan Mares, M.D. University Hospital Fakultni Nemcnine Olomouc I.P Pavlova 6 Czech Republic	Protocol EFC 6049 Number of subjects: 28	1/16-20/2012	NAI

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; the EIR has not been received from the field and complete review of EIR is pending.

1. **Paul O'Conner, M.D.**
   Toronto, Canada M5B 1W8

a. What Was Inspected: The number of INDs associated with the inspected entity in CDER's database is 12, and the result of the past inspection was NAI. At this site, 55 subjects were screened, 4 subjects were reported as screen failures, 48 subjects were randomized, and three subjects were withdrawn from the study due to lack of efficacy. Two subjects were relocated to a different site, and two subjects were withdrawn due to adverse findings (elevated liver enzymes). A total of 42 subjects completed the study.

An audit of 14 subjects' records was conducted. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent prior to enrollment. Inspection revealed that source documents were organized and complete. Comparison of the source documents, case report forms, and data listings noted that these were in agreement. A two item Form FDA 483 was issued, and discussed with the clinical investigator, who adequately responded to the inspectional findings in a letter dated November 23, 2011.

b. **General observations/commentary:** The violations noted on the Form FDA 483 were:

Failure to notify and submit progress report to the IRB:

The Research Ethics Board (REB) requires submitting the annual progress report for research in a timely manner. The initial approval was dated November 29, 2006. However, the required progress report was not submitted to the REB until February 12, 2007. The clinical investigator acknowledged the observation as an oversight and promised corrective action stating the REB changed its policy such that it now issues reminder letters to the clinical investigators 60 days prior to annual expiry date.

Failure to maintain adequate and accurate case histories:

The clinical investigator did not maintain adequate and accurate records:

1. Subject #1209-008 Neurological Examination, Functional System source document reports the Cerebral Functional score as "1"(mood alteration only). However, the case report form for the same visit indicated a Cerebral Functional Score of "0" (normal). This transcription error changed the Cerebral Functional score to "1.5". However, this change has no significant impact to the outcome of the study given the isolated nature of the finding.

2. Subject #1209-0037 Neurological Examination, Functional System source document reports the Cerebral Functional score as "0" (normal). However,

the case report form for the same visit indicated a Cerebral Functional Score of "1" (abnormal signs without disability). This transcription error does not change the Cerebral Functional score, and therefore does not impact the reliability of the data.

The clinical investigator acknowledged the inspectional findings in a written response dated November 23, 2011, in which he promised to implement corrective and preventive measures to avoid such deviations from occurring in future studies. OSI finds his response acceptable.

The medical records reviewed disclosed no other adverse findings that would negatively impact the reliability of the data. With the exception of the items noted above, the records reviewed were found to be organized and the data verifiable. There were no known limitations to this inspection.

c. Assessment of Data Integrity: Although regulatory violations were noted at Dr. O'Conner's site, the findings are not likely to significantly affect overall data integrity or subject safety as they are considered isolated in nature. The data from Dr. O'Conner's site are considered reliable in support of the application.

2. **Christine Lebrun-Frenay, M.D.**
   06002 Nice Cedex, France

   a. What Was Inspected: At this site, a total of 38 were screened, two subjects were reported as screen failures, 36 subjects were randomized, and seven subjects were withdrawn fro the study. Twenty nine subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

   An audit of all subjects' records was conducted. The medical records/source data for all subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events listing.

   b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Lebrun-Frenay. However, the following items concerning inadequate record keeping were discussed with the clinical investigator.

   1. The failure to collect or save source documents. Protocol instructions concerning the requirements for use of source documents/worksheets were vague. The sponsor provided instructions on how to use these documents, but emphasized that the use of the worksheet was an optional tool to facilitate documentation and data verification. The monitor reminded the clinical investigator of the importance of using the Neurostatus worksheets. The clinical investigator did save most, bur not all, of the source documents with primary and secondary efficacy endpoints. The FDA

investigation found that at least one Neurostatus worksheet for 24 of 36 subjects was missing during the inspection. It is not clear whether the clinical investigator used the case report forms (CRFs) as the source by entering the data directly into the CRFs.

2. For Subject #27, EDSS scores were changed from higher scores to lower scores for multiple visits without providing an explanation for the changes.

3. For Subjects #1, 2, 10, 11, 15, 20, and 21, there was a failure to maintain source documents/worksheets for EDSS scores for some number of visits (3-5 visits/subject). Any change in EDSS (or disability) sustained for at least 12 weeks may affect the efficacy results. This means that a missing source document/worksheet could potentially impair the ability to determine the time that an increase in disability took place. This could impair the ability to determine sustainability of the disability, the secondary endpoint of the trial. Therefore, in the absence of the worksheets we could not verify the EDSS scores reported in their respective case report forms for the seven subjects listed above.

4. The case report forms for Subjects #28, 39, 36 did not include the name and the signature of the qualified neurologist conducting the assessment. he CRF did not have a signature block (a "design issue"). Therefore, it is not clear whether the same examining neurologist was maintained for a given patient throughout the study as required by the protocol.

The clinical investigator acknowledged the inspectional findings and offered no comments.

The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection since the sub-investigator and the clinical coordinator were able to provide the necessary documents and answers to questions raised by the FDA investigator. There were no deaths and no evidence of under-reporting of adverse events. The study appears to have been conducted adequately, and the data generated by this site can be used to support the pending application.

c. Assessment of Data Integrity: Although regulatory deviations were noted, the missing worksheets are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect on overall data integrity to be significant. In general, the data in support of clinical efficacy and safety at Dr. Lebrun-Frenay's site are considered reliable and appear acceptable in support of the pending application. However, the review division may choose to exclude the seven subjects listed above from the final analyses in their assessment of safety and efficacy.

3. **Jan Mares, M.D.**
I.P Pavlova 6 Czech Republic

a. What Was Inspected: At this site, a total 32 subjects were screened, four subjects were reported as screen failures, 28 subjects were randomized into the study, and 17 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 28 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for subjects were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Mares. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The data, in support of the clinical efficacy and safety at Dr. Mares's site are considered reliable and appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this application. The inspection of Dr. Mares revealed no regulatory violations, and the final classification for this inspection is No Action Indicated (NAI). While regulatory violations were identified during the inspections of Drs. O'Connor and Lebrun-Frenay, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect on overall data integrity to be significant. The final classification for the inspection of Drs. O'Connor and Lebrun-Frenay is Voluntary Action Indicated (VAI). Overall, the data submitted from these sites are considered acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
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Susan Thompson, M.D.
Acting Branch Chief
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Office of Scientific Investigations

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/s/

ANTOINE N EL HAGE
08/10/2012

SUSAN LEIBENHAUT
08/10/2012

SUSAN D THOMPSON
08/10/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: August 8, 2012 **Date Consulted:** February 10, 2012

From: Upasana Bhatnagar, M.D.
Medical Officer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa S. Tassinari Ph.D.
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

To: Division of Neurology Products (DNP)

Drug: **TRADENAME (Teriflunomide) -NDA 202992**

Sponsor: Sanofi-Aventis

Subject: Pregnancy and Nursing Mothers Labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of teriflunomide labeling, Draft study protocol to study teriflunomide in pregnancy, PubMed literature search

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of Teriflunomide labeling

INTRODUCTION

On August 12, 2011, Sanofi-Aventis submitted a New Drug Application (NDA) to the Division of Neurology Products (DNP) for Teriflunomide. The Sponsor proposed indication is for treatment of patients with relapsing forms of multiple sclerosis (MS) (b) (4)

(b) (4) Teriflunomide is the active metabolite of Arava (leflunomide) approved for the treatment of active rheumatoid arthritis on September 10, 1998. DNP consulted the Pediatric and Maternal Health Staff's Maternal Health Team (PMHS-MHT) on February 10, 2012 to review the Pregnancy and Nursing Mothers subsections of Sponsor proposed labeling. This review includes PMHS-MHT recommendations for revisions to the Sponsor proposed labeling for Teriflunomide. The Sponsor submitted a draft study protocol to study teriflunomide in pregnancy. PMHS-MHT recommendations regarding the study protocol are also provided in this review.

BACKGROUND

Teriflunomide is a reversible inhibitor of the mitochondrial enzyme required for pyrimidine synthesis that has a proposed indication for the treatment of patients with relapsing form of multiple sclerosis (MS). The dose proposed is 14 mg daily to be taken orally. Due to the biliary recycling of the drug, teriflunomide has a long elimination terminal half-life of an average of 6 months but in some patients up to 2 years. A 11-day regimen of cholestyramine or activated charcoal can be used as a washout procedure to accelerate elimination of Teriflunomide.[1]

The mechanism of the therapeutic effect of Teriflunomide upon patients with MS is not fully understood. However, a hallmark of MS is recurrent CNS inflammation resulting in damage to both the myelin sheath surrounding axons and to axons themselves.[2] Teriflunomide inhibits the proliferation of cells that need synthesis of pyrimidine to proliferate such as the stimulated lymphocytes involved in the inflammatory process of MS. However, slowly dividing or cells in the resting phase remain unaffected.

Approximately 85% of patients have a relapsing form of the disease called relapsing-remitting (RR) MS. T cells migrating across the blood-brain barrier are central in the inflammatory response seen in RRMS patients.[3] This inflammation causes damage resulting in varying degrees of transient and permanent neurological disability. After an initial variable period, the majority of RRMS patients develop the secondarily progressive (SP) form of the disease.[4]

RRMS affects women more commonly than men,[5] and the disease onset is often during the childbearing years between 20-40 years of age. Generally, pregnancy outcomes among women with MS have been good, and women with MS are now planning pregnancy in increasing numbers.[6] When managing MS therapy in women who are pregnant or planning

[1] labeling Arava, revised July 2011
[2] http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/multiple_sclerosis/-accessed 1/6/11
[3] Noseworthy JH, Lucchinetti C, Rodriquez M et al. Multiple Sclerosis. *N Eng J Med*. 2000;343(13):938-952.
[4] Tremlett H, Zhao Y, Rieckmann P et al. New Perspectives in the Natural History of Multiple Sclerosis. *Neurology*. 2010;74:2004-2015.
[5] Orton S-M, Herrera BM, Yee IM et al. Sex Ratio of multiple sclerosis in Canada:a longitudinal study. *Lancet Neurol*. 2006;5:932-36.
[6] Dahl J, Myhr K-M, Daltveit AK, et al. Pregnancy, delivery, and birth outcomes in different stages of maternal multiple sclerosis. *J Neurol*. 2008;255:623-627.

pregnancy, health professionals must consider the potential drug-associated risks to the fetus or infant as well as the benefits of therapy for the pregnant or lactating patient.

REVIEWED MATERIALS

Because teriflunomide is the active metabolite of Arava (leflunomide), available data regarding pregnancy exposures to Arava were reviewed in Sponsor submissions and in the literature review.

Sponsor Submitted Pregnancy Outcome Data

Teriflunomide

Limited human data are available regarding the use of teriflunomide during pregnancy. As of June 1 2011, 57 pregnancies occurred in the teriflunomide clinical program. By the March 20, 2012 Sponsor submission, there were 64 pregnancies among the patients in the teriflunomide studies. Of these 64 pregnancies, 13 pregnancies were among partners of male patients treated with teriflunomide resulting in seven live births with known male-mediated exposure. Among females in the teriflunomide studies, ten live births were reported, but only four of the reported patients had exposure to Teriflunomide during pregnancy. One patient had exposure to the 14mg dose of Teriflunomide and the other three patients had exposure to the 7mg dose of teriflunomide. The other six live births from females in the studies were in a blinded protocol or off the protocol so they had either unknown exposure status or no exposure to Teriflunomide. One infant with a mother in a blinded protocol had "funicle intorsion over the fetus" but the infant had no malformations. Please see **Appendix A** for the tables of pregnancies in females with unknown exposure, pregnancies from male exposures, and of all the submitted narratives.

Table 1. Live Births with Female Patient Exposure

Patient Number	Age Patient	Type MS & Duration	Dose	Days after onset meds	Pregnancy Outcome	Other
3502/0007	29	RRMS,2y	14mg	31-62	Live Birth	Cesarean section, normal female, 3270g, Charcoal washout
840012002	21	RRMS, 4y	7mg	397	Live Birth	Washout Day 405-421 Delivery male infant, no malformations
0014/0054	38	RRMS,5y	7mg	327	Live Birth	Cholestyramine washout given at diagnosis pregnancy, Male infant without malformations
3804/0001	26	RRMS,4y	7mg	163	Live Birth	Healthy female infant, no washout procedure

Leflunomide

A periodic safety update report (PSUR), submitted to the DNP on November 14, 2003, included 303 female related pregnancy exposures to leflunomide with 85 live births among

the 164 known pregnancy outcomes. The PSUR indicates that 7 of the 85 pregnancies (8%) resulted in live births with major malformations of syndactyly, hydrocephalus (in preterm twins), growth retardation with craniofacial dysmorphia, intestinal malrotation, macrosomia, plagiocephaly, and a skull malformation. Of note, all of the malformations were reported in patients with retrospective reports.[7]

Reviewer comment:
The data from the exposed pregnancies within the teriflunomide clinical trials are insufficient to counsel patients regarding the effects of in utero exposure on the human fetus. Among the four exposures in females, only one patient was randomized to the proposed dose for teriflunomide of 14mg. The data from the leflunomide PSUR indicates an increased risk of major malformations from the background risk of 3-4%. However, no pattern of abnormalities could be seen.

The gestational age at exposure was not well reported for either teriflunomide or leflunomide, but appears to be limited to the first trimester of pregnancy. Therefore, the effects of teriflunomide given during the entire gestation remain unknown. In order to more fully inform the prescriber for pregnant and lactating patients and the patients themselves, post-marketing data should be collected to evaluate the maternal, fetal, and infant outcomes of women exposed to teriflunomide during pregnancy.

Literature Review

No studies were found in a PubMed literature search performed to obtain data regarding the use of Teriflunomide during pregnancy and lactation. The LactMed database had no listing for teriflunomide nor for leflunomide. However, studies regarding pregnancy outcomes with leflunomide exposure were reviewed.

In 2010, Chambers et al published a pregnancy outcome cohort study to assess the effects of leflunomide during the first trimester of pregnancy conducted by Sanofi Aventis and The Organization of Teratology Information Specialists (OTIS) Collaborative Research Group from 1999 to 2009.[8] Recruitment into the study was primarily through pregnant patients calling the OTIS counseling services. The 250 patients in the study included 64 pregnant women with rheumatoid arthritis (RA) or juvenile rheumatoid arthritis (JRA) who had exposure to leflunomide, 108 women who had RA or JRA without any exposure to leflunomide or any other teratogen during pregnancy, and 78 healthy pregnant women. Data was obtained throughout gestation through telephone interviews. Ninety five percent of the women in the leflunomide group had at least one course of a cholestyramine washout procedure.

Among live births in the Chambers et al study, the rate of major malformations did not differ among the study groups; 5.4% (3/56) in the leflunomide group, 4.2% (4/95) in the disease matched group, and 4.2% (3/72) in the healthy comparison group. Although a pattern of

[7] Leflunomide, NDA 020905, PSUR March 12, 2003 to September 10, 2003. pgs 38-41
[8] Chambers CD, Johnson DL, Robinson LK et al. Birth Outcomes in Women Who Have Taken Leflunomide During Pregnancy. *Arthritis & Rheumatism.* 2010;62 (5):1494-1503.

minor anomalies was not seen, the rate of minor anomalies was greater in the leflunomide exposed group (47.1%) than the other two groups. The three malformations in the leflunomide group were occult spinal dysraphism that was surgically repaired, unilateral uteropelvic junction obstruction, and microcephaly. In addition, the authors reported that among mothers not eligible for the study there were 19 live born infants. Among these infants, two had malformations (a case of aplasia cutis in a surviving twin and multiple malformations in a infant whose mother was treated for systemic lupus erythematosus with teriflunomide) and two other infants had functional deficits (one with bilateral hearing loss and one with infantile seizures).

The study results indicated an increased risk of preterm delivery and decreased birth weight in both the leflunomide exposed group and the disease matched group when compared to the healthy comparison group. The authors interpreted this increase as related to the inflammatory processes associated with RA. Finally, the authors concluded that although this study did not corroborate the teratogenic effects seen in animals treated with leflunomide, the exposures in this study (an average of 3.1 weeks with the longest exposure of 8.6 weeks after conception) may have been too early in gestation to demonstrate the effects of leflunomide on a developing fetus.

Reviewer comment:
Although this is the largest study of leflunomide exposure during pregnancy, the average patient had exposure for 3 weeks post conception, which includes only the first weeks of embryonic development. As the authors noted, exposure during this early time likely does not provide sufficient data about the effects of leflunomide upon fetal development. Furthermore, the increased risk of small for gestational age seen in this study could be a result of the disease process of rheumatoid arthritis rather than from drug exposure. Studies published from the Swedish and Danish National Registry Data also indicated that maternal rheumatoid arthritis resulted in an increased prevalence of small for gestational age infants.[9]

These study results may not be applicable to the patient population with MS that is going to be treated with teriflunomide because the difference in disease process between RA and MS.

In another study published in 2002 by Chakravarty et al, they reported ten pregnancies with exposure to leflunomide.[10] Data was obtained from questionnaires mailed to rheumatologists to determine the prescribing practices for women of childbearing age and during pregnancy, and pregnancy outcomes related to the medication exposures were analyzed. In this study, six of ten pregnancies with leflunomide exposure had known outcomes (2 full term deliveries, 1 preterm delivery, 2 elective abortions, and 1 spontaneous abortion). Additionally, only two patients had documented administration of cholestyramine but the authors noted that others

[9] Norgaard M, Larsson H, Pedersen L, et al. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. Journal of Internal Medicine. 2010;268:329-337.
[10] Chakravarty EF, Sanchez-Yamamoto D, Bush TM. The Use of Disease Modifying Antirheumatic Drugs in Women with Rheumatoid Arthritis of Childbearing Age: A Survey of Practice Patterns and Pregnancy Outcomes. J Rheumatology.2003;30:241-246.

could have received the treatment from their obstetricians but the details of this treatment were not known. The infants from the two term deliveries were reported as healthy.

Reviewer comment:
One of the study limitations is that it did not include the gestational age at time of exposure for the patients exposed to leflunomide. Details regarding the examination of the infants for malformations and whether the two term pregnancies had cholestyramine treatment were not discussed in the publication.

A case of exposure to leflunomide in pregnancy until 16 weeks gestation was reported by Neville and McNally in 2007.[11] A 43 year old patient with RA had exposure to 20 mg leflunomide for eight months prior to conception until 16 weeks gestation. The patient was given cholestyramine after discontinuation of leflunomide. The delivery was 9 weeks preterm and the infant was diagnosed with cerebral palsy and blindness of the right eye.

Reviewer comment:
In this case report, the effects on infant could be related to prematurity rather than drug effect itself. However, this case study is one of the longest exposures to leflunomide in pregnancy reported in literature.

Sponsor Proposed Teriflunomide Pregnancy Exposure Registry

The Sponsor included a summary of a pregnancy exposure registry protocol with their submission. The proposed prospective, cohort study plans to obtain data regarding pregnancy outcomes for women with MS with teriflunomide exposure during pregnancy, data from women with MS without exposure to teriflunomide, and from women without MS and without exposure to any known teratogen. The study design is modeled after the leflunomide pregnancy registry that was published by Chambers et al in 2010, and will be similarly conducted by the OTIS Research Group. Patients will be enrolled in the study through telephone calls received by OTIS information centers in the US and Canada. The Sponsor also plans other active recruitment strategies such as mailings to physicians, professional journals, establishing a registry website, and registry placement on other websites such as the FDA, neurology, and maternal health interest sites.

Inclusion criteria
The study population includes the following groups:

1. Teriflunomide-exposed pregnant MS women
   - with teriflunomide exposure for any number of days and any dose from the 1st day of the last menstrual period (LMP) up to and including the 12th week after the first day of the LMP

2. Control group 1: pregnant MS women not exposed to teriflunomide

[11] Neville CE, McNally J. Maternal Exposure to leflunomide associated with blindness and cerebral palsy. Letter to the Editor. Rheumatology. 2007;46:1506-1510.

- pregnant women with MS who have not taken teriflunomide at any time during pregnancy nor during the two months preceding the 1st day of the LMP but who may or may not take another medication for multiple sclerosis during the current pregnancy

3. Control group 2: pregnant women who do not have MS
   - pregnant women who do not have a known diagnosis of MS and have no known exposure to a known human teratogen as determined by the referring Teratogen Information Specialists and confirmed by the OTIS Research Center

All patients must provide oral or written consent by 20 weeks gestation, agree to the conditions of the study, and have no prenatal diagnosis in the current pregnancy of fetal abnormality. In the teriflunomide exposed group, women with exposures commencing after the 12th week post LMP, women with exposure in the two months preceding the 1st day of LMP, women who come in first contact after prenatal diagnosis of a fetal abnormality, women who have already enrolled during a previous pregnancy, and other retrospective cases will be followed up but not included in the primary analysis.

Data collection

Enrolled patients will have telephone interviews throughout pregnancy and at six month and one-year post-delivery follow up. History will be obtained regarding pregnancy such as medication exposure and previous pregnancy outcomes, past medical history (including history of MS disease and treatment), and family medical history. Specific data will be collected regarding exposure to Teriflunomide including gestational timing and use of rapid elimination procedures.

Pregnancy outcome data will also be obtained. For live births, data such as the gestational age at delivery, mode of delivery, presence of major malformations, and infant data such as weight, height, and gender will be collected. For other outcomes (such as stillbirths, elective abortions, or spontaneous abortions), the gestational age at outcome, infant data such as gender and weight, and pathology or autopsy results will be collected.

Data Analysis

The data will be adjusted for covariates such as age, MS severity, exposure timing and duration, environmental exposures, planned/unplanned pregnancy, and previous pregnancies.

Sample Size

- The goal is to enroll 75 patients in the Teriflunomide group, and 125 patients in each of the two control groups. With a 10% rate of spontaneous abortion and stillbirth, elective abortion rate of <2%, and 4% loss to follow-up based on previous OTIS experience, the protocol anticipates 64 live born infants in the Teriflunomide group and 106 in each of the two control groups.

Analysis

- The study will be analyzed for the following

    - Prevalence of major structural defects between the exposed group and the control groups
    - Prevalence of a pattern of minor malformations between the exposed and the unexposed group
- With the proposed sample size, 80% power, alpha of 0.05 with a two-tailed test, the study will detect a minimum effect size with an OR from 2.4 to 4.2. For univariate comparisons, the use of chi-square or Fisher's exact test is planned, and logistic regression for multivariate analysis. The rate of pregnancy outcomes and fetal abnormalities will be calculated for all pregnancies. The rate of birth defects will be calculated for live births only. Multivariate analysis will be conducted when there are a sufficient number of birth defects or spontaneous abortions. Cox proportional hazards modeling will be used to evaluate spontaneous abortions.
- The whole cohort of all exposures, including retrospective exposures, will undergo a descriptive analysis.

Reviewer comments:

- *The study endpoints should be clearly stated. The description of the analysis indicates that the endpoints will be to evaluate the prevalence of major and pattern of minor malformations among the exposed population compared to the control population.*
- *The Sponsor has based the rates of pregnancy outcomes on the leflunomide study results, but these rates may not be similar in the teriflunomide treated population leading to fewer patients in the study than anticipated. Additionally, the leflunomide study was conducted for ten years, whereas the current proposed timeline for this study is six years (2013-2019) so fewer patients may be recruited to the study with a shortened recruitment period.*
- *For this proposed study, as with the leflunomide study, the sample size is too small to detect an increase in major malformations above the background risk of 3-4%. In a communication with Sharon Yan,[12] statistician for DNP, the sample size in the proposed study would be appropriate if the background risk for major malformations was 10%. The study design should be reviewed to improve the likelihood that this cohort study can provide sufficient data. Additional methods of increased surveillance should be considered as a Post Marketing Requirement.*

[12] 5/4/12 Personal communication

Table 2. Prevalence of Birth Defects in NDBPS[13] corresponding to the defects Animal embryofetal studies of Teriflunomide			
Malformations in Animal Studies	**Prevalence per 10,000 births in NDBPS**	**95% CI**	**Cases per births**
Ophthalmic abnormalities	1.87	1.73-2.01	1 in 5349
Upper Limb abnormalities	3.49	3.3-3.67	1 in 2869
Lower Limb abnormalities	1.68	1.56-1.81	1 in 5949
Skeletal malformations	No data reported		
Urological malformations	Not data reported		
Cleft lip and palate	10.63	10.32-10.95	1 in 940

Reviewer comments:
Although the findings in the non-clinical studies may not predict the specific malformations in humans, Table 2 is provides the background rate for some of the same malformations in humans.

Sponsors Proposed Pregnancy and Nursing Mothers Labeling
The portions of proposed labeling and medication guide reviewed are included in Appendix B.

DISCUSSION

Teriflunomide is reversible inhibitor of the mitochondrial enzyme required for pyrimidine synthesis with the proposed indication for the treatment of patients with relapsing form of multiple sclerosis (MS). Teriflunomide has a long terminal half-life, up to 2 years in some patients. However a rapid elimination procedure with cholestyramine or activated charcoal can be use to accelerate the clearance of teriflunomide. Teriflunomide is the active metabolite of leflunomide (ARAVA). Because RRMS has a female preponderance, it is likely that Teriflunomide will be used in females of reproductive potential and concerns regarding use must be communicated clearly through labeling.

PMHS-MHT recommends labeling teriflunomide Category X for pregnancy. No studies have been conducted in pregnant women and multiple adverse developmental effects were seen in the embryofetal studies in animals. Pregnancy outcome data from pregnancies

[13] Parker SE, Mai CT, Canfield MA, et al. Updated National Birth Prevalence Estimates for Selected Birth Defects in the United States, 2004-2006. Birth Defects Research (Part A): Clinical and Molecular Teratology.2010;88:1008-1016.

occurring in the clinical trials for teriflunomide are insufficient to assess the risk of pregnancy exposure to teriflunomide. The Pharmacology Toxicology review is pending at the time of this review therefore the labeling recommendations for section 8.1 are not finalized.

To prevent inadvertent exposure to teriflunomide in pregnancy, PMHS-MHT recommends adding section 8.6 Females and Males of Reproductive Potential. Females of reproductive potential should be screened for pregnancy prior to initiation of teriflunomide treatment. Prescribers must balance the benefits gained from an oral treatment of MS with potential risks to a developing fetus. Because of the limited data available regarding exposure during pregnancy and the multiple fetal effects seen in the animal data, females of reproductive potential should be counseled about use of contraception while on the drug and should complete the rapid elimination procedure at the end of treatment. No specific contraceptive requirement for males is supported by the current data. Levels of teriflunomide in semen of male patients treated with the drug have been estimated to be low. Seven live births occurred in the teriflunomide clinical trials through male-mediated exposure. PMHS-MHT recommends adding the data regarding male-mediated exposures to labeling.

PMHS-MHT recommends that nursing mothers be advised to discontinue teriflunomide use or discontinue nursing. No data is available regarding the presence of teriflunomide in breast milk. However, in animal studies, teriflunomide is excreted into rat milk and PMHS-MHT recommends communicating this data in labeling.

Teriflunomide is the active metabolite of leflunomide (Arava), approved for the treatment of Rheumatoid Arthritis (RA) in 1998. A cohort study of first trimester exposure (an average of 3.1 weeks gestation) to leflunomide was published in 2010. However, because exposures in the study occurred so early in gestation, the impact of leflunomide exposure on fetal development cannot be assessed from this study. Other pregnancy outcomes in the study could be related to the disease process of RA rather than drug effect.

The Sponsor submitted a Pregnancy Registry Protocol for a prospective cohort study to determine fetal effects of exposure to teriflunomide during pregnancy. Due to the proposed duration (only 6 years) and anticipated rate of enrollment into the study, the proposed study protocol is likely to be underpowered to assess an increased risk of major malformations with exposure to teriflunomide in pregnancy. Additionally, a much larger cohort would be needed for the study to detect specific malformations. PMHS-MHT recommends a further review and modification of the pregnancy registry protocol to maximize the likelihood of obtaining adequate data of pregnancy outcomes with teriflunomide exposure in the post-marketing setting, and would be happy to assist in this process.

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes

available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

RECOMMENDATIONS

- Teriflunomide should be labeled as pregnancy category X due to multiple developmental effects seen in animal studies and lack of data about use in human pregnancies.

- Nursing mothers should be advised to discontinue teriflunomide use or discontinue nursing.

- Section 8.6 Females and Males of Reproductive Potential should be added to labeling. To prevent inadvertent exposures, females should be screened for pregnancy prior to treatment with teriflunomide and continue contraception until completing a rapid elimination procedure if pregnancy is planned or treatment is discontinued. Data regarding male-mediated exposures in pregnancy should be added to labeling.

- The approach to assessing the risk of malformations associated with teriflunomide in the post-marketing setting needs to be further assessed. The proposed study may be inadequate to determine whether teriflunomide exposure increases the risk for malformations during pregnancy.

- MHT recommended revisions to Sponsor proposed labeling and Medication Guide are below. (b) (4) A track changes version is in Appendix C.

PMHS – Maternal Health Labeling Recommendations

HIGHLIGHTS OF PRESCRIBING

----------**CONTRAINDICATIONS**----------

(b) (4)

- Severe hepatic impairment. (4)
- Pregnancy (8.1)

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

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/s/

UPASANA BHATNAGAR
08/08/2012

MELISSA S TASSINARI
08/08/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

MEMORANDUM TO FILE

Date: August 31, 2012

From: Elizabeth L. Durmowicz, MD, Medical Officer

Through: Hari Cheryl Sachs, MD, Team Leader, Acting OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Jody Green, MD, Clinical Reviewer
Billy Dunn, MD, Clinical Team Leader
Division of Neurology Products (DNP)

Re: NDA Review, PREA Requirements

Sponsor: (b) (4)

Drug: teriflunomide

NDA: NDA 202992

Supporting Doc #: 1

Sequence # 0000

eCTD Link: \\CDSESUB5\EVSPROD\NDA202992\202992.ENX

Dosage form (strength): 14 mg, film-coated tablet

Sponsor: Sanofi Aventis

Proposed Indication: monotherapy for the treatment of [adult] patients with relapsing forms of multiple sclerosis (relapsing MS (b) (4)

Consult Question:
PMHS was requested to participate in the internal meetings and review of the NDA.

Materials Reviewed:
- Pediatric Waiver Request (WR) dated July 20, 2011 (Submitted August 12, 2011)
- Pediatric Deferral Request (November 15, 2011)
- Proposed Pediatric Study Requests (PPSR), January 11, 2011, October 21, 2011 and August 8, 2012
- Inadequate Letters, July 21, 2011 and February 17, 2012
- Sponsor's Proposed Pediatric Labeling

Teriflunomide:
Teriflunomide, an active metabolite of leflunomide, inhibits a key enzymatic step required in pyrimidine synthesis in actively proliferating cells. Per the Sponsor, the exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but may include reduced number of activated lymphocytes in the central nervous system.

Leflunomide, Arava®, was approved in September 1998 for the treatment of active rheumatoid arthritis in adults (100 mg loading dose for 3 days, followed by 20 mg daily), and is also marketed by Sanofi Aventis. In the pediatric trial of Arava® for the treatment of juvenile rheumatoid arthritis (n=94), the active comparator was determined to have a higher response rate (b) (4). Labeling notes that the response rate to Arava in pediatric patients ≤40 kg was less robust than that in patients >40 kg and suggests that dosing was suboptimal in lighter pediatric patients. Leflunomide labeling has a boxed warning for use in pregnancy and hepatotoxicity, is contraindicated in women who are or may become pregnant and includes warnings for hepatotoxicity, immunosuppression and potential/bone marrow suppression, skin reactions and potential malignancy.

Brief Regulatory Background:
The NDA for teriflunomide for the treatment of monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (relapsing MS) (b) (4) was submitted in August 2011. PDUFA date was initially June 12, 2012, but extended to September 12, 2012. Given that teriflunomide is a new molecular entity and that the product does not have orphan status, the Pediatric Research Equity Act (PREA) applies. Of note, the Sponsor is interested in a WR and has submitted three PPSRs. The proposed pediatric development plans submitted January 11 and October 21, 2011 have been unacceptable to the Agency and inadequate letters have been issued in response (See PMHS Consult document March 29, 2012). The third PPSR, submitted August 8, 2012, is under review. The Sponsor has an agreed upon PIP with the European Medicines Agency (EMA).

PREA Requirements:
The Sponsor submitted a partial waiver request for patients birth through nine years of age because the number of pediatric patients less than 10 years of age with MS is too

small and therefore studies are impossible or impracticable. A deferral was requested based on comments from the Agency, specifically that pediatric studies should not be initiated until the nonclinical data are adequate to support clinical studies in the pediatric population, the FDA has determined that the adult trials provide adequate safety and efficacy data to support initiation of clinical trials in the pediatric population, and FDA has agreed to the proposed pediatric clinical development program.

On May 2, 2012, the Pediatric Review Committee (PeRC) agreed with the Division to grant a partial waiver in pediatric patients 0-9 years because there are too few patients with disease/condition to study and a deferral in patients 10-17 years because the product is ready for approval in adults.

The required studies under PREA:

- Nonclinical Studies:
  1. Range finding study in juvenile rats to establish doses to be administered in the definitive juvenile toxicity study
  2. Toxicity study in juvenile rats
- Clinical Studies:
  1. A randomized, blinded, adequately-controlled PK, safety and efficacy study of teriflunomide in pediatric patients 10 to 16 years with multiple sclerosis
  2. A safety extension study

The Established Due Dates:

Protocol Submission: September 28, 2012
Study Completion: August 3, 2016
Study Submission: March 17, 2017

Reviewer Comment:
The PPSR submitted August 2012 proposes May 2013, July 2017 and December 2017 as the dates for protocol submission, study completion and study submission, respectively. Although these dates differ from those presented to support the deferred studies under PREA, given that the proposed dates are in reference to the WR and that the study submission date is earlier than that agreed upon by the PeRC, additional PeRC review is not required.

Pediatric Development Plan:
The Sponsor's proposed pediatric development program to fulfill PREA is also intended to fulfill the requirements of a WR and is consistent with the agreed upon PIP. The Sponsor is currently performing nonclinical studies to support evaluation of teriflunomide in patients 10 to 11 years, n.b. no additional nonclinical data are needed to support studies in patients 12 years and older. (b) (4)

(b) (4)

[redacted]

Although DNP has not agreed to the pediatric development program for teriflunomide, the current thinking is that the pediatric study should be a two year placebo-controlled trial with time to first relapse as an endpoint or an open-label study with an active comparator with an MRI endpoint at 6 months. The study 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.

Proposed Pediatric Labeling:
The Sponsor's proposed labeling provides the following statement in the HIGHTLIGHTS, Use in Specific Populations section: (b) (4) [redacted] In Subsection 8.4, Pediatric Use, in the FULL PRESCRIBING INFORMATION section, the Sponsor has proposed the following statement: (b) (4) [redacted]

Reviewer Comment:
Given that safety and effectiveness have not been established in pediatric patients and no specific pediatric safety signal has been identified, the proposed labeling is acceptable under 21CFR201.57. However, given that the statement included in the HIGHLIGHTS section of labeling under Use in Specific Populations, (b) (4) [redacted]

PMHS participated in the review of the Sponsor's pediatric plan, preparation of the documents for the PeRC and in pediatric labeling discussions.

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

/s/

ELIZABETH L DURMOWICZ
08/31/2012

HARI C SACHS
09/05/2012
I agree with these recommendations

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 31, 2012

To: Hamet Toure, PharmD, MBA
LCDR, USPHS
Regulatory Project Manager
Division of Neurology Products (DNP)

Billy Dunn, MD
Clinical Team Leader, DNP

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DPDP)

Subject: OPDP Comments on draft Prescribing Information (PI) for TRADENAME (teriflunomide) tablets for oral administration

NDA 202292

This consult is in response to DNP's request for OPDP's review of the proposed PI for teriflunomide (FDA version dated 8/24/12). We appreciate the opportunity to provide comments on the PI.

Please see attached PI with our comments incorporated therein.

If you have any questions, please contact Quynh-Van Tran, (301) 796-0185, or quynh-van.tran@fda.hhs.gov.

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/s/

QUYNH-VAN TRAN
08/31/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING MEMORANDUM

Date:	August 29, 2012
To:	Russell Katz, M.D. Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Robin Duer, MBA, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling (Medication Guide)
Drug Name (established name):	teriflunomide
Dosage Form and Route:	tablets
Application Type/Number:	NDA 202992
Applicant:	sanofi-aventis U.S. LLC

1 INTRODUCTION

On August 12, 2011, sanofi-aventis submitted for the Agency's review an original New Drug Application (NDA) for teriflunomide tablets. Teriflunomide is a novel immune modulatory agent with anti-inflammatory properties indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (MS) [redacted] (b) (4)

On April 18, 2012 the Agency notified the Applicant that a 3 month review extension was being added to the NDA review timeline following the receipt of a solicited major amendment on April 13, 2012.

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Medical Policy Programs (DMPP) to provide a review of the Applicant's proposed Medication Guide (MG) for teriflunomide tablets.

2 MATERIAL REVIEWED

- Draft teriflunomide tablets Medication Guide received on August 12, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on August 24, 2012
- Draft teriflunomide tablets Prescribing Information (PI) received on August 12, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on August 24, 2012
- Approved GILENYA (fingolimod) comparator labeling dated May 9, 2012

3 REVIEW METHODS

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the Package Insert (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
08/29/2012

MELISSA I HULETT
08/29/2012

LASHAWN M GRIFFITHS
08/29/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**TRADENAME (teriflunomide) tablets, for oral administration**
Applicant	Sanofi-Aventis U.S. LLC
Application/Supplement Number	NDA 202992
Type of Application	Original NDA
Indication	Treatment of patients with relapsing forms of multiple sclerosis
Established Pharmacologic Class[1]	None stated
Office/Division	Office of Drug Evaluation I/Division of Neurology Products
Division Project Manager	Hamet Touré
Receipt Date	August 12th, 2011
PDUFA Goal Date	September 12th, 2012
SEALD Review Date	August 28th, 2012
SEALD Labeling Reviewer	Abimbola Adebowale
SEALD Labeling Team Leader	Eric Brodsky
SEALD Division Director	Laurie Burke

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *The summarized statement under the heading "Use in Specific Populations" does not reference the section (s) or subsection (s) of the Full PrescribingInformation (FPI).*

We recommend that you delete the optional section heading entitled "Use in Specific Population" because the information provided under this section is the same as the information provided under the required section heading entitled "Contraindication".

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information (SRPI) Revised

• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment: *Recommend that "for oral administration" be changed to "for oral use."*

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *The 4-digit year is missing from the placeholder*

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

NO 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment: *The subject of the Warning (e.g., WARNING: HEPATOTOXICITY AND RISK OF TERATOGENICITY) is missing.*

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

NO 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment: *The current length of the Boxed Warning in the HL is 22 lines. It is very important to reduce the length to 20 lines or less.*

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

N/A 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *The name of the established pharmacologic class is missing from the Indications and Usage statement in the HL. Elist does not list an EPC for this product. When an EPC is available, please include it.*

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment: *Recommend that the words "film-coated" is deleted because identifying characteristics of the dosage form should not be included in Highlights. Only include this information in the FPI.*

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.
Comment:

NO 24. Each contraindication is bulleted when there is more than one contraindication.
Comment: *Bullets for the two contraindication listed are missing.*

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".
Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.
Comment: *The bolded revision date is missing from the placeholder.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.
Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.
Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

For section 5, "Warning and Precautions", the subheadings for 5.1, 5.2, and 5.12 in the TOC do not match the subheadings in the FPI.

For section 7 "Drug Interactions" we recommend using subheadings for the different drug interactions described.

For section 8 ""Use in Specific Populations" the subheadings for 8.2, 8.6 and 8.7 in the TOC do not match the subheadings in the FPI. In addition, subheading 8.6 in the FPI is missing from the TOC.

For section 17 "Patient Counseling Information" the subheadings 17.2, 17.3, 17.4, 17.5 and 17.6 in the TOC do not match the subheadings in the FPI. in addition, subheadings 17.7, 17.8, 17.9 and 17.10 included in the FPI is missing from the TOC.

NO 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: *The same title of the Boxed Warning that appears in the HL and FPI is missing from the beginning of the TOC in UPPER-CASE letters and bold type.*

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment: *Recommend that this heading be justified to the left rather than centered.*

NO 37. All section and subsection headings and numbers must be **bolded**.

Comment: *For Section 4 "Contraindications" subheading 4.1 is missing from the FPI*

For section 5 "Warnings and Precautions" subheading 5.7 number is not bolded

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Selected Requirements of Prescribing Information (SRPI) Revised

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment: *The presentation for cross-references in the FPI for the following sections and subsections need to be changed to the preferred presentation as follows:*

For subsection 5.2: Change [see CONTRAINDICATIONS (4.2)] to [see Contraindications (4.2)]
For section 7: Include cross reference to the more detailed information in section 12.
For subsection 8.8: Change (see WARNINGS (5.7, 5.8) to [see Warnings and Precautions (5.7, 5.8)]

For section 10: Change *[see* WARNINGS AND PRECAUTIONS (5.3) *and Clinical Pharmacology* (12.3)] to *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*]

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

NO 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment: *Subject of the warning is not identified in the heading.*

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

NO 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment: *The verbatim statement needs to be moved up from its current position in the label so that it precedes the presentation of adverse reactions in the "Clinical Trials Experience" subsection of Adverse Reactions.*

47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

N/A

"*The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."*

Comment:

Selected Requirements of Prescribing Information (SRPI) Revised

Patient Counseling Information

NO

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *Change from "See Medication Guide" to "See FDA-approved patient labeling (Medication Guide)" without the quotation marks*

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/s/

ABIMBOLA O ADEBOWALE
08/29/2012

ERIC R BRODSKY
08/29/2012
I agree

LAURIE B BURKE
08/30/2012

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA:	202992
Drug:	Teriflunomide (Aubagio)
Route:	Oral (film-coated tables)
Indication:	Treatment of patients with relapsing forms of multiple sclerosis (RMS) (b)(4) [redacted]
Sponsor:	Sanofi Aventis
Submission Date:	August 12, 2011
Review Date:	July 21, 2012
Reviewer:	Sally Usdin Yasuda, Safety Team Leader Division of Neurology Products, HFD-120

1. Background

Teriflunomide is the active "predominant" metabolite of leflunomide (Arava) that has been approved since 1998 for treatment of rheumatoid arthritis. According to the Sponsor, teriflunomide is a noncompetitive, selective, reversible inhibitor of mitochondrial dihydroorotate dehydrogenase (DHO-DH). This results in blockade of de novo pyrimidine synthesis and subsequent cytostatic effect on proliferating T- and B-lymphocytes in the periphery, with resulting diminished numbers of activated lymphocytes available to enter the CNS. The Sponsor states that slowly dividing or resting cells are unaffected by teriflunomide. The exact mechanism of effect in multiple sclerosis (MS) is unknown.

In terms of the clinical pharmacology of teriflunomide, it is rapidly absorbed orally, with a tmax of 1.2 hours at steady state. Bioavailability is 100%. The median terminal half-life is 19.4 days, and teriflunomide is excreted in the gastrointestinal tract mainly through the bile as unchanged drug.

Known safety concerns for ARAVA include teratogenicity and hepatotoxicity for which there are boxed warnings, as well as potential for immunosuppression/bone marrow suppression, serious skin reactions, peripheral neuropathy, and interstitial lung disease. The ARAVA label also contains a precaution that blood pressure should be checked before and during leflunomide treatment.

The clinical development program for teriflunomide investigated doses of 7 mg/day and 14 mg/day, based on doses active in animal models and on pharmacokinetic data obtained with leflunomide. Teriflunomide exposure after a single 20 mg dose of leflunomide (the dose recommended for use in rheumatoid arthritis), was 70% of that after a single 20 mg dose of teriflunomide. The Sponsor has selected 14 mg/day as the proposed dose based on their assessment that patients will gain more benefit from the higher dose without substantial risk from clinically relevant treatment emergent adverse events. Of note, a loading dose was administered for 1 week in Study 2001, but not in Phase 3. In addition, when study treatment was discontinued, a procedure to accelerate elimination of teriflunomide (cholestyramine or charcoal)

was used in 85% of patients who discontinued in 6049/TEMSO in 100% of subjects in clinical pharmacology studies, in order to reach minimal teriflunomide plasma concentrations in a few weeks instead of months.

This memorandum primarily summarizes the primary safety concerns from Dr. Lourdes Villalba's safety review. Dr. Evelyn Mentari has reviewed Currently Available Treatments for Proposed Indications, Selection Criteria, Discontinuations likely due to adverse events but not categorized as such, Newly identified adverse event: acute renal failure, Hepatic Injury with Beta-Interferons for Multiple Sclerosis, and contributed to the evaluation and discussion of electrolytes and renal function. Dr. Villalba's review incorporates Dr. Mentari's considerations. Please refer to Dr. Villalba's review for detailed safety considerations.

2. Summary of Findings from the Safety Review

2.1 Sources of Data, Exposure, and Demographics

Sources of Data

The integrated summary of safety (ISS) was based on 2 types of pooling as shown in the Table below. Pool 1 is comprised of the two placebo-controlled monotherapy studies: 2001 that was a small phase 2 study of 9 months duration and ECF6049/TEMSO that was a phase 3 study of 2 years duration. Pool 2 consisted of patients who received active treatment in 2001 and ECF6049/TEMSO plus their non-controlled long-term extensions (6048 and LTS6050, respectively).

Table 4 - Integrated summary of safety pooling strategy

Pool	Type	Studies	Treatment duration	Number of patients Placebo	Number of patients Teriflunomide 7 mg	Number of patients Teriflunomide 14 mg	Comparisons
1	Placebo-controlled	EFC6049/TEMSO	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).

Two pools of clinical pharmacology studies were analyzed: a pool of single dose studies (in which no patients received placebo) except the hepatic impairment and renal impairment studies and a pool of repeat dose studies. For interaction studies, only the periods or phases where teriflunomide was administered alone were extracted and included in the appropriate pool.

Ongoing studies (for which only blinded safety data regarding deaths, serious AE and AE leading to discontinuation were included in the original submission) included TENERE that is an open label study of Teriflunomide 7 or 14 mg compared to interferon-β 1a, TOPIC that is a phase 3 monotherapy study of teriflunomide vs placebo, and TERACLES that is a study of teriflunomide vs placebo in which all patients are treated with interferon-β. Unblinded data from TENERE were submitted as part of the 120-day SUR. In addition, an interim safety analysis of TOWER, a 48-152 week placebo-controlled monotherapy study was submitted separately as an amendment to the NDA.

For patients discontinuing treatment and/or not entering a long-term extension, safety data up to 16 weeks after discontinuation were included. Based on the half-life of teriflunomide, I agree with Dr. Villalba that this was appropriate. Approximately 2/3 of patients in the phase 2/3 studies underwent a washout procedure. All patients in clinical pharmacology studies underwent washout, and analysies of AEs in these studies were included up to 1 or 2 weeks after the last dose of study drug.

Exposure

In the Phase 2/3 trials alone, 2000 unique patients were treated with teriflunomide, including 384 patients treated with Teri 14 mg for at least 6 months and 303 treated for at least 1 year. As per the safety update submitted 2/7/12, there is a total exposure of approximately 2600 patients (6000 patient years) to Teri 7 or 14 mg, with at least 643 patients having been exposed to Teri 14 for at least 6 months and 5353 for at least 1 year, with 362 exposed for at least 2 years in completed monotherapy or adjunctive therapy studies. Therefore, exposure to teriflunomide in the MS program exceeds minimum ICH guidance recommendations (minimum 1500 total, 300 subjects for 6 months and 100 for 1 year at a clinically relevant dose). In addition, the exposure after administration of 14 mg teriflunomide is equivalent to that of 20 mg leflunomide that has been approved for rheumatoid arthritis since 1998. *I agree with Dr. Villalba that exposure in the available database is sufficient to adequately assess the safety of teriflunomide.*

Dr. Villalba notes that exclusion criteria restricted the population exposed and suggests that this be considered in labeling. For example, patient with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia were excluded, as were patients with a history of cancer, and patients with a history of elevated serum amylase or lipase. The proposed labeling does not provide specific recommendations for use in these patients.

Demographics

Dr. Villalba notes that the demographics and disease characteristics of the MS population in the ISS are consistent with those in other applications for MS. MS disease characteristics at baseline were similar among treatment groups within each of the studies, and there were no major differences among treatment groups in medical/surgical history or prior medications. In clinical pharmacology studies there was a higher percentage of males (79% and 68% in the single and repeated dose pools, respectively), respectively and a higher percentage of black subjects (11% and 4.5% in single and repeated dose pools, respectively) than in phase 2/3 studies where approximately 72% of patients were female and only 0.6% of patients were Black. In Pool 1, 405 patients (32%) were from the Americas, although only 8 were from the US. Approximately 73% of patients had not received previous MS disease modifying drugs within 2

years prior to randomization. Among those who had taken previous MS medications, the most common prior treatment was interferon-β1b or interferon-β1a. No patient had received mitoxantrone. Five patients had received natalizumab.

2.2 Significant Safety Findings

2.2.1 Deaths

Dr. Villalba notes that there were 8 deaths in teriflunomide-treated patients and 1 death on placebo (a suicide). Four of the 9 deaths occurred during the monotherapy study extensions, and five occurred in ongoing studies. Five of the 8 deaths on teriflunomide were cardiovascular/unknown cause of death during extension studies (one MI, one cardiorespiratory arrest, three found dead at home several years into teriflunomide treatment). The other three deaths on teriflunomide were one suicide, one motor vehicle accident, and one gram negative sepsis. No deaths were reported in Pool 1, adjunctive therapy studies, or clinical pharmacology studies. The cases are briefly summarized below. Please see Dr. Villalba's review for details.

Cardiovascular/unknown deaths - Subject 0030/0009 (LTS6048) , a 54 y.o. female with a past medical history that included hypertension, hyperlipidemia, and coronary artery disease, died from a **myocardial infarction** having been treated with teriflunomide 7 mg for 9 years. Baseline systolic blood pressure was 107/78 mm Hg. After beginning teriflunomide, systolic blood pressure ranged from 110s to 160s. She had an increase in blood pressure after 2.3 years (160/108 mm Hg) on teriflunomide leading to an increase in antihypertensive medication dose. Dr. Villalba believes that is it likely that teriflunomide contributed to this death. As teriflunomide is associated with an increase in blood pressure (discussed in section 2.2.4/AESI/hypertenion of my memo), I agree that a role for teriflunomide in this death cannot be ruled out. Subject 0030/0004 (LTS6048) had been treated with teriflunomide 14 mg for 4.8 years. The patient reportedly had a history of asthma although there was no treatment reported throughout the study. She had AEs of dyspnea, anxiety disorder, depression/elusions, and hypothyroidism during the study, and had 1 episode of pneumonia requiring hospitalization 2 years into treatment, complicated with tachycardia and respiratory failure on day 728. One year prior to death a cardiologist noted heart murmur, aortic insufficiency, and high blood pressure 160/990); ECG was normal; echo showed left ventricular hyperkinesia without increased ventricular diameter. Treatment was discontinued approximately 2 months prior to death. On day 1750 the patient was evaluated for "malaise" and the physician noted "tachycardia > 150 bpm" and blood pressure "90 mm Hg" and patient was hospitalized, at which time blood pressure was 100/60 mm Hg, pulse 90 bpm, normal temperature, and O2 saturation was 90%. No laboratory tests, ECG or chest x-ray were performed. Patient was given oxygen and physiologic "serum", and 5 hours later was administered 1 pill of bromazepam and developed asthma crisis within 30 minutes. She received salbutamol, amiodarone, furosemide, and clorazepate, and 1 hour later developed "cardiac trouble", respiratory failure, and died. I agree with Dr. Villalba that there is insufficient information to characterize the role of teriflunomide this **"cardio-respiratory" death**. Subject 2407/0030 (LTS 6050) was a 41 y.o. female found dead 10 months after starting treatment with teriflunomide 7 mg. She had a history of depression but no cardiac risk factors. Pathology examination showed diffuse anoxic-ischemic edema with involvement of the amygdale, and signs of extended circulatory failure with cardiac necroses, acute pulmonary edema, and centrilobular sinusoidal distension, as well as bronchial

pulmonary lesions. Dr. Villalba notes that neurogenic pulmonary edema and sudden death due to brainstem disease with involvement of cardiorespiratory centers has been reported in patients with MS. I agree that the cause of death in this case is **unknown**. Subject 3203/0010 (LTS6050) was a 41 y.o. male with a history of MS for 11 years prior to study entry with an EDSS score of 5.5 who was found dead 1314 days after the first dose of teriflunomide 14 mg. He had no previous CV risk factors. No autopsy report is available. The cause of death is **unknown**. Subject 3009/0016 (LTS6050) was a 51 yo. male, diagnosed with MS 16 years prior to entry (baseline EDSS of 6), who died at night, during his sleep 3 years and 11 months into teriflunomide treatment. Blood pressure at 16 months was 160/104 and at 22 months was 166/102 mm Hg. Patient was started on tramadol, ramipril, and carbamazepine. At his last visit (3 years and 8 months) serum Na was 129 mmol/L (nl 132-147), his blood pressure was 140/83, and he had lost 33 lbs since the beginning of the trial. I agree the cause of death is **unknown**. Dr. Villalba notes that sudden death has been reported in patients with MS with brain stem involvement. However, I agree that hypertension and hypernatremia may have contributed to his death, and the role of teriflunomide cannot be ruled out. *The role of teriflunomide in these cases is unknown. Two of the patients (one MI, one found dead at home) had hypertension with diastolic blood pressure > 100 mm Hg during the trial that may have contributed to the their cardiovascular risk, although as Dr. Villalba notes, there was no increased risk of myocardial infarction or stroke in the controlled trials.*

Subject 840074/003 (TOWER) had a history of type 2 diabetes, obesity, hypertension, depression, sleep apnea, and possibly Brugada syndrome. On Day 477 he experienced a fatal motor vehicle accident on a country road in a snow storm after colliding head on with another vehicle. He had had no complaints of adverse events in the morning of the accident. *I agree that this death is unlikely related to teriflunomide.*

Subjects 8503/0005 (EFC6260) and 156012/0005 (TOWER) died of suicide after taking placebo (last dose 1 month prior to death) and 14 mg teriflunomide (for 71 days), respectively. Both had a history of depression. *It is difficult to attribute this to teriflunomide.*

Subject 764001/003 (TOWER) was a 24 y.o. female with no notable past medical history other than multiple sclerosis who died from gram negative sepsis after 1.7 years on teriflunomide. *I agree with Dr. Villalba that due to the potential for immunosuppression, this death could be related to treatment with teriflunomide.*

2.2.2 Nonfatal Serious Adverse Events (SAEs)

Treatment emergent SAEs in Safety Pool 1 (placebo controlled studies 2001 and 6049/TEMSO) occurred in 13%, 13%, 16% of patients on placebo, Teri 7, and Teri 14, respectively, as shown in the table below from Dr. Villalba's review. The most common SAEs were in Investigations, Injury, poisoning and procedural complications, and Infections and infestations SOCs. Dr. Villalba notes a suggestion of a dose-response between the 7 and 14 mg/day doses of teriflunomide for these events, although I note that for Investigations, the SAEs in placebo were greater than in either dose group for teriflunomide. In Pool 2, 23.9% and 21.2% of patients treated with Teri 7 and 14, respectively, reported at least 1 serious AE. The most common SAEs

in this pool were in the Investigations SOC (5% in each treatment group) and Infections and infestations (4% in each treatment group). Overall in Pool 2, there was no obvious dose-response. As Dr. Villalba notes, the increase in overall risk in Pool 2 compared to Pool 1 was due to an increase in the risk of Infections and infestation, Investigations, and Neoplasms (<1% in either dose group in Pool 1, and 2% for Teri 7 and 1% in Teri 14 for Pool 2). Dr. Villalba notes that safety findings in the SUR (Safety Pool 2a) were consistent with those in the original application. Selected cases of SAEs are described below. For a complete discussion, please refer to Dr. Villalba's review.

SAEs in Pool 1.

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)
Respiratory, thoracic and mediastinal disorders	0	0	0
Gastrointestinal disorders	1 (0.2)	8 (1.9)	4 (1.0)
Hepatobiliary disorders	2 (0.5)	9 (2.1)	3 (0.7)
Skin and subcutaneous tissue disorders	1 (0.2)	1 (0.2)	0
Musculoskeletal and connective tissue disorders	4 (1.0)	5 (1.2)	3 (0.7)
Renal and urinary disorders	0	0	1 (0.2)
Pregnancy, puerperium and perinatal conditions	1 (0.2)	0	0
Reproductive system and breast disorders	2 (0.5)	6 (1.4)	1 (0.2)
General disorders and administration site conditions	0	0	1 (0.2)
Investigations	13 (3.1)	9 (2.1)	10 (2.4)
Injury, poisoning and procedural complications	4 (1.0)	5 (1.2)	3 (0.7)
Surgical and medical procedures	0	1 (0.2)	0

Blood and Lymphatic system disorders – Dr. Villalba notes an imbalance in the number of SAEs in Pool 1 for this SOC as shown above. Five patients had SAEs of neutropenia/neutrophil count decreased, 1 on placebo and 4 on Teri 14. In 3 cases of neutropenia (002001-124-0014-0002 and 002001-124-0014-0014, 006049-616-3007-0005) the event improved upon discontinuation and in subject 6049/2401/0005 a SAE of neutrophil count decrease normalized approximately 1 month later without discontinuation of study drug. In 1 of those cases it did not recur when drug was re-introduced; in one case a second SAE of neutropenia occurred after the drug was re-introduced but resolved while on drug. The case of neutropenia on placebo was also taking amitriptyline that has been associated with neutropenia and bone marrow suppression. There was an additional SAE of neutrophil count decrease in the Investigations SOC that appeared to be an episode of pancytopenia that resolved spontaneously within 1 month and that could have been a lab error. Dr. Villalba notes that nonclinical studies show that teriflunomide has bone marrow suppression effects, and that ARAVA is associated with bone marrow suppression. *I agree that these effects appear to be manageable and can be addressed with labeling.*

Cardiac – In Pool 1, two patients had SAEs in this SOC, both taking placebo. In pool 2a (including the SUR), seven patients had non-fatal cardiac disorders on teriflunomide. Subject 6049-826-2600-0010 with a history of syncope had several episodes of bradycardia and asystole thought not to be related to teriflunomide, and continued to be treated with teriflunomide. There were 3 nonfatal myocardial infarctions and 1 nonfatal cardiac arrest, all in patients with cardiac risk factors; teriflunomide was continued in all 4 patients. Subject 006049-124-1209-0022 with a history of alcohol use had cardiac valve disease on Day 879 with symptoms of congestive heart

failure; study drug was discontinued and symptoms increased. Subject 002001-124-0017-0009 developed cardiomyopathy during the extension study; the drug was discontinued and the event continued. In that case, the patient was also taking amitriptyline that has been associated with cases of cardiomyopathy in postmarketing reports. In addition, Dr. Villalba notes that although there was no mention of alcohol use in that patient, alcohol use could explain the cardiomyopathy, ALT/lipase elevation, and peripheral neuropathy observed in that case. *I agree with Dr. Villalba that it is difficult to draw conclusions about the cardiac effects in the absence of a control group, and that a role for teriflunomide cannot be ruled out.*

Ear and labyrinth disorders – Dr. Villalba notes 2 events in this SOC in Pool 1: 1 haematotypmanum on Teri 14, discussed in Nervous system disorders, and 1 hypoacusis on placebo, as well as a case of vertigo on Teri 7 in Pool 2. *I agree it is difficult to assess whether these cases were drug related.*

Eye disorders – There were no SAEs in this SOC in Pool 1. There were 5 events in 4 patients in Pool 2 that included uveitis, macular edema, and retinal vasculitis leading to drug dc; chorioretinopathy leading to drug dc; uveitis leading to interruption of therapy; and retinal detachment in which drug was continued. Dr. Villalba notes that nonclinical data with teriflunomide and postmarketing experience with leflunomide do not suggest an effect of teriflunomide in the eye.

Gastrointestinal disorders - In Pool 1 there was an excess of SAE of GI disorders in the teriflunomide groups (1.9% in each group) compared to placebo (0.2%). These included 3 cases of GI inflammatory conditions all on Teri 7: one case of colitis, one Crohn's disease (for which drug was discontinued), and one ulcerative colitis. Because the case of ulcerative colitis occurred 3 months after rapid elimination with cholestyramine, I agree with Dr. Villalba that is it unlikely due to teriflunomide. Dr. Villalba proposes that the other 2 cases could be potentially related to inhibition of DNA synthesis in the GI mucosa, although she would have expected to see cases in the Teri 14 group as well. There were 4 cases of inguinal hernia in the Teri 14 group in Pool 1 and none in placebo or the Teri 7 group. In Pool 1 there was one case each of anal fissure, aphthous stomatitis (for which drug was discontinued), diarrhoea, duodenal ulcer, and intestinal functional disorder in Teri 14 and 1 case each of abdominal pain lower, abdominal wall hematoma, nausea, peritonitis, and toothache in Teri 7.

Dr. Villalba notes that although there was a signal for pancreatic toxicity in non-clinical studies, there were no SAEs of pancreatitis in the Teri treatment groups (1 case 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 (1 case each). Dr. Villalba notes that as per the patient profiles, platelet count, INR, and APTT were normal in most patients except in Subject 006049-616-3007-0004 who had low normal platelet count at entry and intermittently low throughout the study.

General disorders and administration site conditions – There were no events in Pool 1. Dr. Villalba notes that SAEs in Pool 2 consisted of 1 case of asthenia on Teri 14 and one case each

of "adverse drug reaction", death (Subject 2407/0030 (LTS 6050) discussed under "deaths"), and general physical health deterioration in the Teri 7 group.

Hepatobiliary disorders – In Pool 1, there were more SAE of hepatobiliary disorders in Teri 7 (2.1%) compared to placebo or Teri 14 (0.5% each) driven by cholelithiasis. Of the nine events in the Teri 7 group, 6 were cholelithiasis and 2 were cholecystitis. There was 1 case of cholecystitis (chronic) in the Teri 14 group and 1 case of cholelithiasis in the placebo group. Dr. Villalba notes that only 4 patients with cholelithiasis had increased transaminases, including the patient on placebo, but the increase in ALT was < 3X ULN. In the patients with cholelithiasis, the patient on placebo had intermittent increase in bilirubin (but not > 2x ULN); the other cases had normal bilirubin. The role of teriflunomide in cholelithiasis cannot be ruled out because of the imbalance between drug and placebo, although I agree with Dr. Villalba that more cases with Teri 14 would be expected. Other SAEs in this SOC in Pool 1 were hepatitis toxic (1 case, 2%, in TERI 14), and Liver injury (1 case each, 2% each) in Placebo and in Teri 7. Dr. Villalba notes that events in this SOC within the teriflunomide treated groups appeared to be more common in females than in males.

Dr. Villalba notes that some SAEs in the hepatobiliary system were coded under the Investigations SOC. These included alanine aminotransferase increased, hepatic enzyme increased, transaminases increased, and aspartate aminotransferase increased. There was no excess of SAEs in the Investigations, Hepatobiliary HLGT on teriflunomide in Pool 1.

Dr. Villalba has provided narratives of selected SAE cases from Hepatobiliary disorders and Hepatobiliary Investigations in Pool 1. Subject 006049-643-3201-0009 (also reviewed by Dr. John Senior) was a 35 y.o. female who experienced **toxic hepatitis** on day 135 of Teri 14. Laboratory values at screening were normal. She had a medical history of anemia, chronic gastroduodenitis, and pyelonephritis. She was given methylprednisolone sodium succinate from Day 78-70, Day 94-95, and Day 98-100 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 (39º C), vomiting, and dark urine. On day 144 she developed icterus. Labs on Day 148 showed ALT 32X ULN, AST 20X ULN, GGT 4.7X ULN, total bilirubin 1.7X ULN, direct bilirubin 2.5X ULN, and alkaline phosphatase 3.1 X ULN. There is no other information on bilirubin until Day 310. Albumin and PT/PTT are not available. Eosinophil count was 16.4% (normal up to 6.8%). Viral hepatitis serology (HAV IgM, HBsAG, HCVab, and ABcor AB) was negative; viral serologies for CMV, EBV, and Hepatitis E were not done. Metoclopramide, omeprazole, and activated charcoal were given as corrective treatment. Teriflunomide was permanently discontinued, with the last dose on Day 151. She was hospitalized on Day 153 for 5 weeks, and underwent plasmapheresis. ALT was 3x ULN and 1.2X ULN on Days 161 and 172, respectively. She had a washout procedure with cholestyramine from Day 303-316. On Day 310 ALT had decreased to normal range (as had bilirubin) and on Day 319 she was considered recovered. *I agree that teriflunomide-induced severe liver injury cannot be ruled out in this case.*

Subject 0060049-152-3803-0005, with a history of cholecystectomy, developed **liver injury** on Day 141 of teriflunomide 7 mg treatment. She was treated with methylprednisolone MS before study entry and on Day 114-116 for MS relapse. Concomitant therapy included an oral

contraceptive for several years, as well as 1 dose of diclofenac on Day 80 and ibuprofen on Days 80-82. On Day 141 lab results showed ALT 10x ULN, AST 6.4X ULN, and bilirubin 1.2X UL. Drug was discontinued on Day 143. This was followed by a washout procedure including cholestyramine from Days 147-157. Maximum ALT was 23X ULN, maximum AST was 12.3X ULN, and GGT was 5.5X ULN on Day 160, after which values decreased progressively over a month. On Day 160 she was mildly icteric. Abdominal ultrasound showed fatty liver. On that date she also had positive urobilinogen in urine (normal is negative). Maximum alkaline phosphate was 1.8X ULN and total bilirubin was 1.2 X ULN on Day 168. On Day 189 she recovered from liver injury with normal ALT/AST. Dr. Villalba notes that liver function abnormalities are noted in the label of cholestyramine and that could explain the increase in hepatic enzymes after discontinuation of teriflunomide and use of cholestyramine for the washout procedure. A role of teriflunomide cannot be ruled out in the initial event.

Subject 002001-124-0013-0022 experienced ALT and AST elevation Day 171 of teriflunomide 7 mg treatment. She had a history of abnormal liver enzymes. On Day 171 laboratory values showed ALT at 3.8X ULN, AST 5.1X ULN, and GGT 6.8X ULN, with total bilirubin levels within normal limits. The patient was positive for Epstein Barr virus – IgG, which in the absence of additional positive information is not indicative of an acute infection. (In many people, detection of antibody to the early antigen is a sign of active infection, but 20% of healthy people may have this antibody for years, according to the CDC http://www.cdc.gov/ncidod/diseases/ebv.htm, and it is not clear whether she had acute infection). Study medication was discontinued on Day 181. This was followed by a washout procedure with cholestyramine from Day 181 to Day 182. (I note this is a shorter washout procedure than in the cases described above). The enzymes did not come down right away after cholestyramine washout. Liver biopsy on Day 306 showed chronic portal inflammation, grade 0-1 and Fibrosis, stage 1. This case may be confounded, but I agree that a role for teriflunomide, potentially in worsening an underlying liver disorder, cannot be ruled out.

Dr. Villalba presents several additional cases of transaminase elevations with normal total bilirubin that had a temporal relationship with the drug and a positive dechallenge after exposure to cholestyramine (with transaminases returning to normal levels within several months after cholestyramine treatment), although there were confounding factors such as history of alcohol abuse or temporal exposure to medications that have been associated with liver injury such as methylprednisolone, diclofenac, or paracetamol. Additional cases had no mention of hepatitis serology or evaluation of other potential explanations. There were also several cases of ALT increases that recovered without discontinuation of treatment and these also were lacking evaluation of other potential etiologies. Dr. Villalba found that most cases of ALT elevation on placebo had alternative explanations such as underlying disease or concomitant use of hepatotoxic drugs, although several did not have complete workup (including incomplete or absent liver serology, absence of abdominal ultrasound, or history of alcohol use). She notes that liver serologies, when done, were in most cases limited to basic hepatitis A, B, and C virus serologies, with serologies for EBV, herpes viruses, and toxoplasma done in a handful of cases. Hepatitis E is not mentioned in any case.

In Pool 2, in addition to those mentioned in Pool 1, SAEs in the Hepatobiliary system disorders SOC were reported for 7 patients in the teriflunomide 7 mg group: cholecystitis (3 patients),

cholecystitis acute, cytolytic hepatitis (2 patients, both confounded by medications known to be hepatotoxic; no serology or liver ultrasound; both patients recovered, one without drug discontinuation), and cholelithiasis (this patient discontinued). One SAE was reported in this SOC in the teriflunomide 14 mg group: hepatic function abnormal. In Pool 2, in addition to those mentioned in Pool 1, 18 and 14 SAE in the Investigations SOC, Hepatobiliary Investigations HLGT, were reported in the teriflunomide 7 and teriflunomide 14 groups, respectively. Dr. Villalba provides selected narratives, and notes that although some seem to be drug related, there are confounded cases due to presence of other medications, as well as absence of evaluation to rule out other causes. An AE of "drug induced liver injury" was reported during the safety update.

Despite the weaknesses in the cases of liver injury, the role of teriflunomide cannot be ruled out and, as Dr. Villalba notes, is not inconsistent with the known hepatotoxic effects of leflunomide which carries a boxed warning for hepatotoxicity, including fatal liver failure. *I agree with Dr. Villalba that teriflunomide should carry the same boxed warning regarding hepatotoxicity.*

Infections and Infestations – The risk of serious infections and infestations was similar in the placebo (2.1%), Teri 7 mg (1.4%) and Teri 14 mg (2.2%) groups. Dr. Villalba's analysis by High Level Term (HLT) shows the largest number in Urinary tract infections (1 in placebo, and 5 in Teri 14 that included 3 cases of pyelonephritis, one of which may have had a UTI prior to study entry, 1 cystitis that may have been pyelonephritis, 1 renal and perinephric abscess resulting in discontinuation that occurred on Day 43 and not likely due to teriflunomide as it was temporarily interrupted on Day 8, and 1 enterococcal urinary tract infection in the Enterococcal infections HLT.) Other serious infections in Teri 14 were 1 serious bacteremia of periodontal origin, 1 gastroenteritis with elevated lipase, and 1 CMV hepatitis (likely due to reactivation; resulted in discontinuation). Dr. Villalba notes no opportunistic infections of tuberculosis in Safety Pool 1, although 3 cases of tuberculosis (1 ileal and 2 pulmonary) were reported in the ongoing studies. Dr. Villalba notes that none of the patients with available data around the time of infection was severely neutropenic or lymphopenic. The pattern of serious infections in pool 2 is similar to Pool 1, with no obvious dose response. The most common serious infections in Pool 2 were urinary/renal infections (1% of all teriflunomide patients) and respiratory infections (1%). There was 1 case of CMV hepatitis, and no other apparent serious opportunistic infections in Pool 2 except for 1 case of oral herpes. *I agree with Dr. Villalba that it is difficult to draw conclusions from Pool 2 without a comparator group and I agree that in some cases, it is possible that teriflunomide was involved in the serious infections in Pool 1 or Pool 2.*

Injury, poisoning and procedural complications SOC – Dr. Villalba notes that the risk of SAEs in this SOC was twice as high in Teri 14 as in placebo, driven by a higher number of fractures (8 vs 3 in Teri 14 vs placebo), but the numbers are small (2% vs 1%). She notes that teriflunomide is associated with increased urinary excretion of phosphate, and that chronic severe hyphophosphatemia is associated with fractures, but that patients with fractures in this population did not have severe hyphophosphatemia. I note that the risk of SAEs of falls in this group did not appear to be predictive of fractures, with only 2 patients having an SAE of fall in Pool 1 (both in Teri 14, 0.5%). She notes no increase in the incidence of SAE of fractures in TOWER or in evaluation of all serious and non-serious fractures in Pool 1 or Tower. Dr. Villalba reports that the overall risk of SAE in this SOC in Pool 2 was 2.7% on Teri 7 and 2.4%

on Teri 14, higher than in Pool 1 as might be expected with longer exposure, but the pattern of events was similar to that in Pool 1 and there was no evidence of dose-response.

Investigations – SAEs in this SOC in Pool 1 occurred in 2.1%, 2.9%, and 3.1% of patients in the Teri 7, Teri 14, and placebo groups, respectively, as shown in Table 20 of Dr. Villalba's review. The SAEs were primarily liver-related. There was also 1 case of neutrophil decreased (discussed under Blood and lymphatic system disorders, and 2 cases of lipase increased with Teri7. Subject 006049/620/4202/0001 developed elevated serum lipase 5x ULN on Day 253 of Teri 7 treatment, leading to study discontinuation. She underwent washout with cholestyramine from Day 276-282 and recovered from the event on Day 311. She also had colitis with Diarrhea on Day 370 and on Day 405 she was diagnosed with ulcerative colitis. I agree with Lourdes that the increased lipase may be related to teriflunomide, although not the colitis. Subject 6049/1802/0005 developed gastroenteritis on Day 1086 of Teri 7 and asymptomatic lipase elevation (3.5X ULN) on Day 1177 of Teri treatment that resolved without drug discontinuation. In that patient, lipase had fluctuated under 2x ULN throughout the study. In Pool 2, 4.6% of patients on Teri 7 and 4.7% on Teri 14 had SAEs in this SOC. Most were additional SAEs of ALT increased and hepatic enzyme increase. There were 2 additional cases of lipase increased. One was Subject 6049/1802/0005, also described in Pool 1, above. Subject 002001/124/0018/0004 developed elevated lipase on Day 1848 of Teri 7 treatment, and on Day 2940 she had abdominal ultrasound that showed cholelithiasis and hepatic steatosis. Three months later she had abdominal pain and was diagnosed with choledocholithiasis and acute cholecystitis and underwent cholecystectomy. Treatment is ongoing. *I agree with Dr. Villalba that it is difficult to evaluate causality with out a control arm, but that the role of teriflunomide in lipase elevation cannot be ruled out.*

Metabolic and connective tissue disorders – Dr. Villalba notes no imbalance in SAEs in this SOC (1 to 1.2% in each treatment group), and that in Pool 2 there were few events and no evidence of a dose-response. She notes 1 case of rhabdomyolysis (Subject 002001-124-0011-003) in a 31 y.o. female on Teri 7 after a session of spinning on Day 72 of study treatment. CK was 2940 U/L (nl 0-167). Drug was temporarily discontinued and re-started without recurrence of event. CK had returned to normal within 2 weeks and the patient recovered without treatment.

Neoplasms –I agree with Dr. Villalba that the risk of serious neoplasms in Pool 1 was no higher with teriflunomide than in placebo overall. She notes that in Pool 1 the placebo group had one cervix carcinoma, 1 breast cancer, 1 meningioma, 1 thyroid adenoma, and 1 thyroid cancer. The Teri 7 group had 1 uterine leiomyoma and 1 ovarian germ cell teratoma benign. Teri 14 had 1 adrenal adenoma, 1 cervix carcinoma, and 1 uterine leiomyoma. In Pool 2a (updated Pool 2 analysis submitted with the 120-day SUR), there was no evidence of a dose-response. There were 20 malignancies, mostly common neoplasms such as breast, colon, skin, and uterine neoplasms. However, there were 3 renal cell carcinomas, 2.5, 4, and 6 years into teriflunomide treatment. These occurred in males 39-47 years old. A subsequent search in the teriflunomide database other than Pool 2 did not find additional cases in patients treated with teriflunomide, although there was 1 case diagnosed during a screening study in a patient not exposed to teriflunomide. Dr. Villalba cites a study by Haliloglu et al in Int. Urol Nephorl 2001 in which the detection rate of incidental renal carcinoma was approximately 0.2% among subjects 33-90 y.o. (mean 55 years) in a study that evaluated the utility of urinary/renal utlrasonography in

patients with no upper urinary tract symptoms. The incidence in patients treated with teriflunomide who underwent serial ultrasound in the teriflunomide program was 3/1100 (0.3%). *I agree with Dr. Villalba that teriflunomide appears unlikely to have had a role in the development or accelerated growth of these cancers.*

Immune System, Endocrine, and Metabolism and nutrition disorders – There were no SAEs in these SOCs in Pool 1. In Pool 2 there was 1 report of sarcoidosis (Day 2421), one of thyroiditis (Day 1874), and 1 diabetes mellitus (Day 1277), all on Teri 14. Dr. Villalba further describes the case of (pulmonary) sarcoidosis in Subject 2001/124/001/0029, a 43 y.o. female, for which the diagnosis was not definitive. She notes that calcium levels and angiotensin converting enzyme levels were normal in this patient, and therefore not supportive of a diagnosis of sarcoidosis in which these levels may be elevated. A lung biopsy showed multiple granulomas which appear to be non-caseating. Dr. Villalba notes that other causes of non-caseating granulomas are lymphoma, small cell carcinoma, and infections (e.g. histoplasmosis). *I agree with Dr. Villalba that it is difficult to assess causality in the absence of a comparator group.*

Nervous System – Dr. Villalba show that the overall number of SAEs in this SOC was similar between teriflunomide and placebo in Pool 1. Overall there were 1.4% in placebo, 1.2% in Teri 7, and 1.7% in Teri 14, but there was no evidence of dose-response in any 1 preferred term. The event with the greatest number of reports was multiple sclerosis (3 on placebo and 3 on Teri 14). Dr. Villalba notes that DNP requested information about studies to rule out causes of neurologic deterioration (other than MS relapse) for the reports of MS and notes that the tests focused on distinguishing relapse/progression from peripheral neuropathy, with no mention of work-up needed to rule out CNS infection , neoplasia, or vascular events.

Among the other SAEs in Pool 1 were:
Subject 002001/124/0015/002 with loss of consciousness due to a fall (due to MS, lost balance at top of stairs); the patient hit her head and had a skull fracture and haematotympanum.;
Subject 006049/276/2007/0012 with a history of hypertension, started on enalapril and HCTZ on Day 319 which led to hypokalemia and dehydration and hypotensive syncope from which she recovered with IV fluids;
Subject 6049/3801/0017 who developed generalized seizures 1 year into Teri 14 treatment though secondary to old demyelinating lesion of MS. He was given carbamazepine as prophylaxis and continued treatment without further seizures;
Subject 6049/3009/0013 who had status epilepticus on Day 654. She was treated with antiepileptics and recovered, but there was recurrence six weeks later.
Dr. Villalba notes that there was little data in the submission to help characterize the role of teriflunomide in these events.

In Pool 2, Dr. Villalba notes no evidence of dose-response. She notes 3 cases of loss of consciousness and 1 of syncope with Teri 14 and 1 loss of consciousness with Teri 7, 2 of which had been described under Pool 1. The additional cases were in Subject 002001/124/0011/0016 who had loss of consciousness (preceded by dizziness and loss of balance) on Day 1812 of Teri 14 during the extension study and who recovered the same day and continued study drug; and Subject 002001/124/0011/0012 who had loss of consciousness on Day 1496 on Teri 7 and who recovered the same day, and who fell down the stairs and suffered confusion when she woke up.

Dr. Villalba suggests that the latter case could have been a seizure. She notes that there apparently was no workup done for syncope/loss of consciousness and no information about vital signs in these patients. Both patients continued in the trial without repeated events. It is not possible to determine who these events are related to study drug.

Pregnacy, peurperium and perniatal conditions – Dr. Villalba notes 1 SAE of spontaneous abortion on placebo and two on Teri 14. There was 1 post-abortion hemorrhage on Teri 14. There were no events on Teri 7 (in Pool 1). In Pool 2, there were 4 pregnancies in each treatment group. Pregnancy is discussed in more detail in section 7.6.2 of Dr. Villalba's review and addressed later in this memo.

Psychiatric disorders – Dr. Villalba finds no imbalance in the number of serious psychiatric disorders in Pool 1: 4 (1.0%), 4 (0.9%), and 2 (0.5%) on placebo, Teri 7, and Teri 14, respectively. There was 1 suicide attempt and 1 case of depression in the placebo group, 2 of major depression in the Teri 7 group, and 1 suicide attempt in the Teri 14 group (in a patient with a history of mood disorder, but not depressed at study entry; treatment continued and she eventually discontinued due to hypertension) in addition to 2 completed suicides in Pool 1 (I on placebo and 1 on Teriflunomide, discussed under "Deaths"). In Pool 2, there was also no evidence of dose-response in this SOC. There were 2 additional suicide attempts (one on Teri 14 in a patient with a medical history of depression who continued to have suicidal ideation and 2 other suicide attempts during the study; and one on Teri 7 in a patient with a history of "mental disorder"). I agree with Dr. Villalba that it is difficult to assess causality in the absence of a control group, and that there is no evidence that teriflunomide increases the risk of suicide in the controlled database.

Renal and urinary disorders – Dr. Villalba notes 1 SAE of renal colic (the patient apparently continued on teriflunomide and recovered) and 1 of urethral stenosis, both in Teri 14 in Pool 1. In the latter case, it is unclear how the diagnosis was made and how the patient was treated. In Pool 2 there were 2 additional SAE of nephrolithiasis in the Teri 14 group, and 1 case of bladder prolapse, 1 acute renal failure, and 1 urinary retention in Teri 7. Subject 002001/1240010/0003) with nephrolithiasis had normal phosphate at baseline with intermittent mild hyphophosphatemia during the study and low normal phosphate levels at other times. Uric acid was also normal at entry with intermittent hypouricemia during the study. Drug was not discontinued for this event. Subject 006049/250/2407/0034 with nephrolithiasis was hospitalized and required lithotripsy but recovered without sequelae and stud drug was not discontinued. Inorganic phosphorous was low normal and uric acid was normal throughout the study. Subject 006049/152/3083/0003 was a 28 y.o. female diagnosed with acute renal failure on Teri 7 Day 1286; the drug was temporarily interrupted and the event lasted 1 day. She presented with nausea and vomiting leading to hospitalization, laboratory showed serum creatinine 2.5 X ULN, urea 6.2X ULN, uric acid 3x ULN. Approximately 2 weeks earlier inorganic phosphorous was approximately 1.4x ULN, creatinine was approximately 2.4x ULN, urea was approximately 6X ULN, uric acid was approximately 3X ULN, and creatinine clearance was 21 ml/min (down from 138 ml/min at entry). Abdominal ultrasound showed no renal abnormalities but cholelithiasis. She received hydration and recovered the same day without sequelae. I agree with Dr. Villalba that she seems to have had an episode of acute renal failure related to dehydration. Dr. Villalba proposes that the increased risk of renal infections previously noted and obstructions may be related to the

uricosuric effect of teriflunomide. The uricosuric effect of teriflunomide is discussed later in my memo in Section 2.2.8/Laboratory findings/Chemistry.

Reproductive and breast disorders – Dr. Villalba notes no imbalances in this SOC. The risk was 0.5% I placebo, 1.4% in 7 mg, and 0.5% in 14 mg in Pool 1. In Pool 2 there were 5 SAE of reproductive system bleeding (2 menorrhagia on Teri 14, 1 menorrhagia on Teri 7, and 2 metrorrhagia (breakthrough bleeding) on Teri 7), including 1 case of menorrhagia on Teri 14 in Pool 1 and 1 case of metrorrhagia on Teri 7 in Pool 1. Study drug was not discontinued in these patients, and all had normal platelet count, INR, and APTT.

Respiratory, thoracic and mediastinal disorders - In Pool 1, one patient reported a SAE of traumatic hemothroax/pneumothorax after a car accident, and 1 reported pulmonary embolism, both in the Teri 14 group.

In Pool 2 there was 1 report of pulmonary embolism and 2 reports of respiratory failure (1 on Teri 14 and 1 on Teri 7) and one of asthma on Teri 7. The cases of pulmonary embolism were both in patients who also had thrombophlebitis and are discussed in "Vascular disorders", below. The case of respiratory failure on Teri 14 (Subject 002001/250/0030/0004) occurred along with pneumonia and tachycardia. The patient recovered but eventually died 3 years later due to cardiorespiratory arrest (discussed under deaths).

Subject 006049/250/2402/0016 developed mixed ventilatory deficiency coded as respiratory failure on Day 533 of Teri 7 during the extension study, leading to drug discontinuation. Teleradiography on Day 450 of Teri showed normal respiratory dynamics and congestive thickening of the pulmonary interstitium with no focal parenchymatous lesion. On Day 575 she was admitted tot the hospital for worsening of bronchitis with bout of dry coughing; blood gasses showed hypoxia and hypocapnea and chest x-ray showed bilateral increased markings to the based of the lungs. On Day 579 she consulted a specialist for annoying cough which seemed to be increased since the beginning of the study; pulmonary function tests showed mixed ventilatory deficiency with a strong restrictive component. Improvement was noted after treatment was interrupted on Day 683, but dry cough resumed when drug was restarted. Teri was permanently discontinued on Day 775; she underwent rapid elimination procedure, and respiratory function reportedly improved 1 day after drug discontinuation.

Subject 002001/124/0015/0008 was a 43 y.o. male with a history of smoking, glaucoma, headache, and drug hypersensitivity who experienced bronchitis and exacerbation of bronchial asthma on Day 1385 of Teri 7 during the extension period. He developed new onset of hypertension and asthma during treatment with teriflunomide. For details please refer to Dr. Villalba's review. She notes that it is unclear how the diagnosis of asthma was made and that there is no pulmonary function test with FEV1 and DLCO values. According to Sanofi, the investigator did not deem it necessary to follow up this patient. Dr. Villalba hypothesizes that this could be a case of interstitial lung disease/pneumonitis.

I agree with Dr. Villalba's concern with respect to the cases of respiratory failure. She notes that interstitial lung disease (or interstitial pneumonitis) has been reported in association with

leflunomide, and that the cases in this application have not been adequately evaluated to rule out interstitial lung disease.

Skin and subcutaneous tissue disorders – In Pool 1 there was 1 SAE of decubitus ulcer on placebo, 1 eczema with Teri 7, and 1 skin necrosis with Teri 14. In the latter case, in Subject 6049/2409/0002, skin necrosis (4th left toe) occurred on Day 184 of Teri 14. The patient had a previous history of peripheral ischemia. Teriflunomide was discontinued on Day 232 and was followed by a washout procedure from Day 233-246 along with medications to treat the wound. On Day 253 the patient recovered with sequelae. On Day 258 she had mild cutaneous involvement of the first left toe that resolved on Day 378. According to the CRF a "left toe blue" was recorded at the screening visit. It is difficult to determine whether event is drug related, but Dr. Villalba notes that there although there are no cases of peripheral ischemia in the database, there are a few cases of venous thrombosis. In Pool 2, SAEs included 1 case of lichen planus on Teri 7 and 1 case of decubitus ulcer on Teri 14. In the SUR there was 1 SAE of pustular psoriasis that occurred on Day 954 of Teri14 in a patient without a history of psoriasis who had no concomitant viral or bacterial infection; she recovered with local treatment on Day 1056 and study drug treatment is ongoing. I agree with Dr. Villalba that this event is unlikely related to teriflunomide.

Vascular disorders – In Pool 1 there were no SAEs of vascular disorders in placebo, 2 (0.5%) in Teri 7, and 4 (1.0%) in Teri 14 In Teri 7 there was 1 case of varicose vein, and 1 case of venous thrombosis. The case of **venous thrombosis** in Subject 006049/250/2402/0014 occurred in a 32 y.o. female on Day 379 of Teri 7 and was diagnosed as venous thrombosis of the left brachiocephalic trunk, possibly related to the change of the port-a-cath in the prior month that she had for receiving IV steroids. Teriflunomide was temporarily interrupted and she recovered on Day 613. Subject 006049/124/12203/0015 was a 27 y.o female who experienced a SAE of **thrombophlebitis** and **pulmonary embolism** 249 days into Teri 14. Concomitant therapy included oral contraceptive. *I agree with Dr. Villalba that it is difficult to attribute the event to teriflunomide in the presence of an oral contraceptive, but the role of teriflunomide cannot be ruled out.* Subject 002001/250/0021/0002 was a 42 y.o. female who developed **hypertension** on Day 222 of Teri 14. Concomitant meds included oral contraceptive. She had a previous episode of hypertension on Day 203-219 from which she recovered without specific treatment. On Day 223 she was diagnosed with hypertension, at which time her blood pressure was 190/120 mmHg Hg, leading to drug discontinuation. Twenty-seven days after the last dose, blood pressure was still 190/120 mmHg. She completed washout on Day 261 and her blood pressure was then 160/100 mg. Dr. Villalba notes that leflunomide is known to be associated with an increase in blood pressure and blood pressure monitoring is recommended in the leflunomide label. *It is not possible to rule out the role of teriflunomide in this case.* Subject 006049/142/3802/0014 experienced **orthostatic hypotension** on Day 62 of Teri 14, 2 days after being hospitalized for MS relapse, when attempting to stand up from wheelchair. There is no evidence that this is related to teriflunomide. Subject 006049/246/2202/0006 experienced **circulatory collapse** on Day 141 while sitting and was admitted to the hospital for monitoring. She recovered following intervention. This was attributed to an acute infection and pain; there is no information about blood pressure or ECG evaluation at the time of the event. It is not possible to determine a role of teriflunomide.

In Pool 2, eight additional patients had SAEs in this SOC including 4 cases of venous stenosis (2 in each group) that were not AEs but chronic venous insufficiency (CCSVI) that diagnosed during the trial and believed by some to be associated with development of MS, two varicose vein, 1 hypertension, 1 deep vein thrombosis (DVT) and 1 phlebitis, all in Teri 7. Subject 002001/124/0013/0004 was a 22 y.o. female with a history of hypothyroidism and smoking, and with concomitant therapy of levothyroxine and oral contraceptives developed left leg **DVT** on Day 384 of Teri 7 treatment. She was also diagnosed with **pulmonary embolism** which led to drug discontinuation. *Although she was taking oral contraceptives, I agree with Dr. Villalba that a role of teriflunomide cannot be ruled out.* Subject 6049/124/1204/0010 was a 45 y.o. female who experienced **thrombophlebitis** (coded as phlebitis)of the right leg on Day 900 of Teri 14 (Day 145 of the extension study) leading to study discontinuation, followed by the washout procedure. Following treatment she recovered from the event. She had a risk factor of factor V Leiden mutation. An additional case of **pulmonary embolism** was reported as an IND safety report on 7/2/12 in Subject 0001, Study LTS 6050 (3004), a 61 y.o. female at an unspecified time after starting teriflunomide (dose not known). She had no previous history of DVT, denied recent long travel or surgery, and was not obese. She had no risk factors for venous thrombosis.

Overall, Dr. Villalba has identified 4 cases of venous thromboses in the monotherapy studies (1 on Teri 14 and 3 on Teri 7), two of which were associated with pulmonary embolism (one from each group) and an additional IND report of pulmonary embolism on teriflunomide. Except for the patient in the IND report, all had some risk factor for thrombosis. *I agree with Dr. Villalba, that although loss of mobility and venous and lymphatic stasis may increase the risk of venous thromboembolism in patients with advanced MS as discussed in a publication by Arpaia et al (2010) cited in Dr. Villalba's review, a contributory role of teriflunomide cannot be ruled out.*

SAEs in Adjunctive Therapy Studies - In patients receiving Teri as adjunctive therapy to IFN-β (PDY6045+LTS6047), 7 patients experienced a total of 10 SAEs that included 1 ankle fracture and 1 transient ALT increase in the placebo/ IFN-β group; 1 patient in the Teri 14/ IFN-β group who experienced lobar pneumonia, cystitis, and cholecystitis; and 4 patients in the Teri 7/ IFN-β group that experienced 1 DVT after drug discontinuation, 1 musculoskeletal stiffness in a patient with h/o shoulder arthroplasty; 1 pseudoarthrosis after fall and contusion of left wrist, and 1 ALT elevation that led to study drug discontinuation and normalized after discontinuation in a case that is confounded by the use of zafirlukast that has a warning for hepatotoxicity. In patients receiving adjunctive therapy to glatiramer acetate(GA) (PDY6046+LTS6047, 12 patients experienced a total of 17 SAEs as follows: 6 patients in the placebo + GA group experienced 1 paravertebral abscess, 1 facial bone fracture after road accident, 1 muscle spasticity, 1 vertigo, 1 herpes zoster, and 1 cerebral ischemia (30 days after discontinuation); 5 patients in the Teri 7[1] + GA group experienced 1 recurrence of epileptic seizure on oxcarbazepine treatment, 1 ALT increase of 2x ULN that led to study discontinuation, 1 mastoiditis, otitis, hypertension, and ALT increase, 1 suicidal ideation and suicide attempt; 1 suspicious interstitial lung disease in Subject LTS 6047-PDY 6046, 3001/1019 who was a 38 y.o. female and a "severe smoker" was hospitalized for suspected interstitial lung disease 71 days after the first dose of Teri 7 and GA after experiencing difficulty breather. Chest X-ray showed reticular-nodular alterations in

[1] Mistakenly referred to as Teri 14 on page 100 of Dr. Villalba's review, but identified as Teri 7 in the ISS, Section 3.1.3.2, p. 122.

bottom fields of both lungs. Interstitial pneumonia was suspected and Teriflunomide was permanently discontinued. The event improved and she was discharged on Day 83. She received washout with cholestyramine on Days 188-198 and improved with symptomatic treatment and recovered several months after drug discontinuation with residual difficulties in breathing. There was no bronchial alveolar lavage or lung biopsy to confirm the diagnosis and no PFT values are available. *As discussed previously, leflunomide is suspected to be associated with interstitial lung disease, and the teriflunomide monotherapy database has events consistent with interstitial lung disease.* In the Teri 14+ GA group, 1 patient had **tendon rupture**. *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.*

Dr. Villalba notes that the safety profile in teriflunomide in clinical pharmacology studies and ongoing phase 3 studies is consistent with that in Safety Pools 1 and 2. Among the cases of interest are a case of **pulmonary tuberculosis** in the TENERE study in a patient treated with Teri 14 for 1.3 years. The CT scan showed lesions of a residual nature, suggesting a case of tuberculosis reactivation. *Dr. Villalba notes that leflunomide has been associated with serious and opportunistic infections including TB reactivation.* A case of **pulmonary tuberculosis** was also identified in TOPIC in a 34 y.o. female on Day 296 of Teri 7. **Ileal tuberculosis** was identified in a 38 y.o. female patient on Day 74 of Teri 14 in TOWER although the symptoms started 2 weeks into teriflunomide treatment. *I agree with Dr. Villalba that due to the time course, a role of teriflunomide is unlikely but cannot be ruled out.* Also consistent with an immunosuppressive effect of teriflunomide are a report of **osteomyelitis by prevotella species** (an anaerobic agent) 7 months into treatment with Teri 14 in the TOWER study, and a case of infective **enterococcal endocarditis** in a previously healthy individual approximately 1.8 years into Teri 7 (IND report 2011SA081991). Additional SAEs include **subclavaian vein thrombosis** in a 36 y.o. nonsmoking female on Teri 14, nine months into therapy in TOPIC. Risk factors included right shoulder impingement 6 weeks prior to the event, obesity, and use of oral contraceptives, although a role for teriflunomide cannot be ruled out. **Focal nodular hyperplasia of the liver** occurred in a 42 y.o. female in tower, 4.5 months into Teri 14 in TOWER. This has not been reported with leflunomide. A case of hypertensive encephalopathy with hemorrhagic stroke and acute renal failure occurred in a patient with predisposing cardiovascular risks after 2.5 years into blinded therapy TENERE.

2.2.3 Dropouts and Other Significant Adverse Events

Dropouts in the ISS (Pools 1 and 2)

In Pool 1, comparable numbers of subjects in each treatment group completed the study treatment period (approximately 74-78%). Placebo-treated subject discontinued because of lack of efficacy more frequently than teriflunomide subjects. Teriflunomide-treated subjects discontinued because of adverse events more frequently than placebo treated subjects (9.3%, 11.1%, and 7.8% in Teri 7, Teri 14, and Placebo, respectively). Dr. Villalba notes that 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 Dr. Villalba notes no differences between active treatment and placebo. Discontinuations in Pool 2 had a similar profile of reasons for discontinuation with discontinuations due to AEs in 16% and 15.1% of Teri 7 and Teri 14,

respectively. Investigations SOC/Hepatobiliary investigations HLGT was the main contributor in Pool 2. Dr. Villalba notes no evidence of a dose response in terms of discontinuations between Teri 7 and Teri 14, except in Skin and subcutaneous tissue disorders where the risk was twice as high in Teri 14.

Blood and lymphatic disorders and Investigations – No patient discontinued due to AE in Blood and lymphatic system SOC in Pool 1 or 2, although some patients discontinued with events in the Investigations SOC, Hematologic investigations. Two (one from each Teri group) discontinued from Pool 1 because of nonserious events of low neutrophil count; they recovered. Three from Pool 2 discontinued in this SOC due to neutropenia (1 with leukopenia also), all on Teri 14.

GI disorders – in Pool 1 a higher percentage of patients discontinued because of AEs in this SOC from Teri 7 (1.4%) and Teri 14(1.2%) vs placebo (0.2%). Several serious cases were discussed under SAEs. There were 2 cases of non-serious pancreatitis that led to discontinuation, 1 in the placebo group (on Day 721) and 1 in the Teri 14 group (on Day 87), both confounded by choledocholithiasis. Three additional cases led to discontinuation in the Teri 7 group (abdominal pain, abdominal pain upper, diarrhea) and 4 from Teri 14 (abdominal pain, abdominal tenderness, flatulence, hyerchlorhydria, ileus), and Dr. Villalba notes that leflunomide is known to be associated with various GI symptoms. No additional cases of pancreatitis resulting in discontinuation occurred in Pool 2.

General disorders and administration site conditions – A case of pyrexia led to discontinuation from Teri 7 in Pool 1. One case of fatigue and 1 case of gate disturbance led to discontinuation in Pool 2, both on Teri 7.

Hepatobiliary disorders – There was no excess of AEs leading to discontinuation in teriflunomide groups in this SOC (0.5% in placebo, 0.2% in Teri 7 and 0.2% in Teri 14). There was 1 case of hepatitis toxic in Teri 14 and 1 of liver injury in Teri 7, both discussed in SAEs. There was 1 case of liver injury and 1 hypertransaminasemia leading to discontinuation in placebo, both non-serious. There were 3 cases leading to discontinuation in the extension studies: 1 cytolytic hepatitis and 1 cholelithiasis in Teri 7, and 1 hepatic function abnormal in Teri 14.

Infections and infestations – There was no difference in the number of overall events leading to discontinuation in this SOC. There is a dose response between Teri 7 and Teri 14, but placebo is in between (0.2%, 1.2%, and 1.0%, respectively). In Pool 2a the number of events leading to discontinuation were 0.5% in Teri 7 and 1.3% in Teri 14. Most cases were serious and were discussed under SAEs.

Investigations – There was no imbalance in risk of discontinuation in this SOC. Dr. Villalba notes that in both Pool 1 and Pool 2, these were mostly driven by hepatobiliary related investigations. She also notes that 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. SAEs are evaluated in the SAE section of Dr. Villalba's review (and summarized in this memo); non-serious cases would be captured in the

analysis of hepatotoxicity in section 7.3.4.1 of Dr. Villalba's review. Other AEs in this SOC leading to discontinuation were 1 case of heart rate irregular on Day 678 of Teri 7 (reported as recovered, but with little information about the patient) and 1 HIV positive 974 days into Teri 7, both in Pool 2. Dr. Villalba notes that neither case was thought related to study drug.

Musculoskeletal and connective tissue disorders – In Pool 1 there were 2 cases of pain in extremity (one in each Teri group), 1 rheumatoid arthritis on Teri 14 , and 1 of spinal osteoarthritis on Teri 7. There was 1 connective tissue disorder reported in the extension studies on Teri 14 that was diagnosed on Day 260 but discontinued on Day 1030; 3-4 months into treatment the patient presented with Raynaud's and typical SLE rash and was diagnosed as moderate SLE. She was later evaluated by rheumatologists and lab evaluation was consistent with a mixed connective tissue disease; Study drug was discontinued approximately 2 years after initiation of first symptoms of connective tissue disease and at follow-up 3 months after discontinuation her SLE symptoms were worse. The case of rheumatoid arthritis (006049/152/380/0006) was not actually rheumatoid arthritis, but seronegative oligoarthritis with spondylopathy and enthesis involvement that started 2 weeks into study treatment in a 45 y.o. male; the patient did not recover after drug discontinuation/washout; Dr. Villalba does not believe that this is related to study drug and based on the time course I agree.

Nervous system disorders – In Pool 1, 0.5% of patients had events leading to discontinuation in each treatment group. AEs leading to discontinuation included 2 cases of polyneuropathy (one in each Teri group) and 1 case of paresthesia on placebo. In Subject 006049/643/3210/0004, polyneuropathy diagnosed with a nerve conduction study occurred on Day 173 of Teri 7, leading to discontinuation on Day 174; as of the last follow-up (time unknown), patient had not recovered. Dr. Villalba believes that although this (and neutropenia at weeks 18 and 24, from which she had not recovered 9 months after washout) were consistent with a teriflunomide effect, there were multiple medications that may have been confounding, although none is specifically noted. I note that the patient was previously treated with Vitamin B1 and B6 that have been used in other cases to treat peripheral neuropathy. Subject 006049/643/3210/0003 had peripheral polyneuropathy of lower extremity (confirmed by nerve conduction study) on Day 337 of Teri 14 that resulted in discontinuation on Day 343 and lasted for 212 days. The case was confounded by a possible diagnosis of syphilis reactivation. Other events leading to discontinuation in pool 1 included 1 case of headache on placebo, 1 case of MS on Teri 14, and 1 case of new onset status epilepticus almost 2 years into treatment with Teri 7. I agree that the role of teriflunomide in this case cannot be ruled out. AEs leading to discontinuation in Pool 2 a in this SOC were 1.7% for Teri 7 and 0.4% for Teri 14. These included a cases of polyneuropathy, an intracranial aneurysm 3 days into treatment that I agree is not related to study therapy, and a case of seizure 2.5 years into treatment. There was a case of Posterior Reversible Encephalopathy (PRES) 4 years into treatment with Teri 7. Her diagnosis was consistent with PRES, although she did not have documentation of consistently elevated blood pressure (but did have intermittent elevation of blood pressure), and PRES is usually associated with increased blood pressure. CSF JC virus testing and cultures were negative in this case. It is difficult to determine the role of teriflunomide in this case.

Neoplasms – In pool 1 there were few events and a higher percentage of events in placebo (1%) than in either teriflunomide group (0.2% in Teri 14 and none in Teri 7) resulting in discontinuation. The case on Teri 14 was adrenal adenoma. In Pool 2, Dr. Villalba finds no evidence of a dose-response. Two patients discontinued from Teri 7 because of breast cancer, one because of colon cancer, and 1 because of renal

cell carcinoma. One discontinued in Teri 14 because of breast neoplasm and 1 due to adrenal adenoma. An additional patient in the 120 day safety report discontinued Teri 14 due to renal cell carcinoma.

Psychiatric disorders – In Pool 1, the percentage of events leading to drug discontinuation was higher in placebo (0.7%) compared to Teri 7 (0.2%) and Teri 14 (0.5%). On Teri 7 there was 1 AE of anxiety leading to discontinuation; on Teri 14 there was 1 delusional disorder and 1 event of insomnia; on placebo there was one suicide attempt, one event of depression, and 1 of abnormal behavior. In Pool 2 there was an additional case of confusional state on Teri 7 that occurred on Day 2 and led to discontinuation on Day 5, with no information on the workup she had, or whether there was a seizure or changes in vital signs. There were no additional cases on Teri 14.

Skin and subcutaneous tissue disorders – In Pool 1 there was an excess of events leading to drug discontinuation in the teriflunomide groups (no events on placebo, 0.9% on Teri 7, and 3.1% on Teri 14), driven by events of alopecia for which there were 6 patients on Teri 14 and 2 on Teri 7. All events of alopecia occurred in females, age 20-52 years, with mean time to onset of 77 days (range 11-114 days). All were reported to have recovered, and in the 4 patients with available data, time to recovery was approximately 2-6 months after discontinuation. Alopecia is noted in the leflunomide label. There were several other skin reactions, consistent with an allergic reaction, leading to discontinuation in Pool 1, all on teriflunomide: urticaria, pruritus, rash generalized (confounded by recent treatment with minocycline/sulfa), and 2 cases of eczema. These were non-serious, of mild-moderate intensity, and resolved with discontinuation and local treatment. There was 1 additional case of pruritus generalized and two cases of rah in the Teri 7 group in Pool 2. *Dr. Villalba notes that leflunomide carries a contraindication for patients with hypersensitivity to the drug and a WARNING for Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) and I agree with her that although SJS and TEN have not been reported for teriflunomide, it should carry the same labeling as leflunomide regarding skin reactions.*

Dr. Villalba discusses dropouts due to serious AEs in other SOCs in the relevant sections of her discussion of SAEs.

The profile of AEs resulting in discontinuation in the adjunctive studies and in Clinical pharmacology and ongoing studies is consistent with that in Safety Pools 1 and 2. For details please refer to Dr. Villalba's review.

In addition to the events categorized as discontinuations due to AEs by the Sponsor, Dr. Mentari identified additional subjects in Pools 1 and 2 who had ongoing adverse events at the time of discontinuation but were not categorized as discontinuations due to AEs by the Sponsor, but had no other documented reasons for discontinuation. These events included "symptoms that never occurred while on infb. She would like to restart Avonex", an AE of worsening depression, severe flu symptoms, a psychiatric disorder (verbatim term "organic physoxis"), "patient did not wish to continue due to adverse event and lack of efficacy – with no specific AE listed, and dyspepsia/right upper quadrant tenderness/elevated liver enzymes. These are generally consistent with the AEs documented by the Sponsor that resulted in discontinuation.

2.2.4 Significant Adverse Events (Adverse Events of Special Interest [AESI])

DNP and the Sponsor agreed on a list of AESI. Based on Narrow SMQ terms, AESI in safety Pool 1 are shown in the table below, from Dr. Villalba's review.

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.

The risk was greater in the Teri 14 group than for placebo for most AESIs. Only the point estimate for alopecia, bone marrow disorders, nausea, and diarrhea showed a relative risk of >2, with a 95% CI above 1, and hepatic disorders and hypersensitivity have a point estimate above 1, but less than 2, but with a 95% CI above 1, supporting a true increase in risk. Dr. Villalba notes that a point estimate of 1 or less or a point estimate above 1 with a wide CI does not rule out an association.

AESI in TOWER were consistent with Pool 1, with an increased risk of hypertension, alopecia, and bone marrow disorders. In TOWER there is also a suggestion for increased risk of pancreatic disorders and arrhythmias that is not observed in Pool 1.

AESI related to hepatotoxicity – Dr. Villalba shows that the risk of abnormal hepatobiliary investigations was greater in the teriflunomide treatment groups as compared to placebo in Pool 1, as previously suggested (approximately 17-18% on teriflunomide and 10.5% on placebo). She provides a Kaplan-Meier analysis of hepatic disorders AE over time in Pool 1 showing that the curves separate from placebo within 1 month, and the risk persists (almost 2x that of placebo) throughout the 24 month period, with no dose response between Teri 7 and Teri 14. Dr. Villalba notes that the median time to onset of hepatic disorders was 141 days in placebo, 129 days in

Teri 7, and 127 days in Teri 14, and that the median duration of events was 27 days in placebo, 50 days in Teri 7, and 43 days in Teri 14. She notes a suggestion for an increase in risk of hepatic disorders in females as compared to males in patients taking teriflunomide.

In addition to SAEs and AEs leading to drug discontinuation previously discussed, there were 2 cases of focal nodular hyperplasia (1 in each teriflunomide group and none on placebo) in Pool 1, and an additional case reported from TOWER and previously discussed in this memo. As previously mentioned, this AE is not described with leflunomide. *I agree that this is a potential toxicity to follow in the postmarketing setting.*

In Pools 1 and 2, Dr. Villalba did not find clinically relevant changes from baseline in mean and median ALT, AST, alkaline phosphatase, total bilirubin, or GGT. Outlier analyses and evaluation of liver enzyme elevation using NCI CTCAE criteria did not show an increased risk of developing ALT or AST > 3X ULN, or total bilirubin > 1.5X ULN. There was an increased risk of GGT > 5X ULN in teriflunomide (2.1% and 1.2% in Teri 7 and Teri 14, respectively) vs placebo (0.5%), suggesting a cholestatic component for liver toxicity. There was no difference in incidence of elevated alkaline phosphatase. Liver-related laboratory evaluations are presented in more detail in section 7.4.3.2 (beginning on page 191) of Dr. Villalba's review and in Section 2.2.8 of this memo. .

eDish analysis was used to characterize peak values for ALT vs peak values of total bilirubin, and the plot is shown on p. 130 of Dr. Villalba's review. Three patients had ALT > 3X ULN and total BR >2X ULN in Pool 1 (in the Hy's Law range). In Subject 6049/3501/0004, in the placebo group, this was likely related to hepatitis C (discussed under SAE infections). In Subject 6049/2812/0001, on Teri 14 for 9 months (also included under SAE infections) this was likely related to a CMV hepatitis infection confirmed by positive testing for anti-CMV IgG and IgM antibodies. Study medication was discontinued ant the patient recovered within 5 weeks. Subject 6049/3505/0005 on Teri 7 had asymptomatic intermittent increase in ALT (> 3X ULN), AST, GGT, and alkaline phosphatase starting on Day 127 of treatment, with increase total bilirubin on Day 295 (at which time Alt was 1.5X ULN). Serologies were not reported. Concurrent gallbladder disease was suspected. Abdominal ultrasound on Day 337 showed liver enlargement. Normalization of laboratory values occurred while on treatment and patient entered the study extension. Thus there were no clear Hy's law cases due to teriflunomide.

Additional cases of interest included Subject 6049/3802/0019 with a past medical history of Henoch-Schonlein purpura and total bilirubin 1.5X ULN at baseline who had increased values of ALT (2.2 X ULN) and total bilirubin (2X ULN) 1 month after starting Teri 7. Retest 7 days later showed ALT 1.7X ULN and total bilirubin 2.5 X ULN. The maximum value of ALT was 2.9X ULN approximately 3 months after initiation of study treatment. He recovered on Day 170 while still on treatment. There were 5 patients with ALT> 20 X ULN without an increase in bilirubin > 2X ULN in Safety Pool 1, also presented in Dr. Villalba's review under SAEs: Subjects 6049/3207/0003 and 6049/3803/0012 on placebo; methlylprednisolone was a possible alternative explanation in 1 of the cases with no other explanation found in the other. Subject 6049/1209/0040 on Teri 14 had a known history of cholelithiasis and had asymptomatic ALT increase about 3 months after first intake of study medication. Concomitant medications included paracetamol. ALT reached 33X ULN after discontinuation and completion of the rapid

elimination process. Subject 6049/3803/0005 on Teri 7, with a prior history of cholelithiasis and cholecystecotomy had asymptomatic increase in transaminases beginning on Day 141, reaching a peak of ALT 23.3X ULN during the rapid elimination procedure on Day 160. A role for teriflunomide cannot be ruled out (see SAEs for more detail). Subject 6049/3201/0009 on Teri 14 is the case of severe liver toxicity, thought to be drug related, and evaluated by Dr. Senior. (This case is discussed in detail in the section on SAEs).

Two additional subjects in Pool 2 were in the "Hy's law" range: Subject 6050/2602/0001 appears to have a mixed hepatocellular and cholestatic pattern of liver toxicity, with history of cholelithiasis, and a diagnosis of obstructive jaundice 2.9 years into Teri 7 treatment. Subject 60550/2402/0020 had an increase in ALT>20 X ULN and total bilirubin 2X ULN 3.4 years into Teri 14 treatment, with jaundice and asthenia. Serologic testing was positive for Hepatitis A with the presence of anti-HAV IgM antibodies.

Two patients in the Teri 14 group in the extension studies had significant ALT elevation with normal total bilirubin. Subject 002001-124-0013-0017 presented with these elevations on Day 394 of treatment, leading to permanent discontinuation and cholestyramine washout. The event lasted 13 days. *I agree with Dr. Villalba that this case is confounded by alcohol consumption as well as use of paracetamol.* Subject 6050/2007/009 had asymptomatic increase in transaminases with ALT up to 24.4X ULN and normal total bilirubin on Day 595 of the extension study (about 3. years into Teri 14 tr4eatment. No concomitant meds were reported and serology testing was negative except for low positive ANA. Study medication was discontinued on Day 592 and the patient received cholestyramine form Day 595-606 and recovered on Day 711. *I agree that this event appears to be drug related*.

Dr. Villalba notes that there were Hepatic AESI in TOWER consistent with the findings in Pool 1. One patient on placebo had ALT > 20X ULN. Three patients had ALT/BR in the Hy's Law range: 2 on placebo and 1 on Teri 7. The teriflunomide patient had Gilbert's syndrome and maximum total bilirubin did not coincide with maximum ALT elevation. In TENERE (submitted as part of the SUR) the frequency of hepatic disorder AEs was higher in the Rebif group (39.6%) compared to either Teri 7 (13.6%) or Teri 14 (12.7%). The difference was driven by ALT increase (10.9%, 10%, and 30.6% in Teri 7, Teri 14, and Rebif, respectively). The risk of ALT elevation >3X ULN was higher in Rebif (11.9%) vs Teri 7 (4.5%) or Teri 14 (7.3%), but the increase in total BR was greater in the teriflunomide groups (6.3% on Teri 7, 9% on Teri 14, and 3% on Rebif). There were no cases that met Hy's law criteria, but the database is small (100 patients per group), as noted by Dr. Villalba.

As noted in Dr. Villalba's review, leflunomide has the potential to cause severe liver injury and death. As of September 2011, the rata of serious liver injury remains around 4 per 100,000 PYR. I agree with Dr. Villalba that there is no evidence that the risk of severe liver injury with teriflunomide will be lower than with leflunomide, and there is 1 possible case of severe drug-induced liver injury in the teriflunomide database of approximately 3100 patients (including 1500 exposed for 6 months or more). I agree with Dr. Villalba, that if the efficacy of teriflunomide is robust it could be approved with adequate WARNINGS and an appropriately written MedGuide. ARAVA has a boxed warning for hepatotoxicity.

Pulmonary disorders AESI– The search approach used in this category captured 1 case of pneumonitis in a patient receiving placebo in Pool 1; Dr. Villalba notes there is no information about how the diagnosis was made. In Pool 2, two subjects had AE in the interstitial lung disease (ILD) SMQ. One of the cases occurred on Day 1 of teriflunomide treatment and I agree it is unlikely related to study drug. The second subject, Subject 6050/3203/0012, 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. PFTs were apparently not done in this patient. There was no clinical manifestation, and the event did not lead to discontinuation. The event was ongoing 9 months after onset. I agree that drug-related pulmonary toxicity was not adequately evaluated and cannot be ruled out. Additionally, two cases consistent with pulmonary toxicity were reported in the extension studies. Subject 006049/250/2402/0016, previously discussed under SAEs in my memo and in Section 7.3.2 of Dr. Villalba's review, had a SAE of mixed ventilatory deficiency with bilateral increasing markings at the base of lungs on chest X-ray that could be related to teriflunomide. Subject 002001-124-0015-0008, discussed under SAEs on p. 14 of my review, had a history of smoking and hypertension treated with ACE inhibitors. He developed dry cough, dyspnea, and wheezing 3.8 years into Teri treatment for which a role for teriflunomide cannot be ruled out. Subject LTS 6047-PDY 6046, 3001/1019 in an adjunctive therapy study, discussed on p. 17 of my memo, had findings consistent with interstitial lung disease on Day 71 of Teri 7 treatment. In TOWER there were 2 SAE of asthma on placebo and 1 in the Teri 14 group in the Respiratory disorders SOC; there were no events in this SOC in TENERE and there was 1 SAE of dyspnea in TOPIC (still blinded).

Dr. Villalba notes that because of the potential lung toxicity with leflunomide, PFTs have been incorporated into the TOWER study that is still ongoing and blinded, although DNP requested submission of preliminary standard analyses of PFTs in that study. Dr. Villalba notes that these analyses do not show worsening lung function with teriflunomide, but do not allow definitive conclusions as the studies were done in a small subset with 5-6 patients available by week 84, and PFTs may reflect patients with a short exposure to drug. Please refer to Section 7.4.5 of Dr. Villalba's review for further detail.

Dr. Villalba notes that postmarketing surveillance of all patients prescribed leflunomide in Japan showed that 80/5911 patients developed interstitial pneumonia; of these, 27 died, with interstitial lung disease judged to be the primary cause of death in at least 18 cases.

I agree with Dr. Villalba that Teriflunomide should carry the same WARNINGS and PRECAUTIONS as ARAVA with respect to pulmonary disorders.

Peripheral Neuropathy - As discussed in Section 7.3.4.3 of Dr. Villalba's review, overall, the percentage of patients with preferred terms in the peripheral neuropathy Narrow SMQ was slightly higher in the Teri 14 group (6.0%) and in the Teri 7 group (3.7%) compared to placebo (4.8%). In Pool 1, 9 patients developed neuralgia (8 consistent with neuropathic pain) and 4 developed polyneuropathy on teriflunomide treatment and no cases on placebo. All cases were nonserious. As previously discussed, several resulted in discontinuation, but in most cases drug treatment continued. Three cases recovered within 8-105 days without discontinuation. Neuralgia and polyneuropathy were reported in 11 females and 2 males. The risk of peripheral neuropathy starts within the first month and there is a suggestion of dose-response between Teri

14 and Teri 7, as shown in a Kaplan-Meier analysis performed by the sponsor (did not include terms such as dysesthesia, paresthesia and mononeuropathy). When these terms are included, FDA analysis suggests an increased risk of carpal tunnel syndrome, paresthesias, and dysethesias with teriflunomide vs placebo in Pool 1. In TEMSO, peripheral neuropathy was suspected in 2.8-3.6% of patients on teriflunomide and 0.9% on placebo. Of the suspected cases, 4/355 (1.2%) of patients on Teri 7, 6/324 (1.9%) of patients on Teri 14, and no patients on placebo were confirmed by electrophysiological nerve conduction studies. Only 2 of these 10 cases resolved. Of the 10 cases, 5 had available patient profiles, and none of the 5 was associated with hyphophosphatemia that is a potential cause of neuropathy and is an AE associated with teriflunomide. In Pool 2, in addition to the events described in Pool 1, there were 2 reports of polyneuropathy (1 not confirmed with nerve conduction studies and thought to be related to MS), 9 reports of peripheral neuropathy (1 confounded by a history of diabetes), and 5 reports of neuralgia. There was 1 case of sensory motoraxonal neuropathy on Day 2215 that lasted 1.3 years and resolved without treatment discontinuation or corrective treatment. There were 2 additional cases of peripheral neuropathy reported as IND safety reports, for which a role for teriflunomide could not be ruled out, although in 1 case there were other possible alternate causes. ***I agree with Dr. Villalba that teriflunomide should carry a WARNING for peripheral neuropathy, similar to that of ARAVA.*** Dr. Villalba recommends including the information on the analysis of peripheral neuropathy from TEMSO in the labeling.

Malignancy – As suggested by Dr Villalba's review (section 7.3.2) and discussed under SAEs of Neoplasms in my memo, I agree with Dr. Villalba that there is no evidence of increased malignancy in this database, although the database is insufficient to adequately address this question, particularly for long term treatment. I agree that labeling regarding the risk following long-term use should be similar to that of ARAVA (although it is a theoretical risk).

Hypertension – Dr. Villalba shows on p. 145 of her review that in Pool 1, teriflunomide was associated with a higher risk of hypertension related AEs vs placebo (5.4% in Teri 7, 5.5% in Teri 14 and 3.3% in placebo). The median time to onset of TEAEs potentially related to hypertension was 197.5 days on placebo, 406 days on Teri 7 and 310 days on Teri 14. Corrective treatment was administered for approximately 65% of these patients in the teriflunomide groups, and approximately 42% of placebo patients in this group. There was 1 serious report of hypertension on Teri 14 in Pool 1 that led to study treatment discontinuation, as previously discussed in this memo (Subject 2001/0021/0002), and that did not resolve after completion of the elimination procedure. There were 2 non-serious events of hypertensive crisis, one on Teri 7 (although in that case there were no records of severe increases in blood pressure consistent with the reported diagnosis) and 1 on placebo. All other reports of hypertension were non-serious, mild/moderate in severity, and did not lead to treatment interruption or discontinuation. Analysis by gender in Pool 1 suggests a slightly greater risk (vs placebo) in females than in males.

Teriflunomide was associated with an increase in systolic and diastolic blood pressure. For details, refer to Section 7.4.3.1 (p. 209-212) of Dr. Villalba's review. At study endpoint, mean change in systolic blood pressure was 2.6 mmHg on Teri 14 and (-) 1.3 mm Hg on placebo; mean change in diastolic blood pressure was 1.4 mm Hg on Teri 14 and (-) 0.9 mm Hg on placebo. Dr. Villalba notes that analysis of systolic and diastolic blood pressure in Pool 2

indicate that blood pressure continues to increase over time, as presented in section 7.4.3 of her review. Outlier analyses showed that 5.6% of patients on Teri 14 and 1.9% of patients on placebo had at least 1 measurement of systolic blood pressure ≥160 mm Hg AND ≥20 mm Hg higher than baseline, and that 1.4% of patients on Teri 14 and 0.5% of patients on placebo had at least 1 measurement of diastolic blood pressure ≥110 mm Hg AND ≥ 10 mm Hg higher than baseline. (Dr. Villalba notes that these are strict criteria for identifying clinically relevant events; diastolic ≥ 110 mm Hg is considered hypertensive crisis by the American Heart Association).

Dr. Villalba also notes the cardiovascular deaths previously described in this memo, as well as cases of nonfatal MI and cardiac arrest, the types of events that are of concern with a drug that is associated with increased blood pressure. I agree that the labeling should include a WARNING recommending regular monitoring of blood pressure.

Bone marrow disorders AESI– As discussed under SAEs and discontinuations, teriflunomide is associated with an increased risk of AE of neutropenia compared to placebo, but all cases resolved with or without discontinuation, and no cases were associated with serious infections. Although driven by neutropenia (0.5% in placebo, 2.3% on Teri 7, and 4.6% on Teri 14) and neutrophil count decreased (0.5% on placebo, 2.8% on Teri 7, and 2.2% on Teri 14), Sanofi's analysis of this AESI also showed cases of thrombocytopenia, platelet count decreased, and red blood cell count decreased. There were no cases of agranulocytosis in Pool 1. Kaplan-Meier analysis showed that the difference between teriflunomide and placebo for AESI related to all bone marrow effects starts within 1 month of treatment and is observed mostly during the first 6 months, although some cases continue to occur after 6 months of treatment. Hematologic abnormalities are evaluated in Section 7.4.2.3 (p. 197) of Dr. Villalba's review and show a small decrease in mean and median WBC, neutrophil, lymphocyte (decreases of approximately 12-16%), and decreases of approximately 2-6% for hemoglobin, and platelet count with time course of onset and recovery or stabilization varying, depending on the hematologic parameter, beginning during the first 6 weeks. Outlier analyses of WBC, neutropenia (absolute neutrophil count), and lymphocyte count support a bone marrow suppressive effect of teriflunomide, where as there was a slightly higher incidence of eosinophilia in Teri 14 vs placebo (Patients with potential clinically significant increase in eosinophil count in Pool 1 were 7.9% for placebo, 8.4% fore Teri 7, and 11.9% for Teri 14). Slightly more patients had anemia on teriflunomide compared to placebo (13.3% on Teri 7, 15.5% on Teri 14 and 10.7% on placebo had grade 1 anemia; the proportion with grade 2 anemia was similar between treatment groups, and a few patients on teriflunomide had grade 3 anemia (Hemoglobin < 80g/L. *I agree with Dr. Villalba that teriflunomide should carry a WARNING for bone marrow suppression, similar to that of ARAVA.*

Infections and Infestations – Dr. Villalba reports a slight increase in the overall risk of infections on Teri 14 and Teri 7 vs placebo. In Pool 1, 61.7% on Teri 14 and 57.5% on placebo had an AE in this SOC. No febrile neutropenia was reported. In Pool 1, the proportion of patients with AEs related to opportunistic infections was 8.3% in placebo, 9.1% in Teri 7, and 10.6% in Teri 14; with the main contributors being oral herpes and tinea pedis. There was 1 SAE of opportunistic infections in Pool 1 in the teriflunomide group as previously mentioned (CMV hepatitis). There was 1 death due to gram negative sepsis, and 3 cases of tuberculosis in Pool 1 as previous noted under SAEs. Dr. Villalba notes that no case of PML was identified in the teriflunomide

development program, although she notes that none of the adverse event reports of MS relapse mentions CSF evaluation. *I agree that teriflunomide should carry a WARNING for the potential for serious and opportunistic infections, similar to that in ARAVA.*

Hypersensitivity – In Pool 1, the proportion of patients experiencing TEAEs potentially related to hypersensitivity and skin disorders was higher in Teri 7 (19.1%) and Teri 14 (20.5%) vs placebo (14.5%). Median time to onset was 160 days in placebo, 133.5 days in Teri 7, and 129 days in Teri 14. The preferred terms driving the difference are in Skin and Subcutaneous tissue disorders (rash, pruritus, erythema, urticaria), Respiratory, thoracic and mediastinal disorders (primarily cough), and General disorders SOCs (chest discomfort). The search strategy did not include the immune system disorders SSOC, Allergic conditions HLGT; that analysis shows 1 case of erythema multiforme, 2 cases of erythema nodosum, 2 cases of hypersensitivity, and 1 case of photosensitivity allergic reaction in patients taking teriflunomide, none of which led to study drug discontinuation. Eosinophilia or eosinophil count increased was reported as an AE in 10 patients in Pool 1 (3 on Teri 14, 5 on Teri 7, and 2 on placebo)., and more patients in Pool 1 had increased eosinophil counts in the PCSA range on teriflunomide than placebo. *I agree that teriflunomide labeling should have a similar WARNING for skin reactions as ARAVA.*

Pancreatic disorders – Although nonclinical data suggested that the pancreas was a target organ for teriflunomide, the clinical data in Pool 1 do not suggest a increased risk of pancreatitis/pancreatic disorder with teriflunomide. There is a suggestion of increased risk of blood amylase and lipase elevation in TOWER, but these increases were not associated with adverse events. I agree that this should be followed in the postmarketing setting.

Alopecia – In Pool 1, alopecia was more frequent in teriflunomide treated patients (11.4% and 15.2% for Teri 7 and Teri 14, respectively), compared to placebo (4.3%) and the difference started within the first month of treatment. Most cases occurred during the first 6 months of treatment with median time to onset of 90-95 days in the teriflunomide groups vs 119.5 days in placebo. The frequency of reporting was higher in females vs males (18.4% on Teri 14 vs 6.9% on Teri 14). The majority of patients recovered during the observation period in pool 1. As previously discussed, alopecia was the leading cause of discontinuations in the teriflunomide treatment groups in the Skin and subcutaneous disorders SOC. A PK/PD analysis using data from Pool 1 should a relationship with an increase in mean teriflunomide trough concentrations. *I agree that alopecia should be prominently mentioned in labeling.*

Cardiac Arrhythmias - As shown in the table above in this section, there was no increase in cardiac arrhythmia narrow SMQ in Safety Pool 1, the controlled database. Two patients developed atrial fibrillation in Pool 1 (1 on Teri 7 and 1 on placebo), although it is unclear how the diagnosis was made and whether the patients were symptomatic. In the Cardiac Disorders SOC in Pool 1, there is a slight increase in reports of palpitations (3.0% for Teri, 1.9% for Teri 14, and 1.2% for placebo) and tachycardia (0.9% for Teri 7, 1.4% for Teri 14, and 0.5% for placebo) in the teriflunomide groups, but most events were non-serious and did not lead to discontinuation. In Pool 2, there were reports of AEs of cardiac arrhythmia in 6 patients on Teri 1 and 1 on Teri 14 (3 cases of ventricular extrasystoles, 2 of extrasystoles, 1 of irregular heart rate, 1 unspecified) that occurred several years in to teriflunomide treatment. One was diagnosed as unspecific cardiomyopathy and led to discontinuation. The other cases continued study drug.

There is limited information about these events. As Dr. Villalba notes, it is difficult to attribute these relatively common events to teriflunomide in the absence of a control group. She notes that the two events of sudden death in Pool 2 were not captured by this AESI search. There were 3 cases of tachycardia in the adjunctive therapy trials that appeared to be mild and did not require discontinuation. The was a case of transient atrial fibrillation 3 days after a single dose of Teri 7 in a clinical pharmacology trial an I agree that appears unlikely related to study drug.

In TOWER there is a small imbalance in Cardiac Arrhythmias AESI (1.3% in Teri 7, 1.7% in Teri 14, and 0.8% on placebo) but the numbers are small (6 on Teri 14 and 3 on placebo). There were 3 cases of atrial fibrillation (although it was unclear how the diagnoses were made); one was an SAE. Dr. Villalba also notes the case of the patient diagnosed with possible Brugada syndrome at baseline who died in a motor vehicle accident in a snowstorm, and I agree it is impossible to determine whether an arrhythmia played a role in his death.

Dr. Villalba notes that ECGs in study 2001 and TOWERT, and the thorough QT study, did not suggest an increased risk of arrhythmias with teriflunomide, and cardiac arrhythmia has not been associated with leflunomide in the postmarketing database. However, I agree with Dr. Villalba that the 5 cardiovascular/unknown deaths are of concern, as previously discussed. Dr. Villalba has proposed an epidemiologic, observational study of cardiovascular death (including sudden death) and arrhythmias with leflunomide, as a postmarketing requirement for approval of teriflunomide.

Convulsions – There is no evidence that teriflunomide is associated with an increased risk of convulsions in this database, and convulsion has not been identified as an adverse events 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 in this database does not rule out the possibility, and Dr. Villalba suggests that convulsion continue to be followed as an AE of interest in postmarketing surveillance.

Hemorrhages – AESI in this group were slightly higher in Teri 14 (9.4%) vs Teri 7 (6.4%) and placebo (7.4%). The difference was driven by menorrhagia, reported in 2.2% of patients in Teri 14 and 0.5% on placebo. Dr. Villalba notes that platelet counts/INRs were normal in these patients. In Pool 2 the proportion patients with hemorrhage was similar in both treatment groups. *I agree that menorrhagia should be mentioned in the teriflunomide labeling, and that hemorrhage should be followed in the postmarketing setting as an AE of interest.*

Embolic and thrombotic events AESI - In Pool 1, AEs related to these events were reported in 2 (0.4%), 3 (0.7%), and 3 (0.7%) in the Teri 7, Teri 14, and placebo groups, respectively. In the teriflunomide groups these included 1 myocardial infarction, 1 venous thrombosis of the left brachiocephalic trunk associated with a port-a-cath (previously discussed), and 1 case of venous thrombosis, 1 case of pulmonary embolism and thrombophlebitis of left leg(confounded by use of oral contraceptives). There were 2 additional myocardial infarctions and 1 pulmonary embolism with DVT in Pool 2, all in patients with risk factors. There was a subclavian vein thrombosis in TOPIC, also in a patient with risk factors. *I agree there is no evidence of increase d risk, although the possibility cannot be ruled out, and that this should be considering during postmarketing surveillance.*

Nausea and diarrhea – Nausea and diarrhea were more frequent with teriflunomide than with placebo, with evidence of a dose response, as shown in Common Adverse Events, later in this memo. The maximum effect of nausea appears to be within the first 3 months but events continue to occur over time. Median time to onset was 47 days in Teri 7, 42 days in Teri 14, and 126 days in placebo. Most cases were mild, but corrective treatment was administered in approximately 1/3 of patients. The risk of nausea tended to be greater in patients ≥38 years compared to < 38 years. The majority of diarrhea first events occurred during the first 3 months of treatment. Diarrhea was considered serious in 1 patient in the Teri 14 group in whom it started 20 days after first intake and persisted during the extension study. Diarrhea led to treatment discontinuation in 2 patients. It is unclear if any cases underwent workup to rule out infectious diarrhea.

2.2.5 Submission Specific Primary Safety Concerns

As previously discussed and as noted by Dr. Villalba, major safety concerns with teriflunomide are liver toxicity, teratogenicity, potential for immunosuppression, skin reactions, pulmonary toxicity and peripheral neuropathy. In addition, the risk of acute, reversible renal failure with teriflunomide has been identified in this application (see section 7.7 of Dr. Villalba's review and Section 2.2.8 of this memo). A potential increase in cardiovascular risk, with 5 cardiovascular/unknown deaths in the extension studies and additional nonfatal cardiac events in the phase 2/3 database is also of concern.

2.2.6 Common Adverse Events

In Pool 1, preferred terms with an incidence of at least 10% and greater than placebo were nasopharyngitis, influenza, urinary tract infection, paresthesia, diarrhea, nausea, alopecia, and ALT increased. Dr. Villalba's review shows adverse events with incidence ≥5% and greater than placebo. Dr. Villalba notes that common adverse events in TOWER were consistent with those in Pool 1, although she notes that the risk of neutropenia in TOWER was 9.4% in TERI 14, 6.9% on Teri 7, and 2.5% on placebo, but was not among the most common adverse events in Pool 1.

Dr. Villalba also notes other potentially relevant events in Pool 1, including cardiac disorders, driven by palpitations and tachycardia that have already been discussed. Other events include the risk of an adverse event of hypercholesterolemia that 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, and Dr. Villalba notes that it is unclear if this difference contributed to an increased CV risk in the teriflunomide population. Hypokalemia was reported in 3 patients on Teri 14 and none in other treatment groups. Vit B12 deficiency was reported in 1 and 3 patients on Teri 7 and Teri 14, respectively and none on placebo; Dr. Villalba hypothesizes that Vit B12 deficiency may have been related to the higher incidence of diarrhea in teriflunomide treated patients. The incidence of AE in the Skin and subcutaneous tissue disorders SOC was higher in patients taking teriflunomide vs placebo, driven by alopecia terms as well as a slightly higher incidence of skin hypersensitivity/allergic reactions, as discussed under AESI.

2.2.7 Use of rapid elimination process –

As Dr. Villalba notes, 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). Approximately 85% of patients who discontinued prematurely from TEMSO underwent rapid elimination, although only 25% from Study 2001 did so. Dr. Villalba notes that the proposed label includes a section describing time to recovery of ALT after drug discontinuation. I agree with her that it should also mention that most patients underwent rapid elimination along with drug discontinuation.

2.2.8 Laboratory findings

Chemistry - Mean and median changes from baseline in values of electrolytes (sodium, potassium, chloride, phosphorous), metabolic parameters (glucose, total cholesterol, triglycerides, albumin), and renal (BUN, creatinine, creatinine clearance) were minimal over time and did not very between treatment groups in Pool 1 and 2. Dr. Villalba notes there was no measurement of bicarbonate or magnesium in any study. She notes that there was a case report of leflunomide-induced Renal Tubular Acidosis (RTA) that resolved after cholestyramine washout that was published in the literature, and notes that RTA is characterized by metabolic acidosis (low bicarbonate levels).

The only two measurements showing change from baseline in mean/median values were uric acid and creatine phosphokinase. Dr. Villalba shows a dose related decrease in serum uric acid levels in Pool 1 and notes that analyses in Pool 2 were consistent with that. The normal range for uric acid levels is 124.9-428.2 umol/L. In Pool 1, the mean change at endpoint was (-) 77.8 umol/L on Teri 14, (-) 58.3 umol/L on Teri 7, and (-) 3.8 umol/L on placebo. Creatine phosphokinase (CK) was not measured in TEMSO, but was measured in study 2001 and the extension and there is a small increase in CK in study 2001. In 2001, CK showed a mean change from baseline at endpoint of (-)2.89 U/L in placebo, (-2.62 u/L in Teri 7, and (+)10.77 U/L in Teri 14 (normal values for study 2001 were 0-190 u/L). The clinical significance is unclear. Analysis of outliers in Pool 1 did not confirm an increased risk of CK increase, although analysis in TOWER suggested an increase CK elevation >5X ULN with Teri 14 compared to placebo. A small increase in LDH was also observed, the clinical significance of which is unclear.

Outlier analyses of laboratory metabolic and electrolyte abnormalities based on potentially clinically significant abnormalities (PCSA) were unremarkable except for phosphorous for which there was a higher percentage of patients who presented levels below normal (23% and 27% of patients in Teri 7 and Teri 14) vs placebo (9.5%). Dr. Villalba notes that analyses by common terminology criteria adverse events (CTCAE) were generally consistent with PCSA analyses. These decreases were in the range of $\geq$ 0.6 mmol/L and < LLN in 8.6% of placebo, 18% of Teri 7 and 22% of Teri 14, and $\geq$0.3 - < 0.6 mmol/L in 1% of placebo, 5.1% for Teri 7, and 5.8% for Teri 14. By CTCAE criteria, no subject had levels below 0.3 mmol/L which is considered to be clinically severe hyphophosphatemia.

Dr. Villalba notes that the applicant claims that low uric acid and phosphorus have no relevant clinical consequences. ARAVA is noted in the labeling to have a uricosuric effect with a separate effect of hypophosphaturia. Dr. Villalba notes that uricosuric agents are known to be associated with increased risk of lithiasis, and notes that more patients presented urinary tract infections and nephrolithiasis in the teriflunomide treatment groups in the monotherapy studies and in the TOWER study. She notes that moderate hypophosphatemia (0.32-0.79 mmol/L), as observed here, is commonly observed in hospitalized patients and is usually asymptomatic. For

a detailed review of hypophosphatemia and its consequences, please see p. 181 of Dr. Villalba's review. Severe hyphophosphatemia my cause tissue hypoxia and can lead to rhabdomyolysis, weakness, numbness, paresthesia, and encephalopathy , as well as respiratory failure as a result of diaphragmatic weakness, arrhythmias and heart failure and cardiomyopathy, and hematologic manifestations including acute hemolytic anemia. Dr. Villalba notes that as teriflunomide is associated with bone marrow suppression due to inhibition of pyrimidine synthesis, and it would be difficult to distinguish whether hypophosphatemia contributes. Dr. Villalba notes that there are several conditions characterized by ion transport defects in which phosphorous reabsorption is decreased. In Fanconi syndrome, patients excrete increased amounts of phosphorus and uric acid in the urine, resulting in hypouricemia and hypophosphatemia; several drugs have been associated with this syndrome. In a response to a request for information, Sanofi searched for evidence of Fanconi syndrome in the teriflunomide database and concluded that "The overall effect of teriflunomide is that of 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." The Sponsor does report 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 clearance of urate and a reduction in tubular reabsorption of phosphate. A PK/PD analysis showed an increase in mean teriflunomide trough plasma concentration was associated with a decrease in uric acid and phosphates.

Hyperkalemia – In Pool 1, 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. Analyzed by CTCAE categories according to baseline status, the frequency of treatment-emergent hyperkalemia > 7 mmol/L among patients with normal or missing potassium values as 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). Dr. Villalba review narratives and patient files for Pool 1 treatment emergent hyperkalemia ≥ 7 mmol/L and found that 3 teriflunomide-treated subjects had hyperkalemia with acute renal failure. No hemolysis was detected in these cases.

For Pool 1, outlier analyses of urine pH, serum calcium, urine protein, and urine glucose were balanced between treatment groups.

Renal function – Increased creatinine above the PCSA criterion was presented by 9.6% of patients on Teri 7, 10.6% on Teri 14, and 8.1% on placebo. Ten patients (5 on Teri 7 and 5 on Teri 14) presented doubling of serum creatinine from baseline compared to none on placebo. Of those with doubling of creatinine, 6 had an increase 3X ULN. Also, 3 patients in Teri 7 and 4 in Teri 14 presented severe renal impairment (CrCl < 30 ml/min). Each of these patients was exposed to teriflunomide for over 3 years and most are still participating in the extension study. In each case, the re-test showed creatinine values within the normal range, and the low value of estimated creatine clearance was never confirmed. Although the Sponsor believes that a single unconfirmed value of elevated creatinine does not raise a safety signal, all cases occurred on teriflunomide and none on placebo.

Dr. Mentari conducted a detailed evaluation of the renal effects on teriflunomide. Her findings are summarized on p. 187 of Dr. Villalba's review and included in detail in Section 7.7.1, p. 224 of Dr. Villalba's review. The summary is provided here. Evaluation of renal function identified 10 patients (2 males, 8 females, ages 19-51 y.o.) with serum creatinine above normal and nadir creatinine clearance of 8 to 96 ml/min (the latter in an obese patient who had a baseline CrCl of 250 ml/min) in Pool 1. Seven of the 10 had creatinine clearance < 30 ml/min as mentioned in the paragraph above. These measurements occurred between 12 weeks and 2 years after the first dose, and in all 10 subjects the serum creatinine level was normal on the next reported measurement (6-48 days later). All 10 had other tests that corroborated the diagnosis of acute renal failure (e.g. increased BUN, serum phosphorus, and serum uric acid), making laboratory error an unlikely explanation for the increased frequency of serum creatinine increase. Three of the 10 had serum potassium levels of 6.7 – 7.3 mmol/L (normal 3.4 to 5.4 mmol/L). Three additional subjects in the Extension studies had increased creatinine > 100% from baseline: 1 while receiving Teri 14 who had a single increase in serum creatinine with a normal subsequent measurement; 1 on Teri 7 who had increased creatinine for over 2 months during a kidney infection, and 1 who was hospitalized for acute renal failure which resolved after treatment with IV saline. That subject had nausea and vomiting "in the last few weeks" but the dates and timing in relation to acute renal failure are unclear. Although the investigator thought the acute renal failure might have been due to gastroenteritis leading to dehydration, Dr. Mentari proposes that nausea and vomiting may have been a symptom of uremia related to acute renal failure.

Dr. Mentari suggests that acute uric acid nephropathy is a likely explanation for the cases of transient acute renal failure. 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, and these cases have been accompanied by loin pain, abdominal pain, or fever. In the teriflunomide case, an increased frequency of loin pain associated with acute renal failure has not been documented, although Dr. Mentari notes that symptoms before and after the events of acute renal failure were not systematically documented. 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. She specifically recommends that the Sponsor should evaluate reported cases of acute renal failure, as well as cases of loin or flank pain, as part of their ongoing studies and postmarketing reports. *I agree with her recommendation.*

Urinalysis – In Study 2001 the majority of subjects had normal findings at baseline and endpoint. Abnormal findings in glucose and nitrate were reported in no more than 5 subjects in any single treatment group. Dr. Villalba notes that 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. In TEMSO there was no mention of sediment or abnormal findings in urinalysis.

Dr. Villalba reports that Chemistry analyses in Pool 2 were consistent with Pool 1, as were analyses in adjunctive therapy studies. The thorough QT study TES10852 (teriflunomide 70 mg qd for 4 days followed by 14 mg QD for 8 days in 61 subjects) showed a decrease in serum uric acid that returned to baseline during rapid elimination, but no relevant decrease in serum phosphorous. Laboratory results in TOWER were consistent with findings in Pool 1 and 2, with mean changes and outlier analyses showing decreased uric acid and phosphorus serum levels. Although a renal function effect was not observed, as Dr. Villalba notes, the exposure to teriflunomide in these studies was shorter.

Liver-related laboratory evaluations – As previously mentioned, an evaluation of measures of central tendency in *Pool 1 and 2* showed no clinically relevant differences between teriflunomide and placebo, or between teriflunomide doses, in changes from baseline in liver enzyme values (ALT, AST, Alk Phos, total bilirubin) over time in Pool 1 or 2. Changes from baseline in ALT in Pool 1 were slightly greater in the teriflunomide groups compared to placebo, but I agree they do not appear to be clinically relevant. Although percentage of patients with ALT elevation ≤3X ULN was greater in teriflunomide groups vs placebo, the incidence of ALT elevations > 3X ULN was similar in all groups in Pool 1. The risk of GGT > 5X ULN was higher in teriflunomide treated patients (2.1% and 1.2% in Teri 7 and Teri 14, respectively, vs placebo (0.5%), suggesting a cholestatic component of liver toxicity. There was no difference in the incidence of elevated alk phos. More patients developed bilirubin > 1.5X ULN in placebo vs teriflunomide, although Dr. Villalba notes that the majority of these (including the teriflunomide patients with bilirubin increase) had elevated bilirubin at baseline. ALT elevations ≤3X ULN resolved without drug discontinuation in 90% of cases. As per protocol, patients with ALT > 3X ULN twice were discontinued from the study, and most also underwent rapid elimination/washout. As per Table 79 in Dr. Villalba's' review, for patients who discontinued due to ALT > 3X ULN or with ALT ≥3X ULN at time of discontinuation/completion, 29% on Teri 14 and 14% on Teri 7 did not resolve vs 47% who did not resolve on placebo. However, Dr. Villalba notes that evaluation of the narratives of these case confirmed that most of the cases listed as "not resolved" actually resolved. The risk of ALT elevation > 3X ULN in *TOWER* was greater in patients treated with teriflunomide vs placebo, however for elevations > 5X ULN it was similar to or lower than placebo. In Tower, for elevations ≥3X ULN, approximately half the cases occurred during washout. In TENERE, there seems to be a dose response in numbers 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 (57.4% for Rebif, 36.4% for Teri 7, and 42.7% for Teri 14) , although the risk of any increase in total bilirubin was greater in teriflunomide (6.3% and 9% on Teri 7 and Teri 14, respectively), than on Rebif (3%). This study was not adequately powered to evaluate differences in safety between teriflunomide and Rebif. Dr. Mentari has summarized information about hepatic injury with beta-interferons for multiple sclerosis, including labeling and the published literature. I note that the risk of ALT elevations in TENERE is higher for Rebif than that reported in the PRISMS trial (27%). Please refer to Dr. Mentari's discussion in Appendix 7, page 269 of the Safety Review.

Hematologic findings are discussed under AESI/ Bone marrow disorders in this memo. For details please refer to Section 7.4.2.3, p. 197, of Dr. Villalba's review.

Coagulation parameters – Coagulation parameters were not collected in studies 2001 and LTS6048. Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) were collected in 6049/TEMSO and LTS 6050. There was no difference in mean and median change from baseline in PT and PTT in teriflunomide patients vs placebo at the endpoint. There was no difference in 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 teriflunomide and placebo groups. Lower numbers of patients presented high APTT values at least once during the study in the teriflunomide groups (32.1% and 28.9% for Teri 7 and Teri 14, respectively vs 34.4% for placebo); the clinical significance of this finding is unclear. In the combination therapy studies, there was a slight decrease in APTT values in both teriflunomide groups, the clinical significance of which is not clear.

2.2.9 Vital Signs

Blood pressure findings are summarized in the AESI/Hypertension section of this memo. Please refer to Dr. Villalba's review Section 7.4.3.1, p. 212) for details.

Heart rate – change from baseline in placebo-controlled study 2001 based on ECGs was 2.2 bpm, -0.2 bpm, and -0.2 bpm in placebo, 7 mg and 14 mg groups at Week 36, and 2.1 bpm, 0.3 bpm, and 0.4 bpm at endpoint bpm in placebo, 7 mg and 14 mg groups, respectively. In the pooled data from Study 2001 + LTS6048, changes from baseline at Week 468 were 2.0 bpm and 8.6 bpm for the 7 and 14 mg groups, respectively. Endpoint values were -0,2 bpm and 2.7 bpm for the 2 and 14 mg groups, respectively.

Weight – In Pool 1 baseline weight values were comparable across groups. Teriflunomide treatment was associated with weight loss. As noted by Dr. Villalba, 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 ≥ 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. Dr. Villalba notes that decreased appetite was reported as an adverse event twice as much on Teri 14 as compared to placebo, and proposes that nausea and diarrhea may also contribute to weight loss.

2.2.10 ECGs

Thorough QT study TES10852 evaluated the effect of repeated oral doses of teriflunomide (70 mg for 4 days followed by 14 mg for 8 days) vs placebo, with a moxifloxacin control. The results were reviewed by the QT IRT team (review dated 10/27/11) who found no significant QTc prolongation effect of teriflunomide at exposures that patients are likely to achieve. The largest upper bound of the 2-sided 90% CI for the mean difference between teriflunomide and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was

greater than 5 ms, and the moxifloxacin profile over time is considered to be adequately demonstrated by the IRT, indicating that assay sensitivity was established. Neither prolonged QTcF > 480 msec nor QTcF increase from baseline > 60 msec was observed. I agree with the IRT review that if there are no drug interactions that could result in increased exposure, teriflunomide at the doses used does not prolong QT. Please refer to the IRT review for proposed labeling language.

In the clinical trials, controlled data for ECGs came from Study 2001. ECG data were not collected in the larger study, TEMSO. Additional data came from clinical pharmacology studies, ongoing study 6048, and ongoing TOWER. Mean change from baseline for QTcF at endpoint of Study 2201 aw 0.92 ms, -0.03 ms and 2.73 ms for placebo, teriflunomide 7 mg and 14 mg, respectively. Evaluation of PCSA showed no patients with prolonged PR or QRS. Very few presented prolonged QT interval with small and similar numbers in each group. I agree with Dr. Villalba that there does not seem to be a clinically relevant effect on ECG parameters in the controlled 6-month database. An increase in mean change from baseline for QTcF was 11.40 ms and 8.48 ms for the 7 mg and 14 mg teriflunomide groups, respectively in pooled data from Study 2001 + LTS6048. Few patients had prolonged QTcF (or B). Of these, prolonged QTcF ≥500 msec was reported in 1 patient (1.1%) in Teri 7 vs none in Teri 14. Increase from baseline > 60 msec was recorded in 5 patients (5.6%) in Teri 7 and 4 (4.8%) in Teri 14. I agree with Dr. Villalba that this apparent effect on QT interval is difficult to interpret in the absence of a control arm. Dr. Villalba notes that no events of ventricular tachycardia or torsades de pointes were observed in the teriflunomide database. However, as previously discussed, there were three sudden deaths in uncontrolled studies.

ECG data in the TOWER interim analysis show a small dose dependent increase in heart rate from baseline to endpoint (0.71 bpm on placebo, 1.85 bpm on Teri 7, and 3.59 bpm on Teri 14 (consistent with other studies, although slightly higher). There was a dose dependent decrease in PR from baseline to endpoint (placebo (-).89 msec, Teri 7 (-) 3.17 msec, and Teri 14 (-)6.04 msec) of unclear clinical significance. No other treatment group differences were observed in mean change from baseline. Similarly, the interim analysis of ECG PCSA in TOWER does not suggest a significant effect of teriflunomide on ECG parameters.

2.2.11 Immunogenicity –
Dr. Villalba notes that teriflunomide is not a biologic agent and is not expected to be immunogenic. However, since it induces decreased levels of B and T lymphocytes, I agree that it is likely to affect immunologic responses. Study PDY11684 is an ongoing study looking at antibody response to influenza vaccine in RMS patients treated with teriflunomide and in a reference population of RMS patients.

2.2.12 Other Safety Explorations

Dose and Time Dependency for Adverse events – Throughout the review, Dr. Villalba noted a suggestion of a dose response for some adverse events (e.g. alopecia, ALT elevation, peripheral neuropathy), although the overall risk of SAEs or discontinuations due to AE was similar between dose groups. There is some evidence of time dependency, but it varied for different adverse events.

Drug-Demographic Interactions – Age, gender, race, and weight/BMI were identified as significant covariates influencing teriflunomide PK in the population PK analysis, but these factors did not increase the overall risk of AEs in patients taking teriflunomide vs placebo. Dr. Villalba notes some suggestion that patients age < 38 y.o. on Teri 14 vs placebo had an increased risk of AEs leading to discontinuation compared to patients ≥38 y.o. (mostly related to ALT elevation) and that nausea was more frequent in patients ≥38 y.o compared to < 38 y.o. She notes a suggestion of increased risk of liver function abnormalities, neutropenia, hypertension, and viral infections in females compared to males, although the small numbers do not allow definitive conclusions. Less than 4% of the population was non-Caucasian so that no conclusions can be drawn regarding race. In Pool 1, there was an increased risk of HLTs of alopecia and diarrhea in patients with BMI < 30 kg/m^2 vs ≥30 mg/m^2, in patients treated with teriflunomide 7 or 14 mg vs placebo, but an evaluation of most common AEs by weight did not show an affect.

Drug-Disease Interactions analyses were not performed.

Drug-Drug Interactions – Teriflunomide is a moderate inhibitor of CYP2C8, and a weak inhibitor of CYP3A, and a weak inducer of CYP1A2. Dr. Villalba notes that in a drug interaction study with warfarin, a 25% decrease in peak INR was observed when teriflunomide was co-administered with warfarin compared with warfarin alone. Therefore when warfarin is co-administered with teriflunomide, close INR follow-up and monitoring is recommended.

Teriflunomide was studied as add-on therapy to glatiramer or beta-interferon, and there did not seem to be an increased risk of AE in patients receiving these drugs compared to teriflunomide alone, although Dr. Villalba notes that the database is small. She also notes that concomitant use of other immunosuppressors was not allowed in clinical trials.

2.2.13 Human Reproduction and Pregnancy Data

As of June 1, 2011, a total of 57 pregnancies (in 56 patients) were reported to the Pharmacovigilance database in the teriflunomide clinical program. Forty-five occurred in female patients aged 22-45 y.o. Twelve occurred in female partners of male patients aged 18-53 y.o. Among the 45 pregnancies in exposed female patients, the outcome was as follows, as noted by Dr. Villalba: delivery of healthy newborns in 10, induced abortion in 21, spontaneous abortion in 9, and 5 were still ongoing pregnancy at the time of cut-off. Thirty had received teriflunomide, 1 received beta-interferon, 2 received placebo, and 10 were still blinded. Among the 10 female patients that delivered live newborns: 7 had received cholestyramine, 1 had received activated charcoal, and 2 (1 receiving beta-interferon and 1 receiving placebo) did not receive any treatment for rapid elimination. Among the 12 pregnancies in partners of male patients, there were 8 live births and 1 spontaneous abortion. All 18 newborn babies were healthy without malformation or functional problems. As of the 120 day SUR, 8 additional pregnancies occurred: 2 more live births (one on treatment and 1 still blinded), 1 spontaneous abortion, 4 induced abortions (still blinded) and 1 ongoing pregnancy. The Maternal Health Team is reviewing these data and will make recommendations for labeling. Dr. Villalba anticipates that

the pregnancy section of the teriflunomide labeling will be identical to that of ARAVA. A summary protocol for a Pregnancy Registry has been submitted by the Sponsor.

2.2.14 Postmarketing Risk Management Plan

The Sponsor submitted a MedGuide only REMS to inform patients about the serious risks associated with use of teriflunomide. We plan to include the MedGuide as part of the labeling, and not require a REMS.

2.2.15 Conclusions

I agree with Dr. Villalba that there are no safety concerns that would preclude approval of teriflunomide in patients with MS. Adverse events could be address through appropriate labeling, including WARNINGS and PRECAUTIONS similar to those of leflunomide. A new signal for reversible, acute renal failure should be addressed in labeling.

Routine postmarketing Pharmacovigilence should be conducted, especially for AESI that were evaluated in this database, including those for which an increased risk could not be ruled out: pancreatic toxicity, convulsions, hemorrhage, and thrombosis, and serious or opportunistic infections. As Dr. Mentari has recommended, postmarketing Pharmacovigilence should also collect information related to acute renal failure, including evaluation of cases of acute renal failure, as well as cases of flank and loin pain. Acute renal failure should be evaluated systematically in ingoing studies as well.

Drs. Villalba and Mentari recommend evaluation of the effect of teriflunomide on bicarbonate, magnesium and calcium levels. I agree that this is lacking and would be useful information. Ongoing trials may be an opportunity for collecting this information.

Given the occurrence of 5 cardiovascular deaths, including 3 sudden deaths in the teriflunomide database, and considering related adverse effects of teriflunomide including an increase in blood pressure, Dr. Villalba recommends an observational study to evaluate cardiovascular death and arrhythmia in patients who have received leflunomide. I recommend that such a study be considered. This consideration will require Pharmacoepidemiology input and feasibility considered prior to considering a postmarketing requirement.

Dr. Villalba recommends that the Sponsor submit and updated Integrated Summary of Safety pooling the TOWER completed study with Study 6049 and I agree.

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/s/

SALLY U YASUDA
07/23/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	June 1, 2012
Reviewer:	Jung Lee, RPh Division of Medication Error Prevention and Analysis
Acting Team Leader:	Chi-Ming (Alice) Tu, PharmD Division of Medication Error Prevention and Analysis
Deputy Division Director:	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Teriflunomide Tablets 14 mg
Application Type/Number:	NDA 202992
Applicant/Sponsor:	Sanofi-aventis
OSE RCM #:	2011-3089

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container labels, carton labeling, and insert labeling for Teriflunomide Tablets 14 mg (NDA 202992) in response to a request from the Division of Neurology Products (DNP).

1.1 PRODUCT INFORMATION

- Active Ingredient: Teriflunomide
- Indication of Use: For the treatment of patients with relapsing forms of multiple sclerosis (b) (4)
- Route of Administration: Oral
- Dosage Form: Tablet
- Strength: 14 mg
- Dose and Frequency of Administration: One tablet (14 mg) by mouth once daily, with or without food
- How Supplied:
  - Carton of 28 tablets containing 1 wallet composed of 2 folded blister cards of 14 tablets per blister card
  - Carton of 5 tablets containing 1 wallet composed of a blister card of 5 tablets
- Storage: Store at 68°F to 77°F (20°C to 25°C) with excursions permitted between 59°F to 86°F (15°C to 30°C)
- Container and Closure Systems: (b) (4) blister package composed of (b) (4) which is then packaged into wallet kits and then into appropriate carton boxes

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Blister Card Wallet Labels submitted April 10, 2012
- Wallet Sleeve Labeling submitted April 10, 2012
- Carton Labeling submitted April 10, 2012
- Insert Labeling submitted November 16, 2011

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

The following section describes the deficiencies identified with the proposed product design.

3.1 PRODUCT DESIGN

The current design of the 5 count and 28 count blister card wallets are laid out in a packaging configuration that is error prone (b) (4) [redacted] We also identified other areas of needed improvement in the insert labeling and on the container label and carton labeling. We provided recommendations in section 4.1 and 4.2 of this review.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container label, carton labeling and product design are unacceptable and introduce vulnerability that can lead to medication errors. We advise the following recommendations be implemented prior to approval:

4.1 COMMENTS TO THE DIVISION

A. General Comments

1. We recommend adding a unit of measure immediately following all numbers, as appropriate. For example, in Section 6.1 under Clinical Trial Experience, revise "7 or 14 mg once daily" to read "7 mg or 14 mg once daily".

2. We recommend keeping numbers next to units or symbols within the same line of text. For example under section 5 (Warnings and Precautions), 1.3 mmHg should all be on one line. Revise the layout so that 1.3 is not at the end of the line of text.

B. The statement under Section 3, Dosage Forms and Strengths, "Tradename is available as pale blue to pastel blue, pentagonal film-coated tablets with imprint on one side dose strength given as number 14…" lacks clarity. Reword this statement to read "Tradename is available as pale blue to pastel blue, pentagonal film-coated tablets with the dose strength, "14", imprinted on one side and engraved with the corporate logo on the other side."

4.2 COMMENTS TO THE APPLICANT

A. 28 Tablets Blister Card Wallet

1. Ensure that the proprietary name will be presented in title case, such as Tradename instead of TRADENAME. The use of all upper case letters is a

form of tallman lettering, and the use of tallman lettering is reserved for drug name pairs that have been confused.

2. Revise the established name so that it is at least half the size of the proprietary name. Ensure that the established name has a prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).

3. Revise the strength statement "14mg" to read "14 mg" (space) "per Tablet".

4. The blue and green ribbons graphic is overly prominent and distracts from more important information on the label. We recommend removing the graphic, or minimizing and moving the graphic away from the proprietary name so that it does not compete with the prominence of the proprietary name, established name, and product strength.

5. The "Rx Only" statement is overly prominent. Debold the "Rx Only" statement.

6. The net quantity statement is overly prominent and competes with the product strength. Debold and decrease the prominence of the net quantity statement.

B. 5 Tablets Blister Card Wallet

1. See comments A.1 and A.6 above.

(b) (4)

C. Carton Labeling (28 Tablets, 5 Tablets)

1. See comments A.1 to A.6 above.
2. The active ingredient statement, (b) (4) is on the side panel and repeats again on the principal display panel (PDP). Remove the active ingredient statement from the PDP.

D. 28 Tablets Wallet Sleeve

1. See comments A.1 to A.6 above.
2. Ensure the lot number and expiration date are printed on the label per 21 CFR 201.17 and 21 CFR 201.18.

If you have further questions or need clarifications, please contact Laurie Kelley project manager, at 301-796-5068.

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

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/s/

JUNG E LEE
06/01/2012

CHI-MING TU
06/04/2012

KELLIE A TAYLOR
06/05/2012

CAROL A HOLQUIST
06/05/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202992 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name (b) (4) Established/Proper Name: Teriflunomide Dosage Form: Tablets Strengths: 14mg		
Applicant: Sanofi-Aventis Agent for Applicant (if applicable):		
Date of Application: August 12, 2011 Date of Receipt: August 12, 2011 Date clock started after UN:		
PDUFA Goal Date: June 12, 2012	Action Goal Date (if different):	
Filing Date: October 11, 2011	Date of Filing Meeting: September 28, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	✓			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		✓		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		✓		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	✓			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***		✓		

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	✓			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	✓			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	✓			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	✓			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			✓	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* August 17, 2011 <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:		✓		Sponsor submitted an Abuse Liability Assessment but did not include a proposal for scheduling.

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	✓			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		✓		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	✓			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***		✓		Included in 74-day letter dated October 25, 2011.
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		✓		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	✓			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***	✓			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	✓			
Is the PI submitted in PLR format?[4]	✓			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** Yes	✓			Maternal Health (2/10/12) OSE (11/17/11) DSI (10/3/11) Biostat (9/29/11) IRQT (8/22/11) Pediatrics (8/17/11)

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

				Controlled Substance Staff (8/17/11) OPDP (8/17/11) OSE (8/17/11)
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** Minutes were included in the NDA submission. ***If yes, distribute minutes before filing meeting***	✓			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** March 28, 2011 ***If yes, distribute minutes before filing meeting***	✓			
Any Special Protocol Assessments (SPAs)? **Date(s):** CAC SPA agreement letter (2) on December 19, 2007, Clinical SPA No Agreement letter issued on September 29, 2006 ***If yes, distribute letter and/or relevant minutes before filing meeting***	✓			

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 28, 2011

BLA/NDA/Supp #: 202992

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: Teriflunomide

DOSAGE FORM/STRENGTH: 14mg tablets

APPLICANT: Sanofi-Aventis

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (b) (4)

BACKGROUND: Sanofi-Aventis submitted a new drug application (NDA) to support the marketing of teriflunomide (b) (4) as monotherapy for relapsing forms of Multiple Sclerosis (MS) (b) (4)

Teriflunomide is a metabolite of leflunomide (Arava), which was approved on September 10, 1988, for the treatment of active Rheumatoid Arthritis (RA) to reduce signs and symptoms and to retard structural damage as evidenced by X-ray erosions and joint space narrowring.

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for de novo pyrimidine synthesis. The exact mechanism by which teriflunomide exerts its therapeutic effect in multiple sclerosis (MS) is not fully understood, but may include reduced number of activated lymphocytes in the central nervous system.

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

REVIEW TEAM:

Discipline/Organization	Names	
Regulatory Project Management	RPM:	Hamet Touré
	CPMS/TL:	Robbin Nighswander
Cross-Discipline Team Leader (CDTL)	Billy Dunn	
Clinical	Reviewer:	Jody Green (efficacy) Lourdes Villalba (safety) Evelyn Mentari (safety)

	TL:	Billy Dunn (Efficacy) Sally Yasuda (Safety)
Clinical Pharmacology	Reviewer:	Veneeta Tandon
	TL:	Angela Men
Biostatistics	Reviewer:	Sharon Yan
	TL:	Kun Jin
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Richard Houghtling
	TL:	Lois Freed
Product Quality (CMC)	Reviewer:	Prafull Shiromani
	TL:	Martha Heimann
Biopharmaceutics	Reviewer:	Albert (Tien-Men) Chen
	TL:	Angelica Dorantes
OSE/DMEPA (proprietary name)	Reviewer:	Jung E. Lee
	TL:	Alice (Chi-Ming) Tu
OSE/DRISK (REMS)	Reviewer:	Reema Jain
	TL:	Kendra Worthy
DSI	Reviewer:	Antoine El-Hage
	TL:	Tejashri Purohit-Sheth
DMPP Labeling review	Reviewer:	Robin Duer
	TL:	Melissa Hulett
Controlled Substance Staff (CSS)	Reviewer:	Katherine Bonson
	TL:	Silvia Calderon
Pediatric Team	Reviewer: Elizabeth Durmowicz PM: Mildred Wright	
Maternal Health Team	Reviewer: Upasana Bhatnagar PM: Carrie Ceresa	
OSE Regulatory Project Manager	Laurie Kelley	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined o Reason: ***the application did not raise significant safety or efficacy issues***
• Abuse Liability/Potential **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the	☒ Not Applicable

division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☐ YES ☐ NO
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)?	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES

Comments:	☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: Done by ONDQA	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**: No comments	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Robert Temple

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues:

	☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Regulatory Project Manager Date

Chief, Project Management Staff Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

HAMET M TOURE
04/25/2012

ROBBIN M NIGHSWANDER
04/25/2012

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 28, 2012

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Consult on NDA 202992
Teriflunomide (HMR1726, A77 1726)
Abuse potential of new molecular entity
Indication: treatment of multiple sclerosis
Doses: 7 and 14 mg, oral administration
Sponsor: Sanofi Aventis

Materials reviewed: NDA submission (including Drug Abuse Liability Assessment section); proposed drug label; proposal for scheduling

Table of Contents

I. Summary

A. Background

The Division of Neurology Products consulted CSS regarding NDA 202992, teriflunomide (HMR1726, A77 1726), which is a new molecular entity in development for the treatment of multiple sclerosis (MS), (b) (4)

Teriflunomide is the active metabolite of leflunomide (Arava, Sanofi-Aventis), an FDA-approved medication for the treatment of active rheumatoid arthritis. Leflunomide is not scheduled under the Controlled Substances Act (CSA), though its potential for abuse or dependence has not been evaluated by the FDA.

In a pre-NDA meeting with the Sponsor in March 2011, CSS informed the Sponsor that no additional preclinical or clinical abuse-related studies are necessary.

For the present NDA review, CSS evaluated preclinical and clinical data for evidence of central nervous system (CNS) activity and abuse potential. The Sponsor provided a Drug Abuse Liability Assessment (DALA) section to the NDA with a compilation of all abuse-related data. The Sponsor stated in the NDA that teriflunomide should not be scheduled under the CSA.

B. Conclusions:

Data submitted in the NDA for teriflunomide show that this drug:

- Does not have significant CNS penetration
- Does not have a therapeutic mechanism of action that involves CNS activation
- Does not have a chemical structure that is similar to known drugs of abuse
- Does not have affinity for CNS receptor sites
- Does not produce behavioral effects in animals
- Does not produce adverse events in clinical studies or drug diversion indicative of abuse potential
- Does not produce withdrawal signs upon drug discontinuation in animals or humans

Thus, there is no evidence that teriflunomide is CNS active or has abuse potential.

C. Recommendations:

We are not recommending that teriflunomide be scheduled in the CSA.

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/s/

KATHERINE R BONSON
03/28/2012

SILVIA N CALDERON
03/29/2012

MICHAEL KLEIN
03/29/2012

Executive CAC
Date of Meeting: February 21, 2012

Committee: David Jacobson-Kram, Ph.D., OND-IO, Chair
Abigail Jacobs, Ph.D., OND-IO, Member
Paul Brown, Ph.D., OND-IO, Member
Anne M. Pilaro, Ph.D., DHOT, Alternate Member
Lois M. Freed, Ph.D., DNP, Supervisor
Rick A. Houghtling, Ph.D., DNP Presenting Reviewer

Author of Minutes: Rick A. Houghtling

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 202-992
Drug Name: Teriflunomide
Sponsor: Sanofi-Aventis US, LLC

Background: Teriflunomide is a pyrimidine synthesis inhibitor being developed for treatment of patients with relapsing forms of multiple sclerosis, (b) (4)

Teriflunomide was positive in the *in vitro* chromosome aberration assay in human lymphocytes (3 hr incubation, ± metabolic activation); however, it was negative in the other standard *in vitro* and *in vivo* genetox assays.

4-TFMA, a primary metabolite of teriflunomide, was positive for genotoxicity in the *in vitro* Ames, HPRT assay, and chromosome aberration assays. 4-TFMA was negative in the *in vivo* micronucleus assay in mice and in the *in vivo* chromosomal aberration assay in Chinese hamsters, and equivocal in the unscheduled DNA synthesis assay in rats.

Executive CAC recommendations on the mouse and rat carcinogenicity study protocols were communicated to the sponsor on December 19, 2007, under IND 67,476.

Rat Carcinogenicity Study
Crl:CD(SD) rats were administered teriflunomide at doses of 0 (2% potato starch), 0 (2% potato starch), 0 (deionized water), 0.5, 1.5, and 4 mg/kg/day by oral gavage for up to 97 (males) or 104 weeks (females).

In males, decreased survival occurred in the MD and HD groups. The HD group was sacrificed after 92 weeks of treatment, and all other groups were sacrificed after 97 weeks of treatment. In females, there was no effect of teriflunomide on survival; however, there was a significant reduction (>10%) in mean body weight of the HD group, compared to control. No drug-related increases in any tumor type were found in this study.

Mouse Carcinogenicity Study
Crl:CD1(CR) mice were administered teriflunomide at doses of 0 (2% potato starch), 0 (2% potato starch), 0 (deionized water), 1, 4, and 12 mg/kg/day by oral gavage for up to 104 weeks. The survival rate was reduced at the HD in both males and females. Due to reduced survival in HDM, dosing was stopped in this group during week 95. HDM survivors were sacrificed at week 104, as were all other groups. No drug-related increases in any tumor type were found in this study.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee agreed that the study was adequate.
- The Committee concurred that there were no drug-related neoplasms.

Mouse:

- The Committee agreed that the study was adequate.
- The Committee concurred that there were no drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DNP
Freed/DNP
Houghtling/DNP
Toure/DNP
/ASeifried, OND-IO

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/s/

ADELE S SEIFRIED
02/23/2012

DAVID JACOBSON KRAM
02/23/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 9 December 2011

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology (OPE)

TO: Russell Katz, M.D., Director, Division of Neurological Products (DNP)
Lourdes Villalba, M.D., Medical Safety Reviewer, DNP

VIA: Gerald Dal Pan, M.D., Director, OPE; Acting Director, Office of Surveillance and Epidemiology (OSE)

SUBJECT: New information on case of liver injury in Russian woman 35 treated with teriflunomide; consultation request received 18 November 2011, assigned OSE tracking number 2011-4333.

Documents reviewed:

1) Consultation request of 17 November 2011 from Dr. Lourdes Villaba, via Dr. Alice Hughes and LCDR Hamet Touré, concerning patient #006049-643-3201-0009 who was reported to have experienced toxic hepatitis while receiving teriflunomide.
2) Clinical overview, Section 2.5, Sequence 0000 in original NDA 202992 submission dated 12 August 2011 by Sanofi-Aventis, with clinical background information on using teriflunomide (HMR1726) for treating relapsing multiple sclerosis to reduce frequency of exacerbation and accumulation of physical disabilities.
3) Sponsor's response of 31 October to DNP requests of 3 and 12 October for additional safety information, received November as Amendment 0011, Sequence 0011.
4) Selected medical literature articles on teriflunomide, leflunomide, and other items

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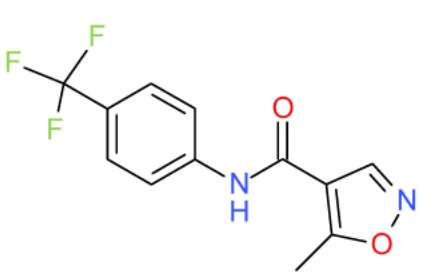
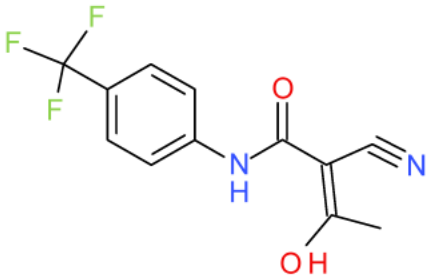
The consultation request provided a narrative summary and links to the electronic document room (EDR), accessible also via DARRTS for NDA 202992, item 14 to Clinical Study Reports (5.5); Reports of Efficacy and Safety Studies, relapsing multiple sclerosis (5.3.5); Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication, efc6049 (5.3.5.1); Individual Subject Data Listing (5.3.5.1.25); Subject Profiles (5.3.5.1.25.7); and that for the subject of index interest, 5.3.5.1.25.7.3201/0009. For background and perspective, the Clinical Overview submitted with the original submission of 12 August 2011 (202992, Sequence 0000, Section 2.5) was helpful.

Teriflunomide (HMR1726), also known as A77 1726, was found to be the active metabolite of leflunomide in studies at Hoechst (Bartlett RR et al., 1991). Leflunomide was approved on 10 September 1998 (NDA 20-905) as ARAVA® (Höchst AG) for treatment of active rheumatoid

arthritis. After approval, rare cases of severe liver injury and dysfunction attributed to use of leflunomide led to considerable controversy as to whether it should continue to be used, but opinions in favor of its use prevailed over those for withdrawal. The ARAVA® labeling updated to 8 July 2011 still carries a black box warning for hepatoxicity, including fatal liver failure in some patients, and is advised not to be used in patients with pre-existing or chronic liver disease or those with pretreatment serum alanine aminotransferase (ALT) activities more than twice the upper limit of the normal range (>2xULN). In the development of leflunomide (HWA486) it was found that teriflunomide was its principal metabolite and responsible for most of its action. The metabolite, teriflunomide, is a malononitrilamide produced by opening of the isoxazole ring of leflunomide to produce a 2-cyano-3-hydroxy-2- butenamide active metabolite that blocks action of the enzyme dihydroorotate dehydrogenase (essential for pyrimidine synthesis).



leflunomide



teriflunomide

Leflunomide, originally approved in 1998 for treating active rheumatoid arthritis, had been found to be a general immunomodulatory drug with a great variety of autoimmune diseases, some of which are relatively rare and considered orphan diseases for which Sanofi-Aventis* has sought approval to treat, to extend patent protection in other countries. The U.S. patent for leflunomide for treating rheumatoid arthritis expired 13 September 2005; it has been marketed as a generic drug since then by several smaller companies (Barr, Apotex, Heritage Pharms, and others). The principal adverse effect found with leflunomide has been rare but sometimes very serious liver toxicity for which the labeling was upgraded from a boldface warning in 2003 to boxed warning on 13 July 2010. In addition, the labeling contains a black-box contraindication against use in pregnancy, and other warnings about bone marrow suppression, severe skin reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis), sometimes persistent peripheral neuropathy even after discontinuing the drug, and increased risk of malignancy, especially lymphoproliferative disorders.

Comment: Because teriflunomide is the principal metabolite of leflunomide, and is known to be responsible for most of its effects, is there any reason to suppose or expect it to be less likely to produce this same spectrum of potentially very serious adverse effects? Does the development program established by the current sponsor fully reflect concerns about these effects, and are adequate data being collected to provide assurance that the drug will be doing more good than harm in the prospective patents to be treated for reduction of relapses of multiple sclerosis? This consideration will be the focal point of evaluating teriflunomide in multiple sclerosis.

* Höchst AG became Aventis Deutschland in 1999 after merging with the French company Rhône-Poulenc S. A., then was acquired by Sanofi-Aventis in 2004 after merger with Sanofi-Sythélabo.

To focus on the index case of concern forwarded by the clinical reviewer for safety, Dr. Lourdes Villaba, it was summarized in the request sent 17 November that approximately 2500 subjects have been exposed to at least one dose of teriflunomide in phase 2-3 clinical trials, 1200 of whom are still currently blinded studies. Among the 1300 or so in completed studies, there were 429 who were exposed to 7 g/day and 415 to 14 mg/day for up to 2 years, compared to 421who were randomized to placebo. Among these, the sponsor reported finding elevations of serum alanine aminotransferase (ALT) activities more then three-fold the upper limit of normal (>3xULN) , in similar proportions of subjects: 25 of 415 (6.02%) on 14 mg/day of teriflunomide; 25 of 429 (5.94%) on 7 mg/day of teriflunomide; and 26/ of 421 (6.18%) on placebo.

Comment: Serum ALT activities are not true measures of any known function of the liver, and the term "liver functions tests, (LFTs)"is a misnomer, and in addition a misleading one. It is a fairly sensitive biomarker that was developed in 1955 initially to diagnose acute myocardial infarction (Karmen et al.) but quickly found also to show even greater increases in a variety of acute and chronic liver disorders. It is, however, not specific to the liver, and may reflect injury to cells in other organs. When there has been sufficient hepatocellular injury to cause overall dysfunction of the liver, as measured by rising serum bilirubin concentration or prolonged prothrombin time the combination of findings is an alarm signal. The highest ALT found in some occasional testing schedule is not a valid measure of either severity or dysfunction, and analyses of group means or incidence of minor abnormalities is not instructive but only misleading. Even with leflunomide, the incidence of really serious liver dysfunction has been quite rare, and not at all likely to be discovered in relatively small groups of about 400 subjects. At best the higher levels of serum ALT found suggest greater urgency to repeat the test immediately to determine if it is falling or rising, and in the latte case to investigate thoroughly to find the probable cause.

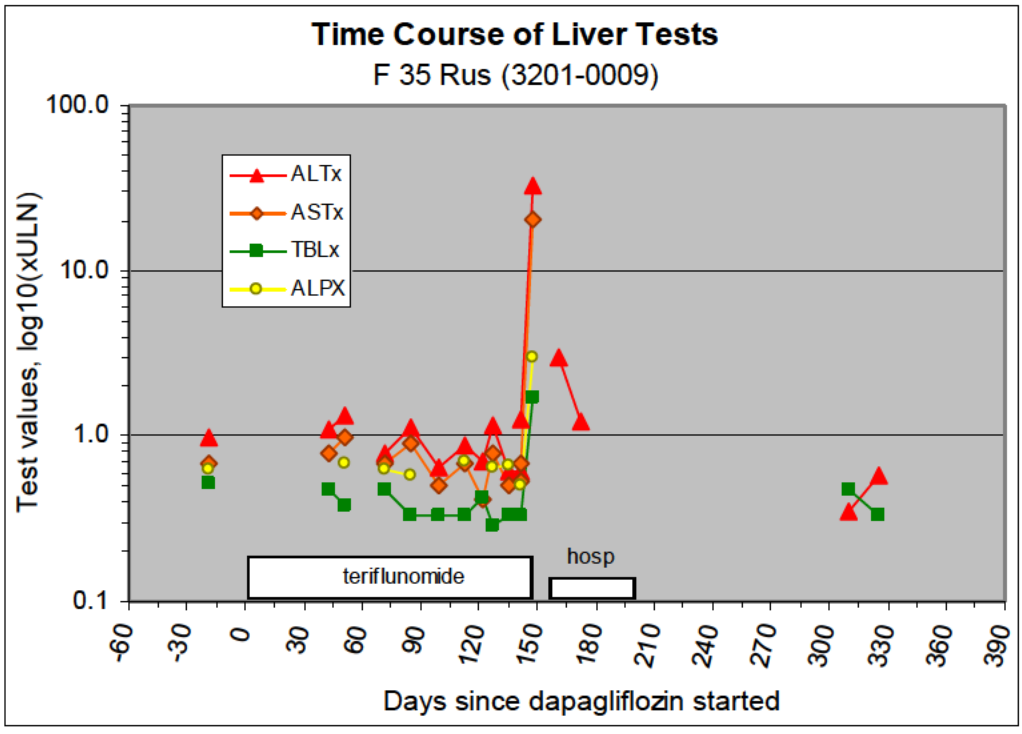
The subject in question #00649-643-3291-0009 is a Russian woman who was 35 on (b) (6) when she was found to have ALT of 1101 at a local laboratory after almost two weeks of adverse symptoms beginning on 22 March with a feeling of heaviness in the right hypochondrium, then pain and fever to 39 C (102.2 F) and bilious vomiting on 28 March. Her ALT had been 43, AST 31, and total bilirubin 7 µmol/L on that evening, reported on 31 March. A gastroenterologist was said to have diagnosed "acute gastritis with biliary dyskinesia and duodenogastric reflux (b) (6) , and abdominal ultrasound examination was not diagnostic. She reported by telephone on April 7th some lessening in retching right hypochondrial discomfort, but said she was still icteric. The gastroenterologist suspected acute viral hepatitis, recommended stopping the study drug, and evaluation by an infectious disease specialist who hospitalized her on (b) (6) and found negative serologies for hepatitis A, B, and C, leading to a diagnosis of "toxic hepatitis." The abnormally elevated laboratory tests improved on 17 April, and she was discharged (b) (6), according to the supplemental narrative information sent by the sponsor on 24 October 2011.

Comment: This potentially serious case occurred in (b) (6) It is not clear that the case was reported at the time, over 5 years ago, but the patient stated she was jaundiced, very high serum enzyme levels had been found in early April 2006, and she was hospitalized for about (b) (6), but no details of the findings from the hospitalization were provided by the sponsor (Sanofi-Aventis) despite the DMEP request of 12 October for information to supplement the abbreviated narrative summary in the routine report of the case listed in the original submission. The reply added very little information beyond what had been listed for the subject among hundreds of narratives submitted originally. Let us look at the data provided (following table and graph):

teriflunomide case #006049-643-3201-0009

N020992 Russian F 35

		central lab ULN	*34*	*34*	*21*	*106*					
date	event		ALT	AST	TBL	ALP	other	DAY	ALTx	ASTx	TBLx	ALPX
20-Oct-05	screen		33	23	11	66		-19	0.97	0.68	0.52	0.62
2-Nov-05			23	19	7	69		-6	0.68	0.56	0.33	0.65
8-Nov-05	start							1				
22-Nov-05			37	27	10			15	1.09	0.79	0.48	
6-Dec-05			45	33	8	73		29	1.32	0.97	0.38	0.69
20-Dec-05								43				
28-Dec-05			27	23	10	67		51	0.79	0.68	0.48	0.63
10-Jan-06			38	31	7	62		64	1.12	0.91	0.33	0.58
17-Jan-06			22	17	7			71	0.65	0.50	0.33	
31-Jan-06			30	23	7	75		85	0.88	0.68	0.33	0.71
14-Feb-06			24	14	9			99	0.71	0.41	0.43	
28-Feb-06			39	27	6	68		113	1.15	0.79	0.29	0.64
9-Mar-06			21	17	7	70		122	0.62	0.50	0.33	0.66
14-Mar-06	wbc 11450		21	18	7			127	0.62	0.53	0.33	
22-Mar-06	RUQ heavy							135				
28-Mar-06	visit 8		43	31	7	73		141	1.26	0.69	0.33	0.50
4-Apr-06	wbc 6300		1101	691	36	326	*local lab*	148	**32.38**	**20.32**	**1.71**	**3.02**
7-Apr-06	stop							151				
(b) (6)	hosp							153				
17-Apr-06			102					161	3.00			
28-Apr-06			42					172	1.24			
(b) (6)	disch							194				
	hosp		17		10			310	0.35		0.48	
28-Sep-06			28		7			325	0.58		0.33	



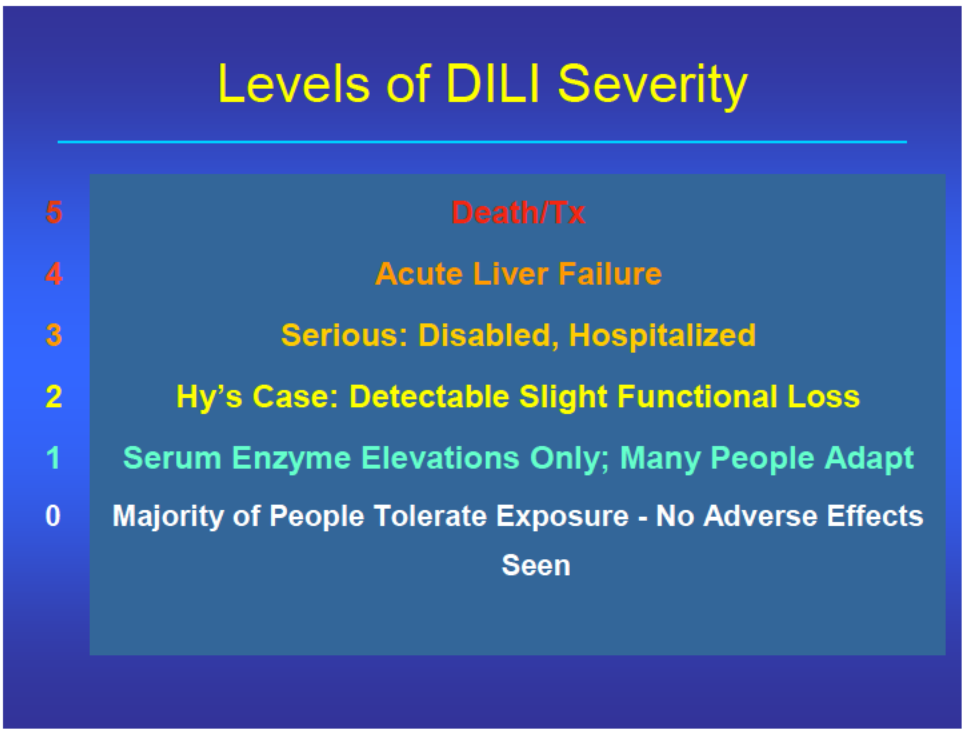
Comment: It is evident that almost no data were reported from the period of hospitalization and treatment of this subject, despite her claim that she was jaundiced and quite ill. The response of the sponsor to the request for more information yielded very little additional except for a couple of approximate ALT values that were said to be lower during the (b) (6) *she was in hospital. The main diagnosis was "toxic hepatitis" and it seems to have taken over 5 years for us to have learned about the case, even for a drug that has a very high likelihood of showing at least occasional or rare cases of serious hepatotoxicity as found after marketing for the parent drug leflunomide. It is usually the case that initial hepatocellular injuries from drugs then cause slowly rising serum bilirubin levels some days later if the injury is severe and extensive enough. No greatly elevated serum bilirubin levels were reported, even though appearance of visible jaundice in skin, sclerae, or mucosae usually requires serum bilirubin levels of 4 to 6 mg/dL or more, depending on pigmentation, lighting conditions, and skill of the observer. One way to avoid peak bilirubin levels of concern is not to look for them, or if found, not to report them.*

The medical safety reviewer had to search through hundreds of narratives to find the case, and it is problematic whether there may be more such inadequately reported cases (such as perhaps the additional case from the same study #006049-152-3803-0005who showed ALT to 23xULN and was "mildly icteric" after several months on teriflunomide, considered by the investigator to be "related to teriflunomide."

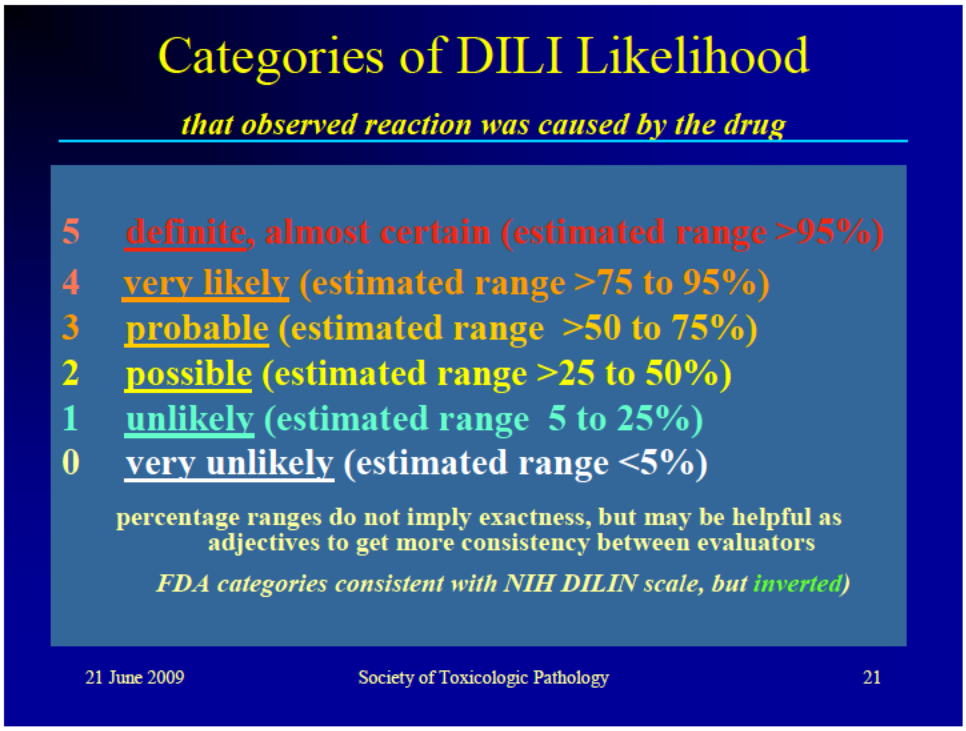
The sponsor's Clinical Overview, section 2.5 of the original submission of 12 August 2011 and which carries the sponsor's date of 6 July 2011 states a relapse rate of 196/363 (54%) in subjects on placebo, compared to 267/723 (37%) in those on teriflunomide, and some delay until onset of the relapses. The higher daily dose of 14 mg did not seem significantly more effective than the 7 mg dose. With respect to the principal adverse effect of concern, hepatoxicity, it was stated that Increased incidence of minor ALT elevations <3xULN were seen in those subjects exposed to teriflunomide, but higher levels and those with bilirubin elevations were about the same in the three groups of patients randomized to placebo, 7 or 14 mg/day of teriflunomide., but the numbers were small, only something over 400 subjects in each group.

Comment: It is astonishing that the Clinical Overview for use of teriflunomide does not seem to mention the extensive world-wide experience with the sponsor's now off-patent drug leflunomide, which has caused great controversy and much concern about hepatotoxicity, leading to serious consideration of removing it from the market, and failing that to a recent black-box warning imposed in July 2010.The Overview simply states (page 10) that leflunomide was approved in 1998, and that over 2 million patient years of exposure have been collected on its safety profile. It is not a simple matter of teriflunomide being in the same class of drugs, but it is well known and granted that some drugs in a given class may be relatively more likely than others to cause liver injury and dysfunction in some recipients (as troglitzone >> rosiglitazone or pioglitazone, alpidem>> zolpidem, bromfenac >> ibufenac, etc.). In this case the relationship is much closer and the new drug is a direct metabolite of the parent compound. There is absolutely no reason to presume that the two compounds will not be found to behave very much the same, and no reason to fail to mention the long and checkered history of leflunomide when introducing teriflunomide to a new and different group of neurologists who may not have been aware of lefluomide's track record known to physicians treating rheumatoid arthritis. The burden of proof should rest upon the sponsor to show evidence that teriflunomide will do more good than harm in patients with multiple sclerosis, and simply hiding the harms caused will simply complicate that assessment.

Assessment of liver injury and dysfunction should not rest only upon statistical data of ALT levels, which do not measure liver function at all, are often asymptomatic and reversible, and unless they lead subsequently to actual dysfunction of the liver, are not clinically important. The grading of "severity" developed by the National Cancer Institute in 1982-3 was based not on data but upon opinions of anonymous consultants, but has been carried forth since without data for verification .It is widely cited and used in the oncology and other medical communities. The NCI grades state that serum enzyme (ALT, AST, ALP, GGT, etc.) elevations in the range of >1-2.5 times upper limit of the normal range (xULN) are "mild"; >2.5-5xULN "moderate"; >5-20xULN "severe"; and >20xULN "life-threatening." This classification, although simple, is obsolete and wrong, but deeply entrenched. The severity of liver injury depends upon the extent of liver cellular loss or impairment, and is dependent upon true functional losses of the liver, as may be shown by impaired ability to clear bilirubin from plasma, conjugate it with glucuronide, and excrete it into the bile. That function is specific to the liver, and not carried out by any other organ, but it is relatively insensitive and often found only in relatively advanced disease. The plasma prothrombin time, or its derivative international normalized ratio (INR), is another test that measures a true liver function, that of synthesizing coagulation factors. Measures of total serum bilirubin concentration (TBL) and plasma prothrombin time (INR) are the only measures of liver function that are routinely carried out in clinical trials. Very slightly elevated TBL that follows acute hepatocellular injury shown by elevated ALT levels, if not caused by disease or predominantly cholestatic, may indicate more than mild liver injury and has been popularized as "Hy's Law" for use in clinical trials. More severe or serious injury is reflected by clinical findings of obvious jaundice (higher levels of TBL), with clinical symptoms of fatigue, nausea, disability, need for hospitalization, and beyond that very severe injury shown by acute liver failure with secondary dysfunction of brain (hepatic encephalopathy) or kidneys (hepatorenal syndrome), and the most severe of all, death or need for initially liver transplantation.



These levels of relative severity from 0 (none) to 5 (death or transplant) have been used both by us at FDA and by the network of hepatologists funded by the National Institutes of Health (NIH) by its drug-induced liver injury network (DILIN) for the past 8 years to evaluate the severity of liver dysfunction. They are based upon clinical findings, and not simply on ALT elevations, and require good clinical information, not simply laboratory tests of blood chemistries. Beyond the severity of cases, it is necessary also to evaluate potentially serious cases for likelihood that the findings were actually caused by the suspected drug, rather than by disease, some other drug or agent. We cannot assess causal likelihood with great precision, but have established categories of likelihood on a comparable scale from 0 to 5, for approximate estimation:



Comment: Obviously, a drug-induced reaction that is both severe and probably caused by the drug is a most compelling concern. The case considered here might be classified as serious because of the hospitalization and the claim of jaundice, even though the sponsor did not obtain the hospital records. It might also be assessed as probably caused by the investigational drug, teriflunomide, lacking any evidence for an alternative cause and as suggested by the opinion of the local investigator as "toxic hepatitis." It remains a mystery as to why the sponsor did not inquire more vigorously or promptly into the matter, given their knowledge about the history of its other product, leflunomide.

The most difficult problem of all, even more so than establishing with confidence the likelihood of drug causality, is whether treatment with the drug will do more good than harm in the patients treated after approval. Those patients may be quite different than subjects selected for study in clinical trials, where the principal aim is to show statistically significant efficacy of at least some modest degree, while avoiding adverse effects by selection of subjects for inclusion and routine monitoring (not to mention failure to report possibly troublesome cases). The real question is how many of those treated will show how much benefit (or harm), how soon it will

occur, and how likely the effects are really attributable to the drug rather than to something else. Balancing the chances of benefits and risks of harms to demonstrate new benefit or treatment is not always easy to determine from clinical trial data that are skewed and biased to favor benefits and support approval. It may take years to discover the true extent of the risks of harms which may be relatively rare, even though sometimes very severe in magnitude, unpredictable in when they occur or in whom, and difficult to distinguish from diseases or cause by other agents taken concurrently. This should be very well studied and proved by the sponsor before approval, which does not seem to be in the program planned for this drug, despite the problematic history of their previously discovered and promoted drug, lefunomide.

Leflunomide was developed by the group led by RR Bartlett at Höchst in the 1980s, patented in 1982, and marketed in 1998. It is not clear why teriflunomide was not selected for development even though they knew it as A77 1726 and to be the active metabolite of lefluomide, responsible for most of its effects, good or bad. Leflunomide is now being marketed as a generic drug by several small companies, but the sponsor has been active in seeking patent extensions in other countries (b) (4) by Sanofi-Aventis, which took over Höchst in a series of mergers, as noted above.

Comment: The sponsor cannot plead ignorance about the highly probable likelihood that this "new" derivative of leflunomide will show that same tendency to cause relatively severe liver injury and dysfunction in some patients, especially after marketing if approved, when larger numbers of patients are treated with it, without selective exclusions or careful monitoring. We do not want to be in position of having to withdraw the drug after approval if the net benefit of using it is found to be negative some years after approval.

There is much explaining to do by the sponsor, who needs to say why so little mention is made of the established risk of serious harm of the drug leflunomide, known by the sponsor to be the precursor of its principal metabolite teriflunomide that they full well know is responsible for most of the effects, both favorable and adverse. Why were these risks not communicated to the investigators, probably mostly neurologists, about the serious risk of harm of leflunomide used for treating rheumatoid arthritis, mostly by rheumatologist? Why was this case of serious liver dysfunction not reported for almost 6 years after it occurred, and why do they still refuse to provide the details about what happened to the patient?

This performance does not inspire confidence in the research program to develop the not-so-new drug teriflunomide for other indications and other physician specialists who may not be fully aware of the history. Glossing over safety problems is not the best way to gain approval for a new treatment that has only modest beneficial effects in reducing relapses in a disabling and troublesome disease, multiple sclerosis.

It is understandable that the sponsor might like to extend the useful life of an old drug leflunomide, now off patent, by seeking new patents and new uses for teriflunomide, but not by concealing adverse effects to physicians who may not be fully aware of them. It is in the best interests of the sponsor, as well as of patients to be treated, to recognize these facts, and make every possible effort to show that teriflunomide is likely to do more good than harm in patients who might be treated with it.

Recommendations:

1. It will be important for the sponsor to revise the manual of advice to investigators to inform them of the hepatotoxicity and other risks of leflunomide and make it clear that teriflunomide is its principal metabolite and responsible for most of its effects.
2. The sponsor must investigate and report promptly all serious adverse effects such as that discovered 6 years after teriflunomide was started in the Russian woman whose report was found buried among hundreds of other minor cases of simple serum ALT increases.
3. To begin, the hospital records and findings for the index case should be obtained and reported to us, even though the admission was back in (b) (6)
4. We suggest that a comprehensive search of all the clinical data on patients exposed to teriflunomide, compared to placebo, be provided in a form suitable for eDISH analysis as prescribed by Dr. Ted Guo, be done, and that competent medically written narratives be provided by the sponsor for all cases of special interest, sufficient for making differential diagnoses of probable causality of the observed findings.
5. We shall be interested in follow-up on these matters, and will consult further.

_____

John R. Senior, M.D.

cc: OSE 2011-4333
L. Villalba, DNP
R. Katz, DNP
G. Dal Pan, OPE/OSE

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/s/

JOHN R SENIOR
12/14/2011

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	202992
Brand Name	None
Generic Name	Teriflunomide (HMR1726)
Sponsor	Sanofi-Aventis
Indication	Treatment of Multiple Sclerosis
Dosage Form	Film-coated Tablets
Drug Class	Inhibitor of Mitochondrial Enzyme Dihydroorotate Dehydrogenase (DHO-DH)
Therapeutic Dosing Regimen	14 mg Orally Once Daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	70 mg QD for ≥ 9 days
Submission Number and Date	SDN 001/ 23 August 2011
Review Division	DNP / HFD 120

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of teriflunomide (70 mg once-daily for 4 days followed by 14 mg once-daily for 8 days) was detected in this TQT study. The largest upper bound of the 2-sided 90% CI for the mean difference between teriflunomide and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

This was a randomized, double-blind, double-dummy, repeated dose, placebo-controlled study. One hundred and ninety-five subjects were enrolled to receive teriflunomide, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for Teriflunomide and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

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

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 Time points is 9.5 ms.

The multiple doses of teriflunomide produces a mean C_{max} of 30.5 µg/mL (range: 12.3 to 53.0 µg/mL) at a median T_{max} of 4 hours and C_{trough} of 24.8 µg/mL (range: 10.7 to 47.0).

These values are within the range of exposure observed in patients; however, no information is available regarding whether they are above those for the predicted worst case scenario (CYP/transporter-based drug interactions). At these concentrations there are no detectable prolongations of the QT-interval. There is no significant difference in teriflunomide exposure with mild and moderate hepatic impairment, as well as severe renal impairment.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL:

The sponsor proposed the following language in the label.

(b) (4)

2.2 QT-IRT PROPOSED LABEL:

We have the following recommendations which are suggestions only. We defer all final labeling decisions to the review division.

12.2 Pharmacodynamics:

The effect of teriflunomide following 70 mg once-daily for 4 days followed by 14 mg once-daily for 8 days on the QT interval was evaluated in a randomized, double-blind, placebo- and active-controlled (moxifloxacin 400 mg) parallel study in 195 subjects. In a study with demonstrated ability to detect small effect, the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The tested dose is adequate to represent the median steady state therapeutic exposure. No apparent intrinsic and extrinsic factors are identified to increase teriflunomide exposure.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Teriflunomide is a de novo pyrimidine synthesis inhibitor with antiproliferative and anti-inflammatory activity. It is currently under investigation for the treatment of relapsing, remitting multiple sclerosis.

3.2 MARKET APPROVAL STATUS

Teriflunomide is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From eCTD 2.6.2

"The potential effects of teriflunomide on IKr currents in CHO cells stably expressing the human cardiac human ether-a-go-go related gene (hERG) channel were evaluated using the

whole-cell patch-clamp technique. Increasing concentrations of 10, 30, 100 and 300 µmol/L teriflunomide (batch 0500024551) were sequentially tested.

"Teriflunomide at concentrations of 10 and 30 µmol/L inhibited hERG channel current by an average of 6.6 and 11.1%, respectively. At a concentration of 100 µmol/L, somewhat less inhibition was observed (4.9%). Teriflunomide at 300 µmol/L increased the hERG currents by 4.2 to 22.1% on 5 out of 6 cells tested suggesting that at high concentrations, teriflunomide acts as a weak activator of hERG. The positive control cisapride (0.10 µmol/L) inhibited hERG currents by 80.8% and 78.6% for the 2 cells tested, demonstrating the expected effects of the model. In conclusion, teriflunomide produced little or no inhibitory effects on hERG but at very high concentrations may have weak activator properties.

"In vitro effect on action potential parameters in the isolated rabbit Purkinje fiber. Teriflunomide (batch W001) was evaluated for effects on resting membrane potential (RP), action potential amplitude (APA), maximal rate of rise (Vmax) of action potential and action potential duration (APD50 and APD90) of rabbit Purkinje fibers stimulated electrically (see 2.6.3, Study FIP0156 [TS 2.6.3.4.5]). Six Purkinje fibers were tested at 0 (Krebs solution containing 0.25% DMSO), 0.1, 1, 10 and 100 µmol/L teriflunomide (ie 0, 0.027, 0.27, 2.7 and 27 µg/mL, respectively) sequentially applied every 30 minutes. Reversibility of the effects was evaluated by superfusion of control solution for 30 minutes. The fibers were stimulated at the basal rate of 1 pulse per second (1 Hz). Higher (3 Hz) and lower (0.25 Hz) stimulation rates were also tested.

"Concentrations of 0.1, 1, and 10 µmol/L teriflunomide had no effect on resting membrane potential or action potential parameters (APA, Vmax, APD50 and APD90), whatever the stimulation rate. At 100 µmol/L, teriflunomide induced a slight and statistically significant shortening in the action potential duration (APD50 and APD90). The mean APD90 was shortened by 7%, 15% and 23% at 3 Hz, 1 Hz and 0.25 Hz, respectively. The resting membrane potential and the other action potential parameters (APA, Vmax) were not changed. The mean effects on APD50 were slightly more marked than on APD90 (-11%, -24%, -45% at 3 Hz, 1 Hz and 0.25 Hz, respectively). The effect was reversible after 30 minutes of washout.

"Teriflunomide was orally administered to telemetered Beagle dogs (3/sex, 18 to 38 months old) at 0 (0.5% hydroxyethylcellulose), 3 or 10 mg/kg. Dogs were dosed once per week for 3 weeks using a crossover design. Clinical signs were observed. Cardiovascular parameters [systolic, diastolic, and mean arterial blood pressure, heart rate, and electrocardiogram (ECG) waveforms (lead II) - PQ, QRS, QT, QTc (Bazett's formula), and RR] were evaluated pretreatment and up to 24 hours post-dosing. Teriflunomide had no significant effect on any cardiovascular parameter."

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4 and ISS

"ECGs in phase 2/3 monotherapy studies. A clinical electrocardiographic evaluation was performed in Study 2001 and its extension study, LTS6048. The results of this evaluation are presented in this section. The results of these analyses have to be interpreted with caution as this study was not specifically designed to analyze QT effect and because of the lack of standardization of ECGs procedures.

"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.

"In adjunct Phase 2 studies, the incidence of PCSAs in ECG was low and generally balanced among the 3 treatment groups. No patient had a QTcB or QTcF value ≥500 ms."

Study 2001

"No patients had QTcF ≥500 ms or QTcB ≥500 ms in any treatment group. Few patients had prolonged QTcF or QTcB (>450 ms in male and >470 ms in female) with no differences across treatment groups (Table 2). Similar proportion of patients within each treatment group experienced increase versus baseline >60 ms for QTcF (3.3% in placebo and teriflunomide 7 mg and none in 14 mg) and QTcB (4.9%, 3.3% and 3.5% in placebo, teriflunomide 7 mg, and 14 mg, respectively)."

Table 2: ECG - Number of patients with abnormalities (PCSA) according to baseline status - Safety population – Study 2001

ECG parameter Baseline Status PCSA criteria	Placebo (N=61)	teriflunomide 7 mg (N=61)	 14 mg (N=57)
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
Normal/Missing			
Borderline: 431-450 ms (Male);451-470 ms (Female)	3/60 (5.0%)	3/59 (5.1%)	1/57 (1.8%)
Prolonged: >450 ms (Male); >470 ms (Female)	0/60	1/59 (1.7%)	0/57
≥ 500 ms	0/60	0/59	0/57
Borderline: 431-450 ms (Male);451-470 ms (Female)			
Prolonged: >450 ms (Male); >470 ms (Female)	0/1	1/1 (100%)	0/0
≥ 500 ms	0/1	0/1	0/0
Prolonged: >450 ms (Male); >470 ms (Female)			
≥ 500 ms	0/0	0/0	0/0
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

PCSA: Potentially clinically significant abnormalities
[a] Regardless of baseline status
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.
For PCSA including condition based only on change from baseline, the denominator is restricted on patients having a baseline and a post-baseline values.
For QTc Bazett and Fridericia, a patient who experienced at least one value greater than 500 ms is counted also in the prolonged category.
For other categories of PCSA related to QTc, a patient who experienced one PCSA in several categories is counted only in the worst category.
PGM=PRODOPS/HMR1726/OVERALL/CSS/REPORT/PGM/ecg_pcsa_s_t.sas OUT=REPORT/OUTPUT/ecg_pcsa_s_t_p1_i.rtf (20JUN2011 - 19:32)

Source: ISS, table 46

Reviewer's comments: No large effects in QT prolongation was detected in study 2001. No AEs as per ICH E14 Guidance were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of teriflunomide's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 67,476. The sponsor submitted the study report TES10852 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Effect of repeated oral doses (70 mg for 4 days followed by 14 mg for 8 days) of teriflunomide on ventricular repolarization, compared to placebo with moxifloxacin (400 mg single dose) as a positive control in healthy subjects: A randomized, double-blind, double-dummy, 3-parallel group study

4.2.2 Protocol Number

Clinical Study Report – HMR1726-TES10852

4.2.3 Study Dates

First subject enrolled: 04 March 2010
Last subject completed: 14 February 2010

4.2.4 Objectives

Primary objective: To assess the effect of teriflunomide administered as repeated doses (70 mg for 4 days followed by 14 mg for 8 days) on QTcF interval compared to placebo.

Secondary objectives:

- To assess the effect of teriflunomide on heart rate (HR), QT, QTcB, and QTcN, compared to placebo.
- To assess the clinical and laboratory safety of teriflunomide.
- To document the plasma concentrations of teriflunomide at the time of electrocardiogram (ECG) investigation

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, single-center, randomized, double-blind, double-dummy, repeated dose, placebo-controlled study, stratified by gender, conducted in 3 parallel groups. After a screening period of 3 to 21 days and randomization, the study treatment phase included:

- a pre-inclusion visit
- a placebo run-in day
- a randomized treatment period including 12 treatment days as follows:
  - Teriflunomide 70 mg once a day for 4 days followed by 14 mg once a day for 8 days

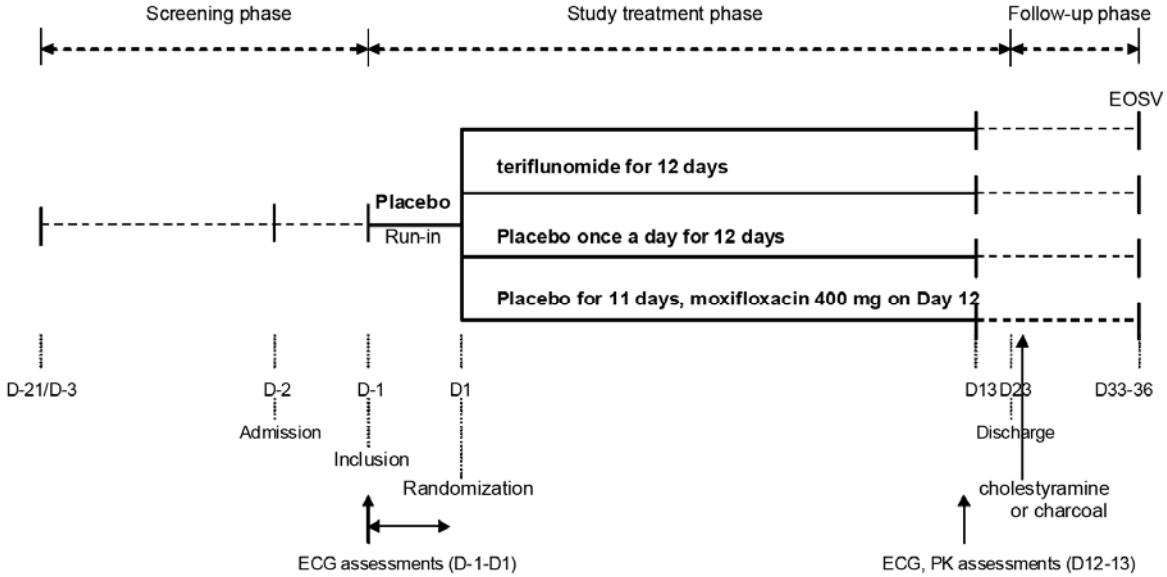
- Placebo for 12 days
- Placebo for 11 days followed by 1 single dose of moxifloxacin 400 mg on Day 12

These treatments were followed by a wash-out period of at least 11 days with cholestyramine or activated charcoal (treatment randomly assigned).

The end of the study was 10 to 13 days after the last dose of cholestyramine or activated charcoal, and if teriflunomide concentration was ≤0.02 µg/mL.

The study design is presented in Figure 1.

Figure 1: Study Design



D = Day; ECG = electrocardiogram; EOSV = end-of-study visit; PK = pharmacokinetic

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach.

4.2.5.4 Treatment Arms

This study was conducted in a 3-parallel group design. Each subject received 1 of 3 treatment conditions:

Teriflunomide: 70 mg once a day for 4 days followed by 14 mg once a day for 8 days.

Placebo: Once a day for 12 days.

Placebo/Moxifloxacin: Placebo once a day for 11 days followed by a single dose of moxifloxacin 400 mg.

4.2.5.5 Sponsor's Justification for Doses

"Given the long half-life for teriflunomide, it takes approximately 6 weeks for once-daily administration of 14 mg to approach steady state plasma concentration. In order to attain the steady state condition quickly, a loading dose of 70 mg for 4 days was administered in the trial followed by a maintenance dose of 14 mg for 8 days to maintain the steady state condition".

Reviewer's Comment: Acceptable. However, the study did not contain a treatment arm of supratherapeutic dose. Effect of QT prolongation at a supratherapeutic dose therefore cannot be ruled out.

4.2.5.6 Instructions with Regard to Meals

"As food may shift the time of peak drug concentration ($T_{max)}$, teriflunomide was administered in fasted state on the day of ECG recording, in this study".

Reviewer's Comment: Acceptable.

4.2.5.7 ECG and PK Assessments

ECG Assessment: ECGs were extracted from continuous 24-hour 12-lead ECG (Holter) recordings on Day -1 and Day 12 at 30 min pre-dose, then 1, 2, 3, 4, 5, 6, 8, 12 and 24 h post-dose.

PK Assessment: Blood samples were collected at pre-dose on Day 12, at pre-dose, 1, 2, 3, 4, 5, 6, 8, 12, 24h pose dose. Blood samples were also collected on Day 1 to Day 5 and on Day 10 to 12 to assess plasma concentration observed before administration (C_{trough}).

Reviewer's Comment: Acceptable. The selected timing points cover the time of maximum plasma drug concentration (T_{max}).

4.2.5.8 Baseline

The sponsor used time-matched on Day -1 as QTc baseline values.

4.2.6 ECG Collection

Triplicate 10-second ECGs were extracted from continuous 24-hour 12-lead ECG (Holter) recordings on Day -1 and Day 12.

These ECGs were centrally read. A computer-assisted, semi-automatic, on-screen measurement of the extracted digital ECG waveforms was performed by the ECG reading center (b) (4) using SCP manager software® (b) (4) and a standardized methodology (in accordance with the sanofi-aventis ECG Central Reading Requirements, and after checking interobserver reproducibility and repeatability). Review of the ECGs for a particular subject was performed by a single reader.

All interval measurements (PR, QRS, and QT) were based from the global superimposed median beats. Each median beat was mathematically derived from the available 10 second-recording of the corresponding lead. The 12 individual median beats were graphically displayed as temporally aligned and overlapped (or superimposed) on each other.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

194 subjects were randomly assigned to 1 of 3 treatment groups:

- Placebo: 65 subjects
- Teriflunomide: 61 subjects
- Placebo (for Day 1 to 11)/ moxifloxacin (single dose on Day 12): 68 subjects

Of these 194 subjects, 2 subjects discontinued the study prematurely, both of them due to adverse events. Both of these subjects were assigned to teriflunomide treatment. No subjects in the study were replaced.

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Table 3: Demographics and subject characteristics at baseline – safety population

	Placebo (N=65)	Teriflunomide (N=61)	Placebo/Moxifloxacin (N=68)	All (N=194)
Age (years)				
Number	65	61	68	194
Mean (SD)	41.5 (15.6)	41.6 (16.8)	41.9 (16.4)	41.7 (16.2)
Min : Max	18 : 65	19 : 64	18 : 65	18 : 65
Sex [n (%)]				
Number	65	61	68	194
Male	32 (49.2%)	30 (49.2%)	33 (48.5%)	95 (49.0%)
Female	33 (50.8%)	31 (50.8%)	35 (51.5%)	99 (51.0%)
Race [n (%)]				
Number	65	61	68	194
Caucasian/White	64 (98.5%)	60 (98.4%)	66 (97.1%)	190 (97.9%)
Black	1 (1.5%)	1 (1.6%)	1 (1.5%)	3 (1.5%)
Other	0	0	1 (1.5%)	1 (0.5%)
Weight (kg)				
Number	65	61	68	194
Mean (SD)	66.1 (9.4)	67.0 (10.8)	67.1 (10.2)	66.8 (10.1)
Min : Max	48 : 94	48 : 94	48 : 92	48 : 94
BMI (kg/m^2)				
Number	65	61	68	194
Mean (SD)	23.43 (2.44)	23.37 (2.62)	23.49 (2.26)	23.43 (2.43)
Min : Max	19.3 : 27.8	18.8 : 27.9	18.8 : 27.7	18.8 : 27.9
Height (cm)				
Number	65	61	68	194
Mean (SD)	167.9 (8.7)	168.9 (8.8)	168.7 (9.2)	168.5 (8.9)
Min : Max	149 : 187	155 : 193	154 : 197	149 : 197

Note : Treatment is either teriflunomide, placebo, or moxifloxacin (Placebo Day 1-11, single dose on Day 12) followed by cholestyramine or charcoal administration

PGM=PRODOPS/HMR1726/TES10852/CSR/REPORT/PGM/dem_dmsc_s_t.sas
OUT=REPORT/OUTPUT/dem_dmsc_s_t_i.rtf (15APR2011 - 9:02)

Source: CSR, Table 7

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary endpoint was the largest time-matched mean difference between teriflunomide and placebo in QTcF on Day 12. The sponsor used a linear fixed-effect model and the result is presented in Table 2. The model included treatment and gender as fixed effects and time-

matched baseline as covariate. The upper limit of the 2-sided 90% CI for teriflunomide treatment group was below 10 ms.

Table 4: Sponsor's results for ΔΔQTcF for Teriflunomide and Moxifloxacin 400 mg on Day 12

		Time-matched mean difference estimate between T1h and T12h				
Change from time-matched baseline[a] in ECG Parameters	Comparison	Theoretical time	N under active	N under placebo	Estimate[b]	2-sided 90% CI
QTc Fridericia (ms)	Teriflunomide vs. Placebo	T1H	56	63	3.21	0.31 6.10
		T2H	56	64	3.26	0.90 5.62
		T3H	56	64	3.46	0.47 6.45
		T4H	56	64	2.67	-0.04 5.38
		T5H	56	64	2.63	0.13 5.13
		T6H	56	64	0.54	-1.87 2.95
		T8H	56	64	1.80	-0.46 4.06
		T12H	56	64	0.95	-1.60 3.51
	Moxifloxacin vs. Placebo	T1H	62	63	8.66	5.84 11.48
		T2H	62	64	9.36	7.06 11.66
		T3H	62	64	13.37	10.46 16.29
		T4H	62	64	12.78	10.14 15.42
		T5H	61	64	9.85	7.41 12.29
		T6H	61	64	8.37	6.01 10.72
		T8H	62	64	8.98	6.78 11.18

		Time-matched mean difference estimate between T1h and T12h				
Change from time-matched baseline[a] in ECG Parameters	Comparison	Theoretical time	N under active	N under placebo	Estimate[b]	2-sided 90% CI
		T12H	62	64	8.56	6.06 11.06

Source: Sponsor's CSR Table 14.2.6.3.1 on page 67/549

4.2.7.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze ΔQTcF effect for moxifloxacin. The analysis results were presented in Table 4. The lower boundary of the 90% CI of the estimate of the mean difference between moxifloxacin and placebo for the change from TM baseline in QTcF across T3h, T4h, and T5h was 10 ms.

Reviewer's Comments: We will provide our independent analysis result in Section 5.2.

4.2.7.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's absolute QTc>500 ms and ΔQTc>60 ms.

4.2.7.3 Safety Analysis

Disorders SOC, with similar frequencies during teriflunomide and placebo treatments (20% to 25%), followed by Nervous System Disorders with a similar frequency between teriflunomide and placebo groups.

Treatment-emergent adverse events that were most frequently reported with teriflunomide during the study were nausea (8.2% of subjects), headache (6.6% of subjects), and diarrhea (4.9% of subjects). Constipation, abdominal pain upper, anxiety, presyncope, and oropharyngeal pain were reported by 2 (3.3%) subjects each n the teriflunomide group. With placebo alone or before moxifloxacin administration, the pattern of TEAEs was similar to that of teriflunomide with respect to gastrointestinal events: nausea, 4.6% of subjects; abdominal pain, 6.2% of subjects; and constipation 9.2% of subjects in the placebo group, and diarrhea 5.9% of subjects in the placebo group of the placebo/moxifloxacin group. Headache and presyncope were reported with similar frequencies in all treatment groups.

Treatment-emergent adverse events were less frequently reported during single-dose moxifloxacin treatment. Only 3 subjects experienced a TEAE; headache, presyncope, and constipation in 1 subject each.

During treatment with teriflunomide (Day 1 to Day 12), 1 subject reported a serious TEAE (urticaria) and discontinued the study. A second subject discontinued the study due to an asymptomatic increase in pancreatic enzymes, which was not considered serious

There were no deaths reported during the study.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

The PK results of teriflunomide are summarized in Table 5 and presented in Figure 2.

Table 5: Teriflunomide Pharmacokinetic Parameters

Pharmacokinetic parameter	Teriflunomide
N	59
C_{max}	30.5 ± 8.32
(µg/mL)	(29.3) [27.3]
t_{max}[a]	4.00
(h)	(0.00 - 23.83)
AUC_{0-24}	627 ± 168
(h•µg/mL)	(604) [26.8]
C_{trough} on Day 12	24.8 ± 8.05
(µg/mL)	(23.5) [32.5]

Tabulated values are Mean ± SD (Geometric Mean) [CV%].

AUC_{0-24} = area under the concentration versus time curve calculated from 0 to 24 hours ; C_{max} = maximum plasma concentration; C_{trough} = plasma concentration observed before administration; N= number of subjects; t_{max} = time of peak drug concentration

a Median (Min-Max)

Source: Sponsor's CSR Table 23 on page 103

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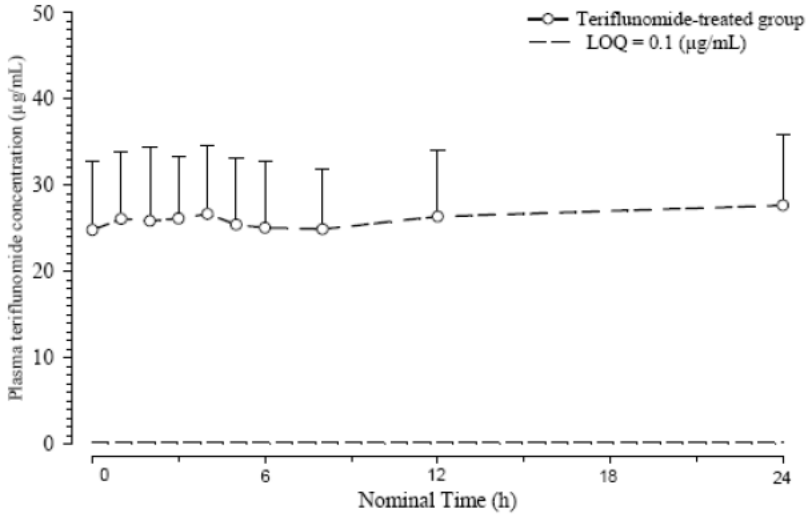
Figure 2: Mean (Standard Deviation) Teriflunomide Plasma Concentration-Time Profile on Day 12 after Repeated Once-daily Oral Administration (N = 59)

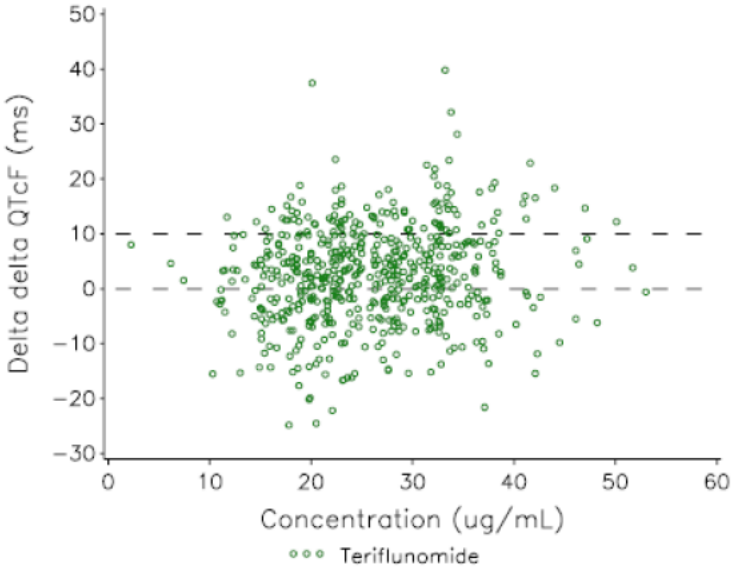


Source: Sponsor's CSR Figure 11 on page 101

4.2.7.4.2 Exposure-Response Analysis

Exposure-response analysis was conducted. A plot of ΔΔQTcF *vs.* terflunomide concentration demonstrated below indicated no evident exposure-response relationship.

Figure 3: Scatter Plot of Double Delta QTcF versus Teriflunomide Concentration



Source: Sponsor's CSR Figure 14 on page 104

Reviewer's Analysis: The reviewer performed independent exposure-response analysis. The results are present in section 5.3.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

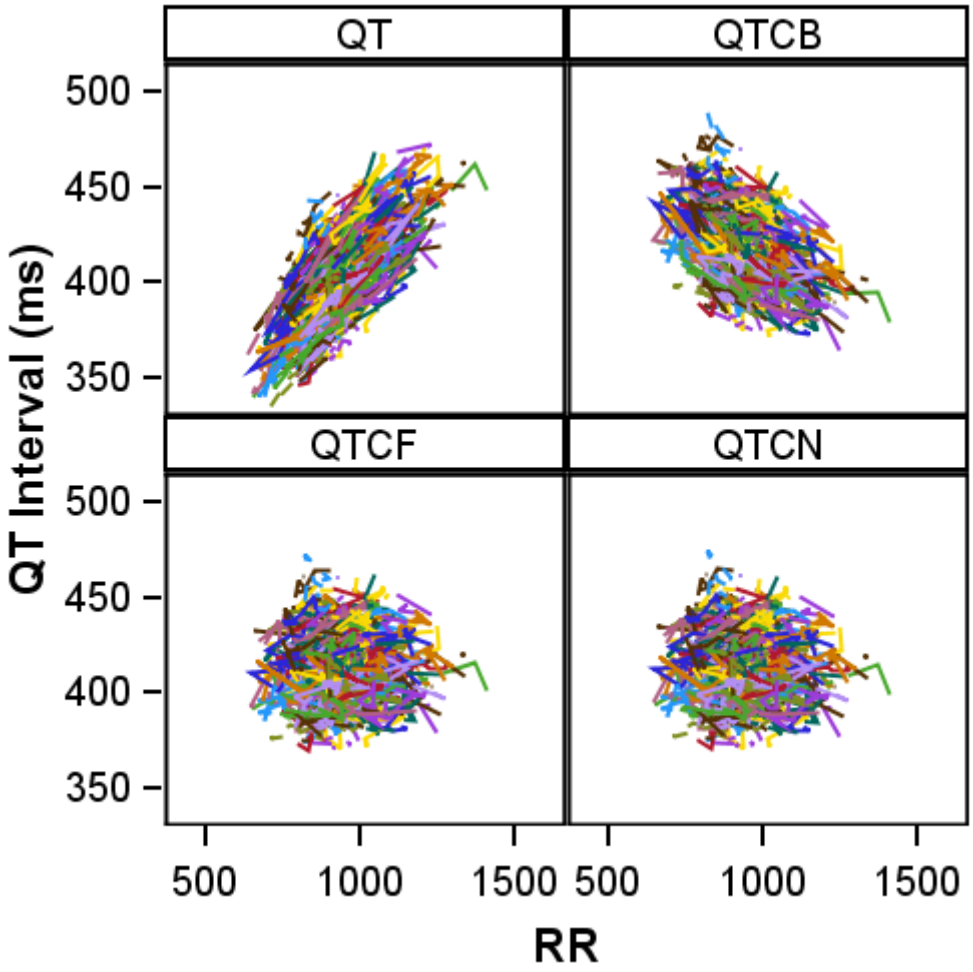
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it appears that QTcF and QTcN are equally better than QTcB. This statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the primary endpoint selected by the sponsor.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcN	
	N	MSSS	N	MSSS	N	MSSS
Moxifloxacin	68	0.0041	68	0.0022	68	0.0019
Placebo	65	0.0042	65	0.0024	65	0.0021
Teriflunomide	61	0.0042	61	0.0030	61	0.0027
All	194	0.0042	194	0.0025	194	0.0023

The QT-RR interval relationship is presented in Figure 4 together with the Bazett's (QTcB), Fridericia (QTcF), and population specific QT correction (QTcN).

Figure 4: QT, QTcB, QTcF and QTcN vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in **Table 7**. The largest upper bound of the 2-sided 90% CI for the mean difference between Teriflunomide and placebo is 6.8 ms.

Table 7: Analysis Results of ΔQTcF and ΔΔQTcF for Teriflunomide and Moxifloxacin 400 mg

		Treatment Group								
		Moxifloxacin					Teriflunomide			
	Placebo	ΔQTc	ΔΔQTc				ΔQTc		ΔΔQTc	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	Adj. 90% CI	N	LS Mean	LS Mean	90% CI
1	-0.4	66	7.8	8.2	(5.3, 11.2)	(4.2, 12.3)	59	2.6	3.0	(-0.1, 6.0)
2	-1.1	63	8.4	9.5	(7.1, 11.9)	(6.3, 12.8)	59	2.2	3.3	(0.9, 5.8)
3	-2.0	63	11.6	13.6	(10.6, 16.7)	(9.5, 17.8)	59	1.7	3.7	(0.7, 6.8)
4	-1.1	63	11.9	13.0	(10.4, 15.7)	(9.4, 16.7)	59	1.6	2.7	(-0.1, 5.4)
5	-0.5	64	9.4	9.9	(7.5, 12.3)	(6.6, 13.2)	59	2.1	2.7	(0.1, 5.2)
6	0.5	65	9.4	8.8	(6.5, 11.2)	(5.6, 12.1)	59	1.0	0.4	(-2.0, 2.9)
8	1.2	66	10.1	8.8	(6.6, 11.0)	(5.8, 11.9)	59	3.0	1.7	(-0.6, 4.0)
12	0.4	65	9.2	8.8	(6.3, 11.3)	(5.4, 12.3)	59	1.2	0.9	(-1.7, 3.5)
24	-1.4	66	6.4	7.9	(5.4, 10.4)	(4.5, 11.3)	56	2.1	3.6	(1.0, 6.2)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

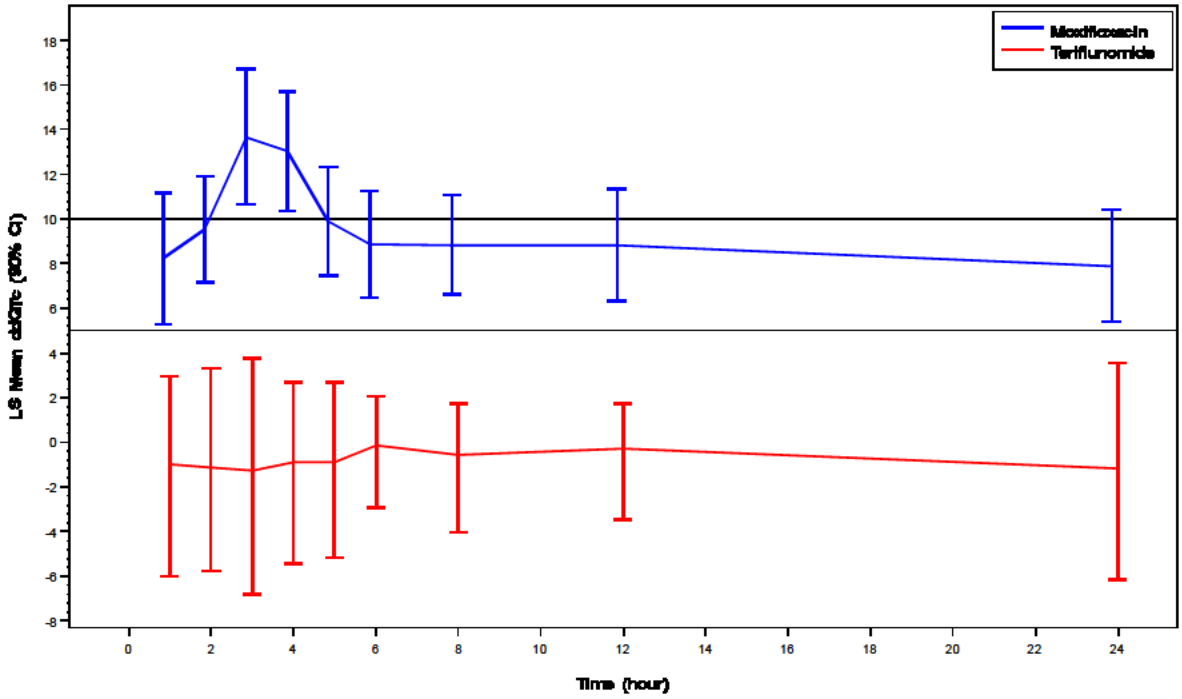
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in **Table 7**. The largest unadjusted 90% lower confidence interval is 10.6 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 9.5 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of ΔΔQTcF Over Time

Figure 5 displays the time profile of ΔΔQTcF for Teriflunomide group and moxifloxacin 400 mg.

Figure 5: Mean and 90% CI ΔΔQTcF Time Course for Teriflunomide and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcF values are ≤450 ms and between 450 ms and 480 ms. No subject's QTcF is above 480 ms.

Table 8: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms
Moxifloxacin	68	58 (85.3%)	10 (14.7%)
Placebo	65	63 (96.9%)	2 (3.1%)
Teriflunomide	59	55 (93.2%)	4 (6.8%)

Table 9 lists the categorical analysis results for ΔQTcF. No subject's change from baseline is above 60 ms.

Table 9: Categorical Analysis of ΔQTcF

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
Moxifloxacin	66	59 (89.4%)	7 (10.6%)
Placebo	65	64 (98.5%)	1 (1.5%)
Teriflunomide	57	55 (96.5%)	2 (3.5%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR interval. The point estimates and the 90% CIs are presented in Table 10. The largest upper bound of the 2-sided 90% CI for the mean difference between Teriflunomide and placebo is 2.9 bpm.

Table 10: Analysis Results of ΔHR and ΔΔHR for Teriflunomide and Moxifloxacin 400 mg

		Treatment Group							
		Moxifloxacin				Teriflunomide			
	Placebo	ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	1.3	66	2.5	1.2	(-0.4, 2.8)	59	2.5	1.2	(-0.4, 2.9)
2	3.2	63	2.8	-0.4	(-2.0, 1.3)	59	3.4	0.2	(-1.5, 2.0)
3	2.2	63	3.2	0.9	(-0.8, 2.7)	59	2.8	0.6	(-1.2, 2.4)
4	1.3	63	1.7	0.4	(-1.1, 1.9)	58	1.7	0.4	(-1.2, 2.0)
5	0.5	64	0.6	0.0	(-1.6, 1.7)	58	0.9	0.4	(-1.3, 2.0)
6	2.3	65	2.2	-0.1	(-2.0, 1.7)	57	2.2	-0.1	(-2.0, 1.8)
8	2.0	66	1.7	-0.3	(-1.9, 1.3)	58	2.3	0.3	(-1.4, 2.0)
12	1.7	65	1.7	-0.1	(-1.7, 1.5)	58	3.0	1.2	(-0.4, 2.9)
24	3.3	62	2.3	-1.0	(-2.9, 0.9)	56	4.3	0.9	(-1.0, 2.9)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% CIs are presented in Table 11. The largest upper bound of the 2-sided 90% CI for the mean difference between teriflunomide and placebo is 0.2 ms. Table 12 presents the categorical analysis of PR. Eight subjects who experienced PR interval greater than 200 ms in teriflunomide treatment groups.

Table 11: Analysis Results of ΔPR and ΔΔPR for Teriflunomide and Moxifloxacin 400 mg

		Treatment Group							
		Moxifloxacin				Teriflunomide			
	Placebo	ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	4.8	66	2.7	-2.1	(-5.0, 0.8)	59	-1.1	-5.9	(-8.9, -3.0)
2	4.3	63	1.2	-3.1	(-5.7, -0.6)	59	0.8	-3.5	(-6.0, -0.9)
3	3.3	63	0.6	-2.7	(-5.2, -0.2)	59	0.7	-2.6	(-5.2, -0.1)
4	2.1	63	-0.1	-2.2	(-4.5, 0.1)	58	-0.9	-3.0	(-5.4, -0.7)
5	1.9	64	-1.4	-3.3	(-5.5, -1.1)	58	-0.4	-2.3	(-4.6, -0.0)
6	2.9	65	-1.6	-4.4	(-6.5, -2.4)	57	-1.2	-4.0	(-6.2, -1.9)
8	1.9	66	-0.8	-2.6	(-4.9, -0.4)	58	-0.2	-2.1	(-4.4, 0.2)
12	2.1	65	-0.0	-2.2	(-4.5, 0.2)	58	-1.2	-3.3	(-5.8, -0.8)
24	3.1	62	1.8	-1.3	(-4.0, 1.5)	56	-1.9	-5.0	(-7.8, -2.2)

Table 12: Categorical Analysis for PR

Treatment Group	Total N	PR < 200 ms	PR >=200 ms
Moxifloxacin	68	67 (98.5%)	1 (1.5%)
Placebo	65	58 (89.2%)	7 (10.8%)
Teriflunomide	59	51 (86.4%)	8 (13.6%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% CIs are presented in **Table 13**. The largest upper bound of the 2-sided 90% CI for the mean difference between teriflunomide and placebo is -0.1 ms. Table 14 presents the categorical analysis of QRS. Three subjects who experienced QRS interval greater than 200 ms in teriflunomide treatment group.

Table 13: Analysis Results of ΔQRS and ΔΔQRS for Teriflunomide and Moxifloxacin 400 mg

		Treatment Group							
		Moxifloxacin				Teriflunomide			
	Placebo	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	0.3	66	0.5	0.1	(-0.8, 1.1)	59	-0.5	-0.9	(-1.9, 0.1)
2	0.4	67	-0.4	-0.8	(-1.7, 0.1)	59	-0.9	-1.3	(-2.2, -0.3)
3	0.3	66	-0.3	-0.6	(-1.6, 0.4)	59	-1.0	-1.2	(-2.2, -0.2)
4	0.4	68	0.1	-0.3	(-1.3, 0.7)	58	-0.6	-1.0	(-2.0, 0.1)
5	0.7	67	0.3	-0.4	(-1.3, 0.5)	58	-0.6	-1.3	(-2.2, -0.3)
6	0.3	67	-0.6	-1.0	(-1.9, -0.0)	57	-0.4	-0.7	(-1.7, 0.3)
8	0.4	68	0.4	0.0	(-0.9, 0.9)	58	-0.7	-1.0	(-2.0, -0.1)
12	0.3	68	-0.6	-0.9	(-1.8, 0.1)	58	0.0	-0.3	(-1.3, 0.7)
24	1.1	66	1.6	0.5	(-0.7, 1.6)	56	-0.7	-1.8	(-2.9, -0.6)

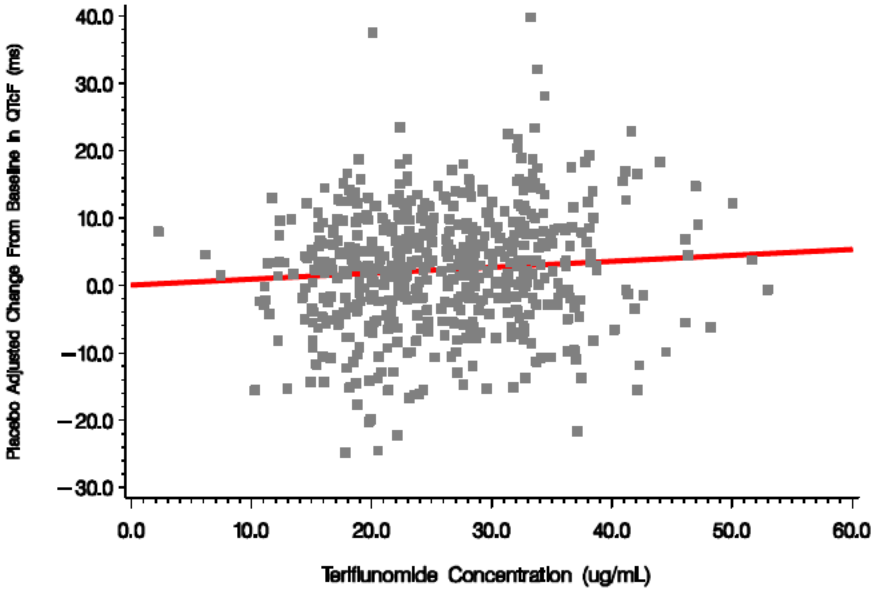
Table 14: Categorical Analysis for QRS

Treatment Group	Total N	QRS < 110 ms	QRS >= 110 ms
Moxifloxacin	68	62 (91.2%)	6 (8.8%)
Placebo	65	57 (87.7%)	8 (12.3%)
Teriflunomide	59	56 (94.9%)	3 (5.1%)

5.3 Clinical Pharmacology Assessments

The relationship between ΔΔQTcF and teriflunomide concentrations is visualized in Figure 6. A shallow uptrend with a slope of 0.06662 (p-value =0.0162) was observed. However, since the effect of intrinsic and extrinsic factors on teriflunomide exposure is insignificant, the positive relationship between ΔΔQTcF and teriflunomide concentrations may not be a clinical concern.

Figure 6: ΔΔQTcF vs. Teriflunomide Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. According to ECG warehouse statistics less than 0.5% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

40% of the subjects had less ECGs.

5.4.3 PR and QRS Interval

Eight subjects had a PR>200 ms at baseline and post baseline increases were never >10% over baseline and PR values did not exceed 220 ms.

Three subjects had a QRS>110 ms, two of them at baseline. None of the post baseline values was >122 ms.

Overall none of the findings reported were clinically relevant.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	14 mg once daily (QD)	
Maximum tolerated dose	In healthy subjects, the maximum repeated doses tested were 70 mg (QD) administered for 3 days followed by 14 mg QD for 8 to 11 days (Study INT6040, 14 subjects and Study INT10563, 26 subjects) or 70 mg QD administered for 9 to 14 days (Study TDR10892, 9 subjects). The main limiting effect was increase in transaminases linked to the duration of treatment at the dose of 70 mg. In the first 2 studies, 2 subjects had increases in transaminases >2 x ULN, reversible and asymptomatic. A dose of 70 mg QD for 9 to 14 days was well tolerated clinically, but asymptomatic, moderate, and reversible increases in transaminases (>1-fold ULN to 6-fold ULN) were observed in all 9 subjects either at the end of treatment (1 subject at D10) or 5 to 15 days after treatment completion during cholestyramine treatment which was given to accelerate the elimination of teriflunomide. In conclusion, in healthy subjects the dose of 70 mg QD for ≥9 days was considered as a maximum tolerated dose (MTD). Thus, a 4-day treatment with 70 mg QD followed by a maintenance dose of 14 mg for 8 days is acceptable.	
Principal adverse events	In healthy subjects, the most common adverse events were in gastrointestinal disorders, investigations (mainly transaminases increases) and nervous system disorders (mainly headache). Reversible and moderate increases in transaminases without increase in bilirubin were observed, mostly after treatment completion during the cholestyramine/activated charcoal period. No relevant abnormalities were observed in vital signs or electrocardiogram (ECG) values in Phase 1 studies.	
Maximum dose tested	**Single dose**	100 mg
	Multiple dose	70 mg QD for 14 days
Exposures achieved at maximum tested dose	**Single dose**	At 100 mg (N = 16): C_{max}: 13.4 µg/mL (17 %CV) AUC_{0-24}: 240.9 (12% CV)
	Multiple dose	At 70 mg QD for 7 days (N = 9) C_{max} = 66.9 µg/mL (25 %CV) AUC_{0-24}= 1360 µg.h/mL (22 %CV) At 70 mg QD for 14 days (N = 3) C_{max} = 113µg/mL (39 %CV) AUC_{0-24} = 2370 µg.h/mL (39%CV)
Range of linear pharmacokinetics	Dose proportionality was observed after 7- and 14-mg single oral doses in healthy subjects and after 7- and 14-mg multiple oral doses in patients with multiple sclerosis (MS). Teriflunomide exposure appears proportional to dose from 7 mg up to 100 mg, the maximal dose.	
Accumulation at steady state	None of the repeated-dose studies in healthy subjects were long enough to assess steady state achievement. The use of a loading dose could only achieve a "pseudo-steady state" with plasma concentrations in the range steady state observed in patients with MS after a few months. However, a population pharmacokinetic (PopPK) analysis of teriflunomide in healthy subjects and patients with MS showed that plasma concentrations of teriflunomide accumulate over time following multiple oral doses of teriflunomide. Based on post-hoc individual predicted pharmacokinetic (PK) parameters from the PopPK model, the estimated AUC_{0-24} accumulation ratio was 30.3 for 7 mg (median, 5th - 95th percentile: 25.8, 12.0 - 62.9) and 33.6 for 14 mg (median, 5th - 95th percentile: 28.1, 11.8 - 73.7).	

Metabolites	Following a 70 mg single oral ^{14}C-teriflunomide administration in healthy subjects, teriflunomide was moderately metabolized. Unchanged teriflunomide was the only component detected in plasma. In feces, unchanged teriflunomide was the predominant component detected (37.5% of administered dose) with at least 3 metabolites (<2%). In urine, in addition to a small amount of unchanged teriflunomide (≤1.3%), at least 9 metabolites were detected, where 4-TFMA (4-trifluoro-methylaniline) oxanilic acid was the predominant urinary metabolite (18.1%). All others accounted for <3% of the administered dose. 4-TFMA, 4-TFMA glycolanilide (previously detected during the in vitro metabolism in microsomes) and A813226 (b) (4) a minor metabolite) were not detected in plasma or excreta. Following multiple oral doses of 14-mg teriflunomide QD for 36 weeks to patients with MS, low 4-TFMA concentrations were observed and ranged from 0.5 to 5.3 ng/mL (which is up to 17 000 times lower than teriflunomide concentrations). All metabolites detected in human samples were observed in at least 1 animal species. The primary biotransformation pathway for teriflunomide was hydrolysis, with oxidation being a minor pathway. Secondary pathways involved oxidation, N-acetylation, and sulfate conjugation.	
Absorption	Absolute bioavailability[a]	~100%
	t_{max}[b] (steady-state, 14mg)	Median 1.17 h 5th - 95th percentile: 0.828 - 6.25 h
Distribution	Vd (IV)	11 L (7%CV)
	% bound	99.7% (0.01%CV)
Elimination	Route	Following a single oral 70-mg dose of ^{14}C-teriflunomide, radioactivity was excreted in feces (37.5%, of which 35.7% was unchanged drug) and in urine (22.6%, of which ≤1.3% was changed drug) with total mean recovery of 60.1% of the administered dose in samples collected up to 21 days postdose. Administration of cholestyramine increased the overall mean recovery of radioactivity to 83.2% of the administered dose over 28 days (61.3% in feces and 21.9% in urine). Overall, the predominant clearance pathway for teriflunomide was biliary excretion of parent compound along with direct gastrointestinal secretion, representing approximately 2/3 of the total clearance of the molecule. Metabolic clearance represented the remaining one third of total clearance. Renal clearance represented ≤1.3% of the unchanged dose (over 28 days).
	$t_{½}$[b] (steady-state, 14mg)	Median 466 h (~19 days) 5th – 95th percentile: 192 - 1250 h
	CL (IV)	30.5 mL/h (25%CV)
Intrinsic factors	Age[b]	C_{max} and AUC_{0-24}: increase of ~5% for patients older than 44 years (75th percentile) compared to patients younger than 31 years of age (25th percentile) for both doses
	Sex[b]	C_{max} and AUC_{0-24}: increase of 30-31% (7 mg) and 17% (14 mg) for women versus men
	Body weight[b]	C_{max} and AUC_{0-24}: increase of 35% (7 mg) to 26-27% (14 mg) for patients weighing less than 59.5 kg (25th percentile) compared to patients weighing more than 79.8 kg (75th percentile)

	Race[b]	C_{max} and AUC_{0-24}: Increase of 5% and 26% for 7 mg and 14 mg doses, respectively, in non-Caucasians as compared to Caucasians (96% of population).
	Hepatic and renal impairment	There is no significant difference in teriflunomide exposure with mild and moderate hepatic impairment, as well as severe renal impairment.
	Acetylator status	Subjects' acetylator statuses has a minimal effect on the pharmacokinetics of teriflunomide after oral administration of teriflunomide
Extrinsic factors	Drug interactions	See table below.
	Food effects	A high-fat breakfast produces a small and statistically significant decrease in C_{max} (18%) and a small delay in t_{max} (~3 hours), therefore food is judged to have no clinically relevant effects on the pharmacokinetics of teriflunomide
Expected high clinical exposure scenario	Among the sources of intrinsic variability identified, the effects remained limited (≤31% change in AUC_{0-24}). In addition, no drug-drug interaction leading to increase in teriflunomide plasma concentration is expected. The drug is moderately metabolized, and no single CYP has been identified as the primary enzyme responsible for teriflunomide metabolism. The dose proposed in the protocol TES10852 was 70 mg QD for 4 days followed by 14 mg QD for 8 days. The loading dose of 70 mg QD was given to reach steady state more rapidly. Steady state mean concentrations of teriflunomide of 30.5 µg/mL [minimum-maximum: 12.3-53 µg/mL] have been reached and were within the range of exposure seen in patients. No supratherapeutic dose was investigated in TES10852 due to the increased risk of transaminases increase after a longer exposure at the dose of 70 mg.	

a Based on cross-study comparison (Studies 1001 and 1024)
b Based on population pharmacokinetic analysis in healthy subjects and MS patients (POH0290)

Drug-drug interactions

Effect of other drugs on teriflunomide

Mechanism	Interacting drug (dose)	Substrate (dose)	Substrate ratio (90%CI) [a]	
			C_{max}	AUC
CYP/transporters	Rifampicin (600 mg QD for 22 days)	Teriflunomide (70 mg SD on Day 8)	1.17 (1.11, 1.22)	0.61 (0.55, 0.67)

Effect of teriflunomide on other drugs

Mechanism	Interacting drug (dose)	Substrate (dose)	Substrate ratio (90%CI) [a]	
			C_{max}	AUC
CYP2C8	Teriflunomide (70 mg QD for 4 days then 14 mg QD for 8 days)	Repaglinide (0.25 mg on Day 12)	1.64 (1.44, 1.87)	2.30 (2.06, 2.56)
CYP3A	Teriflunomide (70 mg QD for 3 days then 14 mg QD for 11 days)	Midazolam (2 mg SD on Day 14)	1.13 (1.00, 1.28)	1.27 (1.15, 1.42)
Oral contraceptives	Teriflunomide (70 mg QD for 4 days then 14 mg QD for 10 days)	Ethinylestradiol (0.03 mg QD for 21 days)	1.58 (1.48, 1.68)	1.54[b] (1.46, 1.63)
		Levonorgestrel (0.15 mg QD for 21 days)	1.33 (1.24, 1.42)	1.41[b] (1.34, 1.49)
CYP1A2	Teriflunomide (70 mg QD for 3 days then 14 mg QD for 9 days)	Caffeine (100 mg SD on Day 12)	0.82 (0.77, 0.87]	0.45 (0.40, 0.50)
		Paraxanthine (100 mg SD on Day 12)	1.06 (1.03, 1.10)	0.58 (0.55, 0.62)
CYP2B6	Teriflunomide (70 mg QD for 4 days then 14 mg QD for 8 days)	Buproprion (150 mg SD on Day 12)	1.03 (0.94, 1.12)	0.93 (0.87, 0.99]
CYP2C9	Teriflunomide (70 mg QD for 3 days then 14 mg QD for 8 days)	S-warfarin (25 mg SD on Day 5)	1.08 (1.00, 1.16)	1.12 (1.08, 1.15)
		R-warfarin (25 mg SD on Day 5)	1.10 (1.04, 1.17)	1.00 (0.95, 1.05)
CYP2C19	Teriflunomide (70 mg QD for 4 days then 14 mg QD for 8 days)	Omeprazole (20 mg SD on Day 12)	0.93 (0.82, 1.05)	0.90 (0.82, 0.98)
CYP2D6	Teriflunomide (70 mg QD for 4 days then 14 mg QD for 8 days)	Metoprolol (100 mg SD on Day 12)	1.06 (0.97, 1.17)	0.99 (0.93, 1.06)

QD=once daily; SD=single dose.

a Coadministered treatment)/(reference treatment alone) ratio

b $AUC_{0\text{-}24}$

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/s/

MOH JEE NG
10/18/2011

JOANNE ZHANG
10/18/2011

FANG LI
10/25/2011

HAO ZHU
10/25/2011

MONICA L FISZMAN
10/26/2011

NORMAN L STOCKBRIDGE
10/27/2011