U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-462 / S-033
Drug Name:	Pemetrexed (Alimta®)
Indication(s):	Pediatric patients with solid tumors
Applicant:	Eli Lilly and Company
Date(s):	Submission Date: September 17, 2010
	PDUFA Date: March 17, 2010
	Review Completion Date: December 17, 2010
Review Priority:	Priority (pediatric)
Biometrics Division:	Division of Biometrics V (HFD-711)
Statistical Reviewer:	Lijun Zhang, Ph.D.
Concurring Reviewers:	Shenghui Tang, Ph.D., Team Leader
	Rajeshwari Sridhara, Ph.D., Director
Medical Division:	Division of Drug Oncology Products (HFD-150)
Clinical Team:	Amy Mckee, M.D., Medical Reviewer
	John Johnson, M.D., Medical Team Leader
Project Manager:	Diane Hanner

Keywords: pediatric written request, recurrent solid tumor, sample size

Table of Contents

List of Tables

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The current submission of pemetrexed (ALIMTA®) is to fulfill the Pediatric Written Request (PWR) issued by the FDA on October 2001 and subsequently amended on 3 July 2002, 7 May 2004, 16 April 2007 and 2 July 2010.

Per the PWR, the current submission includes results from two pediatric studies: a dose-finding Phase 1 study (H2E-US-JMFC), and a Phase 2 single-arm efficacy and safety study (H2E-MC-JMHW). The applicant only seeks pediatric exclusivity rather than any pediatric indication based on this application.

Study H2E-US-JMFC determined the maximum tolerated dose (MTD) as 1910 mg/m^2 (or 60mg/kg if patient <12 months old) as a 10 minute IV infusion once every 21 days in children and adolescents with recurrent solid tumors. Dose-limiting toxicities (DLTs) were neutropenia and rash. No objective antitumor responses were observed. Pharmacokinetic evaluation is deferred to clinical pharmacology review.

Study H2E-MC-JMHW evaluated efficacy and safety of pemetrexed in pediatric patients. No objective responses were observed. The number of patients enrolled in this study has met the requirement specified in the PWR. This submission fulfilled the Pediatric Written Request from a statistical perspective.

Based on the current application the Pediatric Review Committee determined that the applicant met the conditions in the Written Request and pediatric exclusivity has been granted on December 3, 2010.

1.2 Brief Overview of Clinical Studies

This application is based on two pediatric studies – one Phase 1 study (H2E-US-JMFC) and one Phase 2 study (H2E-MC-JMHW). Both studies were conducted by the Children's Cancer Group. For simplicity, the last 4 characters of each study ID will be used to represent each of these two studies throughout the whole review.

Study JMFC was a dose-finding and pharmacokinetic Phase 1 study of pemetrexed in patients (age from 1 to 21) with recurrent solid tumors. This study was opened in 14 centers in the United States and Canada. Out of 33 patients enrolled, 32 patients have been treated. The objectives of the study were to establish MTD, DLTs, and pharmacokinetics of pemetrexed in the pediatric patient population. The study was conducted from 06 April 2004 to 02 March 2006.

Study JMHW was a Phase 2 study evaluating efficacy and safety of pemetrexed in pediatric patients (age from 3 to 23) with recurrent or refractory solid tumors including osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma / supratentorial PNET, or non-brainstem high-grade glioma. This study was conducted in the United States and Canada, from 25 September 2007 to 03 February 2010. Seventy-two patients enrolled have been treated at the MTD dose (1910 mg/m^2 or 60mg/kg if patient < 12 months old as a 10 minute intravenous infusion once every 21 days) of pemetrexed

as determined in the Phase 1 JMFC study. Patients could remain on therapy up to a maximum of 17 cycles. The study used a two-stage design within each tumor type. The primary efficacy endpoint was response rate. Per the Written Request, at least ten pediatric patients in each of the following tumors have been enrolled: osteosarcoma, Ewing sarcoma/peripheral PNET, neuroblastoma, while at least nine patients have been enrolled in a rhabdomyosarcoma tumor stratum. This Phase 2 study has met the sample size requirement.

1.3 Statistical Issues and Findings

There are no statistical issues identified for this application. No objective responses were observed from either study.

2. INTRODUCTION

2.1 Overview

Pemetrexed (Alimta®, LY231514) is a pyrrolopyrimidine-based antifolate cytotoxic drug. Pemetrexed was approved in 2004 for the treatment of mesothelioma in combination with cisplatin. Subsequently, pemetrexed (as a single agent) received initially an accelerated approval for patients with previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC) on 19 August 2004. Pemetrexed was then approved in combination with cisplatin as initial chemotherapy in advanced NSCLC (29 September 2008) and as a single-agent maintenance therapy in advanced nonsquamous NSCLC (07 July 2009).

The Pediatric Written Request was issued by the FDA on 5 October 2001 and subsequently amended on 3 July 2002, 7 May 2004, 16 April 2007 and 2 July 2010. PWR requested reports of the two studies to be submitted by 15 October 2010. The applicant submitted the NDA supplement containing the reports of the requested studies on 17 September 2010.

2.2 Data Sources

Electronic submission and datasets are located in \\cdsesub1\EVSPROD\NDA021462\0065 .

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This application is based on two pediatric studies – a Phase 1 study (JMFC) and a Phase 2 study (JMHW). No objective response was observed in a total of 104 treated pediatric patients with various types of solid tumor in the two studies.

3.1.1 Study JMHW

Study JMHW is a Phase 2, multicenter, open-label, single-arm study of pemetrexed in children and adolescents with a variety of recurrent or refractory solid tumors. The primary objective of this study was to estimate the response rates in pediatric patients with relapsed or refractory osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET, or non-brain stem high-grade glioma and to further define and describe the toxicities of pemetrexed.

Study Design

In this single-arm pemetrexed study, patients were to be treated at the MTD dose of pemetrexed as determined in the Phase 1 study, i.e., 1910 mg/m^2 (or 60 mg/kg if patient <12 months old) as a 10-minute IV infusion once every 21 days, for a maximum of 17 cycles, in combination with dexamethasone, vitamin B12, and multivitamin.

The primary endpoint of this study was response rate. A two-stage design was used, with an initial enrollment of 10 patients within each tumor type (Table 1). Pemetrexed would not be further evaluated in a tumor type if the true response rate is ≤ 5%. With the rule described in Table 1, the design would have 88% power to detect a true response rate of 25% with a type I error rate of 0.07.

Table 1. Study Design for Each Tumor Type, Study JMHW

Stages	Cumulative Number of Responses (CR or PR)	Decision
Stage 1: Enter 10 patients	0	Terminate the trial: agent ineffective
	1 or more	Inconclusive result, continue trial (proceed to stage 2)
Stage 2: Enter 10 additional patients	2 or less	Terminate the trial: agent ineffective
	3 or more	Terminate the trial: agent effective

The primary efficacy analysis was to estimate the objective response rate in each tumor stratum, within 6 treatment cycles according to modified guidelines of RECIST criteria, except for brain tumors. For brain tumors, response criteria were assessed based on the product of the longest diameter and its longest perpendicular diameter of the tumor. All patients that received at least 1 dose of study drug and who had sufficient information were categorized as having a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). All other patients have been considered non-responders.

Sample Size Consideration

The study used a two stage design. According to the study design and PWR, at least 9 or 10 patients and a maximum of 20 patients were to be enrolled for each tumor stratum. Out of 75 patients who entered the study (i.e., signed the consent documents), 72 patients were enrolled and received at least 1 dose of study drug. Forty-one patients were enrolled in the tumor categories listed in the PWR. Table 2 shows the number of patients treated with at least one dose of pemetrexed within each tumor stratum by country.

Table 2. Distribution of Treated Patients by Tumor Type and Country, Study JMHW

Tumor Stratum	Institution Country		Overall
	USA	Canada	
Osteosarcoma	7	3	10
Ewing Sarcoma/Peripheral PNET	7	4	11
Rhabdomyosarcoma	8	1	9
Neuroblastoma (measurable disease)	5	0	5
Neuroblastoma (MIBG + evaluable)	5	1	6
Ependymoma	9	1	10
Medulloblastoma / Supratentorial PNET	10	1	11
Non-Brainstem High Grade Glioma	10	0	10
Overall	61	11	72

Note: Country is for the institution, not the patient's residency

Reviewer's Comment:

Sample size requirement for the Phase 2 study was outlined in the PWR as "*Phase 2: Enrollment of at least 10 pediatric patients in each of the following disease strata: osteosarcoma, Ewing sarcoma/peripheral PNET, and neuroblastoma. At least nine patients should be enrolled in a rhabdomyosarcoma stratum.*"

Neuroblastoma stratum included two subtypes, measurable disease and MIBG+ evaluable disease, with a total of 11 patients enrolled and treated. Overall, the number of patients enrolled in each stratum has met the requirement specified in the PWR. In addition, the study enrolled more tumor categories than those listed in the PWR.

Study Results

Summary of demographics and baseline characteristics in the treated population are listed in Tables 3 and 4. Forty males and thirty-two females were enrolled and treated. Of those patients 48 were Caucasian, 14 were Black, and 10 were other. Median age was 11.5 years (range from 3-23). Forty-eight patients (66.7%) had Karnofsky Performance Score of 90 or Lansky Play Score of at least 90.

The best overall tumor response by tumor stratum is summarized in Table 5. None of the 72 treated patients had a CR or PR. Five patients had a best overall tumor response of SD and have received at least 4 cycles of treatment. Four patients were not evaluable for response assessment.

Table 3. Patient Demographic Characteristics at Baseline, Study JMHW

Parameter		Osteo-sarcoma (N=10)	Ewing Sarcoma/ Peripheral PNET (N=11)	Rhabdo-myosarcoma (N=9)	Neuro-blastoma (measurable disease) (N=5)	Neuro-blastoma (MIBG + evaluable) (N=6)	Ependymoma (N=10)	Medulloblastoma / Supratentorial PNET (N=11)	Non-Brainstem High-Grade Glioma (N=10)	Total (N=72)
Gender [n (%)]										
	Number of Patients	10	11	9	5	6	10	11	10	72
	Male	6 (60%)	3 (27.27%)	3 (33.33%)	4 (80%)	5 (83.33%)	7 (70%)	7 (63.64%)	5 (50%)	40 (55.56%)
	Female	4 (40%)	8 (72.73%)	6 (66.67%)	1 (20%)	1 (16.67%)	3 (30%)	4 (36.36%)	5 (50%)	32 (44.44%)
Age (Years)										
	Number of Patients	10	11	9	5	6	10	11	10	72
	Mean	14.94	18.24	8.74	6.23	9.62	8.42	12.00	12.75	11.96
	SD	4.28	3.35	4.96	2.98	5.38	4.59	7.13	5.15	5.97
	Median	13.93	19.18	8.22	4.87	8.41	7.45	9.88	12.30	11.52
	Minimum	7.98	12.33	3.05	3.92	4.51	3.41	3.68	4.53	3.05
	Maximum	21.46	22.46	16.73	11.35	18.16	17.84	23.46	19.21	23.46
Weight (Kg)										
	Number of Patients	10	11	9	5	6	10	11	10	72
	Mean	56.42	67.14	32.38	21.16	30.85	43.39	38.29	44.72	44.27
	SD	24.12	32.39	15.94	6.15	18.60	33.19	24.58	20.86	27.11
	Median	59.40	57.50	31.00	21.30	26.65	29.00	29.30	38.30	36.25
	Minimum	20.10	28.80	9.40	12.70	15.10	13.30	10.90	16.80	9.40
	Maximum	89.70	119.40	55.60	30.00	63.00	107.50	89.90	73.40	119.40
BSA (m^2)										
	Number of Patients	10	11	9	5	6	10	11	10	72
	Mean	1.56	1.72	1.04	0.81	1.04	1.10	1.18	1.34	1.27
	SD	0.44	0.49	0.37	0.17	0.42	0.50	0.52	0.43	0.50
	Median	1.63	1.63	1.07	0.80	0.97	0.93	1.01	1.23	1.20
	Minimum	0.82	1.05	0.48	0.59	0.66	0.59	0.52	0.69	0.48
	Maximum	2.12	2.47	1.55	1.06	1.72	2.06	2.15	1.91	2.47
Race [n (%)]										
	Number of Patients	10	11	9	5	6	10	11	10	72
	American Indian or Alaska Native	0 (0%)	0 (0%)	2 (22.22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2.78%)
	Asian	0 (0%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	2 (2.78%)
	Black or African American	4 (40%)	0 (0%)	0 (0%)	2 (40%)	1 (16.67%)	1 (10%)	3 (27.27%)	3 (30%)	14 (19.44%)
	White	4 (40%)	8 (72.73%)	7 (77.78%)	2 (40%)	4 (66.67%)	9 (90%)	8 (72.73%)	6 (60%)	48 (66.67%)
	Other	1 (10%)	1 (9.09%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (4.17%)
	Unknown	1 (10%)	1 (9.09%)	0 (0%)	0 (0%)	1 (16.67%)	0 (0%)	0 (0%)	0 (0%)	3 (4.17%)

Abbreviations: kg = kilograms; m = meters; MIBG+ = metaiodobenzylguanidine positive; N = total treated patients in each column; n = number of patients in each category; ; PNET = primitive neuroectodermal tumors; SD = standard deviation.

Source: Table JMHW 11.1 in CSR

Table 4. Summary of Karnofsky Performance Score or Lansky Play Score at Baseline, Study JMHW

Parameter	Osteo-sarcoma (N=10)		Ewing Sarcoma/ Peripheral PNET (N=11)		Rhabdo-myosarcoma (N=9)		Neuro-blastoma (measurable disease) (N=5)		Neuro-blastoma (MIBG + evaluable) (N=6)		Ependymoma (N=10)		Medulloblastoma / Supratentorial PNET (N=11)		Non-Brainstem High-Grade Glioma (N=10)		Total (N=72)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Karnofsky Performance Score																		
Number of Patients	4		7		0		0		1		1		3		2		18	
100	0	0	2	18.18	0	0	0	0	0	0	1	10.00	0	0	0	0	3	4.17
90	3	30.00	3	27.27	0	0	0	0	1	16.67	0	0	1	9.09	1	10.00	9	12.50
80	0	0	1	9.09	0	0	0	0	0	0	0	0	0	0	1	10.00	2	2.78
70	0	0	1	9.09	0	0	0	0	0	0	0	0	1	9.09	0	0	2	2.78
50	1	10.00	0	0	0	0	0	0	0	0	0	0	1	9.09	0	0	2	2.78
Lansky Play Score																		
Number of Patients	6		4		9		5		5		9		8		8		54	
100	1	10.00	1	9.09	3	33.33	4	80.00	2	33.33	2	20.00	2	18.18	3	30.00	18	25.00
90	1	10.00	3	27.27	3	33.33	1	20.00	1	16.67	2	20.00	3	27.27	4	40.00	18	25.00
80	2	20.00	0	0	2	22.22	0	0	2	33.33	3	30.00	2	18.18	0	0	11	15.28
70	0	0	0	0	0	0	0	0	0	0	1	10.00	0	0	1	10.00	2	2.78
60	1	10.00	0	0	1	11.11	0	0	0	0	1	10.00	1	9.09	0	0	4	5.56
50	1	10.00	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.39

Source: Table JMHW 11.2 in CSR

Table 5. Summary of Best Overall Tumor Response, Study JMHW

Overall Response	Osteo-sarcoma (N=10)	Ewing Sarcoma/ Peripheral PNET (N=11)	Rhabdo-myosarcoma (N=9)	Neuroblastoma (measurable disease) (N=5)	Neuroblastoma (MIBG + evaluable) (N=6)	Ependymoma (N=10)	Medulloblastoma / Supratentorial PNET (N=11)	Non-Brainstem High-Grade Glioma (N=10)	Total (N=72)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Complete Response	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Partial Response	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stable Disease	1 (10%)	1(9.1%)	0 (0%)	0 (0%)	1 (17%)	1 (10%)	1(9.1%)	0 (0%)	5 (6.9%)
95% CI	0.3%-45%	0.2%-41%	0%-34%	0%-52%	0.4%-64%	0.3%-45%	0.2%-41%	0%-31%	2.3%-15%
Progressive Disease	9 (90%)	6 (55%)	8 (89%)	5 (100%)	4 (67%)	9 (90%)	7 (64%)	9 (90%)	57 (79%)
95% CI	55%-99.7%	23%-83%	52%-99.7%	48%-100%	22%-96%	55%-99.7%	31%-89%	55%-99.7%	68%-88%
Patients not evaluable	0 (0%)	1 (9.1%)	1 (11%)	0 (0%)	1 (17%)	0 (0%)	1 (9.1%)	0 (0%)	4 (5.6%)
Non-responders[a]	0 (0%)	3 (27%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (18%)	1 (10%)	6 (8.3%)
Number of Responders (CR+PR)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of Clinical Benefit (CR+PR+SD)	1 (10%)	1(9.09%)	0 (0%)	0 (0%)	1 (17%)	1 (10%)	1(9.09%)	0 (0%)	5 (6.9%)
95% CI[b]	0.3%-45%	0.2%-41%	0%-34%	0%-52%	0.4%-64%	0.3%-45%	0.2%-41%	0%-31%	2.3%-15%

Abbreviations: CI=confidence interval; CR=complete response; N=total treated patients in each column; n = number of patients in each category; MIBG+ = metaiodobenzylguanidine positive; PNET = primitive neuroectodermal tumors; PR=partial response; RECIST = Response Evaluation Criteria in Solid Tumor; SD=stable disease.

[a] Patients without sufficient information to assess for RECIST response: considered non-responders for statistical analyses.

[b] Exact conditional marginal confidence interval.

Source: Table JMHW 11.3 in CSR

Note: Patients not evaluable (n=4) included two ineligible patients and two eligible but not evaluable patients due to either pre-therapy scans completed more than 2 weeks prior to enrolling or incompleteness of first dose and no follow-up scans.

Non-responders (n=6) included six patients who had no sufficient information to be RECIST classifiable.

Reviewer's Comment:

Pemetrexed therapy did not demonstrate activity/efficacy as per protocol specification.

3.1.2 Study JMFC

Study JMFC was a Phase 1 multicenter, open-label, dose-escalation and pharmacokinetic study of pemetrexed in children and adolescents with recurrent solid tumors. A standard 3+3 design was used for dose escalations. Cohorts of 3 to 6 patients were enrolled at dose levels of 400, 520, 670, 870, 1130, 1470, 1910, and 2480 mg/m^2. For further details regarding the pharmacokinetic study of pemetrexed in children and adolescents with recurrent solid tumors, please refer to the clinical pharmacology review by Dr. Fourie Zirkelbach.

In JMFC, a total of 33 patients with refractory solid tumors were enrolled, with 21 males and 12 females (Table 6). The median age of the patients treated was 12 years with a range of 1 to 21 years. Majority of the patients were white (n=23, 69.7%).

Table 7 provides a summary of the baseline disease characteristics in all enrolled patients. The majority of the carcinomas were located locally (16 patients, 48.5%), and the most common diagnosis was osteosarcoma (12 patients, 36.4%).

Efficacy was not a primary endpoint of this Phase 1 study. Table 8 presents a summary of best overall tumor responses in patients treated by the study drug using RECIST criteria. There were no CRs or PRs. Four patients had best overall tumor response of SD and received 4 or more cycles of pemetrexed therapy.

Table 6. Patient Demographic Characteristics at Baseline, Study JMFC

Characteristic	Total N=33
Age	
N	33
Median (minimum, maximum)	12.0 (1.0, 21.0)
Sex, n (%)	
Male	21 (63.6)
Female	12 (36.4)
Race, n (%)	
White	23 (69.7)
Black	3 (9.1)
Filipino	2 (6.1)
Laotian	1 (3.0)
Other Asian	1 (3.0)
Other White and Asian	1 (3.0)
Unknown	2 (6.1)
Ethnicity, n (%)	
Non-Spanish or non-Hispanic	28 (84.8)
Spanish or Hispanic	2 (6.1)
Mexican	1 (3.0)
South or Central American	1 (3.0)
Unknown	1 (3.0)
Karnofsky Score	
N	23
Mean (STD)	87.0 (10.20)
Median (minimum, maximum)	90 (60, 100)
Lansky Score	
N	10
Mean (STD)	92.0 (6.32)
Median (minimum, maximum)	90 (80, 100)

Abbreviations: N = number of patients in population; n = number of observed patients; STD = standard deviation.

Source: Table JMFC 6.1 in CSR

Table 7. Patient Baseline Disease Characteristics, Study JMFC

Parameter		Total N = 33 n (%)
Disease Stage at Diagnosis		
Local		16 (48.5)
Distant		7 (21.2)
Regional		2 (6.1)
Unknown		8 (24.2)
Tissue Diagnosis and Disease		
Bone	All	14
	Osteosarcoma	11
	Ewing sarcoma	3
Brain	All	8
	Brain stem tumor (glioma malignant)	3
	Anaplastic astrocytoma	1
	Ependymoma	1
	Glioblastoma multiformae	1
	Glioma	1
	Medullablastoma	1
Renal	All	3
	Renal cell	2
	Wilm's tumor	1
Hepatic	Hepatoblastoma	2
Other	Gastrointestinal stroma tumor	1
	Liposarcoma	1
	Lung osteosarcoma	1
	Nasopharyngeal adenocarcinoma	1
	Pilocytic astrocytoma	1
	Rhabdomyosarcoma	1

Abbreviations: N = number of patients in population; n = number of observed patients.

Source: Table JMFC 6.2 in CSR

Table 8. Summary of Best Overall Tumor Response, Study JMFC

Best Overall Tumor Response	Total (N = 32) n (%)
Response [a]	0 (0.0)
Clinical Benefit Response [b]	5 (15.6)
Best Overall Response [c]	
Complete Response	0 (0.0)
Partial Response	0 (0.0)
Stable Disease	5 (15.6)
Progressive Disease	24 (75.0)
Not Available	3 (9.4)

Note: The total excludes Patient ID # 742406 who withdrew consent prior to administration of the study drug.

Abbreviations: ID = identification; N = number of patients in population; n = number of observed patients.

[a] Including complete response and partial response.

[b] Including complete response, partial response, and stable disease.

[c] Using Response Evaluation Criteria in Solid Tumor (RECIST).

Source: Table JMFC 7.4 in CSR

3.2 Evaluation of Safety

Please refer to clinical review of this application for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Both studies submitted in this application were small pediatric studies. No objective responses were observed in either study. Therefore, gender, race and age specific subgroups do not show any differences in this case.

4.2 Other Special/Subgroup Populations

No other special populations have been identified.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There are no statistical issues identified in this application.

5.2 Conclusions and Recommendations

In response to a PWR, the applicant submitted results from two pediatric studies – a dose finding Phase 1 study of pemetrexed (JMFC), and a Phase 2 single-arm study (JMHW) evaluating efficacy and safety of pemetrexed. The applicant seeks only pediatric exclusivity rather than any pediatric indication based on this application. No objective responses were observed among all the 104 pemetrexed treated pediatric patients with various types of solid tumor in the two studies. The number of patients enrolled in each study has met the requirement specified in the PWR.

From a statistical perspective, the Phase 1 and Phase 2 studies in this submission have fulfilled the PWR. Based on the current application the Pediatric Review Committee determined that the applicant met the conditions in the PWR and pediatric exclusivity has been granted on December 3, 2010.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Lijun Zhang, Ph.D.
Date: December 17, 2010

Concurring Reviewers: Shenghui Tang, Ph.D.
Team Leader

Rajeshwari Sridhara, Ph.D.
Director, Division of Biometrics V

cc:
HFD-150/Ms. Diane Hanner
HFD-150/Dr. Amy McKee
HFD-150/Dr. John Johnson
HFD-150/Dr. Robert Justice
HFD-711/Dr. Shenghui Tang
HFD-711/Dr. Rajeshwari Sridhara
HFD-700/Ms. Lillian Patrician

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

/s/

LIJUN ZHANG
12/17/2010

SHENGHUI TANG
12/17/2010

RAJESHWARI SRIDHARA
12/17/2010