CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-462/S-015

Trade Name: Alimta Injection, Powder, Lyophilized, For Solution for Intravenous use 100 mg and 500 mg vials

Generic Name: pemetrexed disodium

Sponsor: Eli Lilly and Company

Approval Date: September 26, 2008

Indications: Provides for the use of Alimta (pemetrexed disodium) Injection, Powder, Lyophilized, For Solution for Intravenous use 100 mg and 500 mg vials for the following indications: (i) Non-Small Cell Lung Cancer - Combination with Cisplatin; and (ii) Non-Small Cell Lung Cancer - Single Agent

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-462/S-015

Eli Lilly and Company
Attention: Colleen Mockbee, R.Ph., RAC
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Mockbee:

Please refer to your supplemental new drug application dated August 27, 2007, received August 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alimta® (pemetrexed disodium) Injection, Powder, Lyophilized, For Solution for Intravenous use 100 mg and 500 mg vials.

Please also refer to your submission dated June 24, 2008, received June 24, 2008, which extended the due date for this application to September 28, 2008.

We acknowledge receipt of your submissions dated September 20, October 18, 30, November 19, 2007; February 8, March 19, June 24, and September 11, 16, 18, 19, 20, 22, 23, and 24 (all electronic except the 20th), 2008.

This supplemental new drug application provides for the use of Alimta® (pemetrexed disodium) Injection, Powder, Lyophilized, For Solution for Intravenous use 100 mg and 500 mg vials for the following indications.

Non-Small Cell Lung Cancer — Combination with Cisplatin

ALIMTA is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer. ALIMTA is not indicated for treatment of patients with squamous cell non-small cell lung cancer.

Non-Small Cell Lung Cancer — Single Agent

ALIMTA is indicated as a single-agent for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy. ALIMTA is not indicated for treatment of patients with squamous cell non-small cell lung cancer.

We have completed the review of this supplemental application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve Alimta® (pemetrexed disodium) Injection, Powder, Lyophilized, For Solution for Intravenous use 100 mg and 500 mg vials for use as recommended in the enclosed labeling text. Accordingly, the application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert).

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-462/S-015."

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study (Subpart H Phase 4 commitments) specified in your submission dated August 3, 2004. This commitment, along with any completion dates agreed upon, is listed below.

2. H3E-MC-JMEN: Multicenter, Randomized Phase III Study of Maintenance Therapy with Single-Agent Alimta versus Best Supportive Care after Treatment with Gemcitabine plus Carboplatin in Chemo-naive Patients with Advanced Non-Small Cell Lung Cancer.

   Status: Planned number of patients enrolled: 660
   First patient visit: March 2005
   Last patient visit: May 2008
   Final study report: November 2008

   We acknowledge receipt of your submission dated September 15, 2008, which includes a study report for H3E-MC-JMEN (Study JMEN).

Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to these Phase 4 commitment**s** must be clearly designated "**Subpart H Phase 4 Commitments**."

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "**Phase 4 Commitments**."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Carl Huntley, Regulatory Project Manager, at (301) 796-1372**.**

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Justice
9/26/2008 06:46:57 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALIMTA safely and effectively. See full prescribing information for ALIMTA.

ALIMTA (pemetrexed disodium) Injection, Powder, Lyophilized, For Solution for Intravenous use

Initial U.S. Approval: 2004

---------- RECENT MAJOR CHANGES ----------

Indications and Usage, Non-Small Cell Lung Cancer — Combination with Cisplatin (1.1) 09/2008

Indications and Usage, Non-Small Cell Lung Cancer — Single-Agent (1.2) 09/2008

Dosage and Administration Combination Use with Cisplatin (2.1) 09/2008

---------- INDICATIONS AND USAGE ----------

ALIMTA® is a folate analog metabolic inhibitor indicated for:

- Nonsquamous Non-Small Cell Lung Cancer: initial treatment in combination with cisplatin. (1.1)
- Nonsquamous Non-Small Cell Lung Cancer as a single-agent after prior chemotherapy (1.2)
- Mesothelioma: in combination with cisplatin (1.3)

---------- DOSAGE AND ADMINISTRATION ----------

- Combination use in Non-Small Cell Lung Cancer and Mesothelioma: Recommended dose of ALIMTA is 500 mg/m^2 i.v. on Day 1 of each 21-day cycle in combination with cisplatin 75 mg/m^2 i.v. beginning 30 minutes after ALIMTA administration. (2.1)
- Single-Agent use in Non-Small Cell Lung Cancer: Recommended dose of ALIMTA is 500 mg/m^2 i.v. on Day 1 of each 21-day cycle. (2.2)
- Dose Reductions: Dose reductions or discontinuation may be needed based on toxicities from the preceding cycle of therapy. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

- 100 mg vial for injection (3)
- 500 mg vial for injection (3)

---------- CONTRAINDICATIONS ----------

History of severe hypersensitivity reaction to pemetrexed. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Premedication regimen: Instruct patients to take folic acid and vitamin B_{12}. Pretreatment with dexamethasone or equivalent reduces cutaneous reaction. (5.1)
- Bone marrow suppression: Reduce doses for subsequent cycles based on hematologic and nonhematologic toxicities. (5.2)
- Renal function: Do not administer when CrCl <45 mL/min. (2.4, 5.3)
- NSAIDs with renal insufficiency: Use caution in patients with mild to moderate renal insufficiency (CrCl 45-79 mL/min). (5.4)
- Lab monitoring: Do not begin next cycle unless ANC ≥1500 cells/mm^3, platelets ≥100,000 cells/mm^3, and CrCl ≥45 mL/min. (5.5)
- Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised to use effective contraception measures to prevent pregnancy during treatment with ALIMTA. (5.6)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (incidence ≥20%) with single-agent use are fatigue, nausea, and anorexia. Additional common adverse reactions when used in combination with cisplatin include vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- NSAIDs: Use caution with ibuprofen or other NSAIDs (7.1)
- Nephrotoxic drugs: Concomitant use of these drugs and/or substances which are tubularly secreted may result in delayed clearance. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling

Revised:09/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer — Combination with Cisplatin

ALIMTA is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer. ALIMTA is not indicated for treatment of patients with squamous cell non-small cell lung cancer.

1.2 Non-Small Cell Lung Cancer — Single-Agent

ALIMTA is indicated as a single-agent for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy. ALIMTA is not indicated for treatment of patients with squamous cell non-small cell lung cancer.

1.3 Mesothelioma

ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Combination Use with Cisplatin

Non-Small Cell Lung Cancer and Malignant Pleural Mesothelioma

The recommended dose of ALIMTA is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours beginning approximately 30 minutes after the end of ALIMTA administration. Patients should receive appropriate hydration prior to and/or after receiving cisplatin. See cisplatin package insert for more information.

2.2 Single-Agent Use

Non-Small Cell Lung Cancer

The recommended dose of ALIMTA is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

2.3 Premedication Regimen

Vitamin Supplementation

To reduce toxicity, patients treated with ALIMTA must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of ALIMTA; and dosing should continue during the full course of therapy and for 21 days after the last dose of ALIMTA. Patients must also receive one (1) intramuscular injection of vitamin B_{12} during the week preceding the first dose of ALIMTA and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as ALIMTA. In clinical trials, the dose of folic acid studied ranged from 350 to 1000 mcg, and the dose of vitamin B_{12} was 1000 mcg. The most commonly used dose of oral folic acid in clinical trials was 400 mcg *[see Warnings and Precautions (5.1)]*.

Corticosteroid

Skin rash has been reported more frequently in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after ALIMTA administration *[see Warnings and Precautions (5.1)]*.

2.4 Laboratory Monitoring and Dose Reduction/Discontinuation Recommendations

Monitoring

Complete blood cell counts, including platelet counts, should be performed on all patients receiving ALIMTA. Patients should be monitored for nadir and recovery, which were tested in the clinical study before each dose and on days 8 and 15 of each cycle. Patients should not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm^3, the platelet count is ≥100,000 cells/mm^3, and creatinine clearance is ≥45 mL/min. Periodic chemistry tests should be performed to evaluate renal and hepatic function *[see Warnings and Precautions (5.5)]*.

Dose Reduction Recommendations

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in Tables 1-3, which are suitable for using ALIMTA as a single-agent or in combination with cisplatin.

Table 1: Dose Reduction for ALIMTA (single-agent or in combination) and Cisplatin - Hematologic Toxicities

Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3.	75% of previous dose (both drugs).
Nadir platelets <50,000/mm^3 without bleeding regardless of nadir ANC.	75% of previous dose (both drugs).
Nadir platelets <50,000/mm^3 with bleeding[a], regardless of nadir ANC.	50% of previous dose (both drugs).

[a] These criteria meet the CTC version 2.0 (NCI 1998) definition of ≥CTC Grade 2 bleeding.

If patients develop nonhematologic toxicities (excluding neurotoxicity) ≥Grade 3, treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to guidelines in Table 2.

Table 2: Dose Reduction for ALIMTA (single-agent or in combination) and Cisplatin - Nonhematologic Toxicities[a,b]

	Dose of ALIMTA (mg/m^2)	Dose of Cisplatin (mg/m^2)
Any Grade 3[c] or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

[a] NCI Common Toxicity Criteria (CTC).

[b] Excluding neurotoxicity (see Table 3).

[c] Except Grade 3 transaminase elevation, for which no dose reduction is needed.

In the event of neurotoxicity, the recommended dose adjustments for ALIMTA and cisplatin are described in Table 3. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

Table 3: Dose Reduction for ALIMTA (single-agent or in combination) and Cisplatin - Neurotoxicity

CTC Grade	Dose of ALIMTA (mg/m^2)	Dose of Cisplatin (mg/m^2)
0-1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

Discontinuation Recommendation

ALIMTA therapy should be discontinued if a patient experiences any hematologic or nonhematologic Grade 3 or 4 toxicity after 2 dose reductions (except Grade 3 transaminase elevations) or immediately if Grade 3 or 4 neurotoxicity is observed.

Renally Impaired Patients

In clinical studies, patients with creatinine clearance ≥45 mL/min required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this group of patients *[see Clinical Pharmacology (12.3)]*. Therefore, ALIMTA should not be administered to patients whose creatinine clearance is <45 mL/min using the standard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DPTA serum clearance method:

$$\text{Males: } \frac{[140 - \text{Age in years}] \times \text{Actual Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} = \text{mL/min}$$

Females: Estimated creatinine clearance for males × 0.85

Caution should be exercised when administering ALIMTA concurrently with NSAIDs to patients whose creatinine clearance is <80 mL/min *[see Drug Interactions (7.1)]*.

2.5 Preparation and Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of ALIMTA. The use of gloves is recommended. If a solution of ALIMTA contacts the skin, wash the skin immediately and thoroughly with soap and water. If ALIMTA contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available *[see References (15)]*.

ALIMTA is not a vesicant. There is no specific antidote for extravasation of ALIMTA. To date, there have been few reported cases of ALIMTA extravasation, which were not assessed as serious by the investigator. ALIMTA extravasation should be managed with local standard practice for extravasation as with other non-vesicants.

2.6 Preparation for Intravenous Infusion Administration

1. Use aseptic technique during the reconstitution and further dilution of ALIMTA for intravenous infusion administration.
2. Calculate the dose of ALIMTA and determine the number of vials needed. Vials contain either 100 mg or 500 mg of ALIMTA. The vials contain an excess of ALIMTA to facilitate delivery of label amount.
3. Reconstitute each 100-mg vial with 4.2 ml of 0.9% Sodium Chloride Injection (preservative free). Reconstitute 500-mg vial with 20 mL of 0.9% Sodium Chloride Injection (preservative free). Reconstitution of either size vial gives a solution containing 25 mg/mL ALIMTA. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted ALIMTA solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.
4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is observed, do not administer.

5. An appropriate quantity of the reconstituted ALIMTA solution must be further diluted into a solution of 0.9% Sodium Chloride Injection (preservative free), so that the total volume of solution is 100 ml. ALIMTA is administered as an intravenous infusion over 10 minutes.
6. Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or ambient room temperature [see USP Controlled Room Temperature] and lighting. When prepared as directed, reconstitution and infusion solutions of ALIMTA contain no antimicrobial preservatives. Discard any unused portion.

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). ALIMTA is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used. Coadministration of ALIMTA with other drugs and diluents has not been studied, and therefore is not recommended. ALIMTA is compatible with standard polyvinyl chloride (PVC) administration sets and intravenous solution bags.

3 DOSAGE FORMS AND STRENGTHS

ALIMTA, pemetrexed for injection, is a white to either light-yellow or green-yellow lyophilized powder available in sterile single-use vials containing 100 mg or 500 mg pemetrexed.

4 CONTRAINDICATIONS

ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed or to any other ingredient used in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Premedication Regimen

Need for Folate and Vitamin B_{12} Supplementation

Patients treated with ALIMTA must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related hematologic and GI toxicity *[see Dosage and Administration (2.3)]*. In clinical studies, less overall toxicity and reductions in Grade 3/4 hematologic and nonhematologic toxicities such as neutropenia, febrile neutropenia, and infection with Grade 3/4 neutropenia were reported when pretreatment with folic acid and vitamin B_{12} was administered.

Corticosteroid Supplementation

Skin rash has been reported more frequently in patients not pretreated with a corticosteroid in clinical trials. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction *[see Dosage and Administration (2.3)]*.

5.2 Bone Marrow Suppression

ALIMTA can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia) *[see Adverse Reactions (6.1)]*; myelosuppression is usually the dose-limiting toxicity. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum nonhematologic toxicity seen in the previous cycle *[see Dosage and Administration (2.4)]*.

5.3 Decreased Renal Function

ALIMTA is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance ≥45 mL/min. Insufficient numbers of patients have been studied with creatinine clearance <45 mL/min to give a dose recommendation. Therefore, ALIMTA should not be administered to patients whose creatinine clearance is <45 mL/min *[see Dosage and Administration (2.4)]*.

One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B_{12} died of drug-related toxicity following administration of ALIMTA alone.

5.4 Use with Non-Steroidal Anti-Inflammatory Drugs with Mild to Moderate Renal Insufficiency

Caution should be used when administering ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Other NSAIDs should also be used with caution *[see Drug Interactions (7.1)]*.

5.5 Required Laboratory Monitoring

Patients should not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm^3, the platelet count is ≥100,000 cells/mm^3, and creatinine clearance is ≥45 mL/min *[see Dosing and Administration (2.4)]*.

5.6 Pregnancy Category D

Based on its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. Pemetrexed administered intraperitoneally to mice during organogenesis was embryotoxic, fetotoxic and teratogenic in mice at greater than 1/833rd the recommended human dose. If ALIMTA 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. Women of childbearing potential should be advised to avoid becoming pregnant. Women should be advised to use effective contraceptive measures to prevent pregnancy during treatment with ALIMTA. *[see Pregnancy (8.1)]*

5.7 Third Space Fluid

The effect of third space fluid, such as pleural effusion and ascites, on ALIMTA is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to ALIMTA administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

In clinical trials, the most common adverse reactions (incidence ≥20%) during therapy with ALIMTA as a single-agent were fatigue, nausea, and anorexia. Additional common adverse reactions (incidence ≥20%) during therapy with ALIMTA when used in combination with cisplatin included vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

Non-Small Cell Lung Cancer (NSCLC) — Combination with Cisplatin

Table 4 provides the frequency and severity of adverse reactions that have been reported in >5% of 839 patients with NSCLC who were randomized to study and received ALIMTA plus cisplatin and 830 patients with NSCLC who were randomized to study and received gemcitabine plus cisplatin. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin B_{12}.

Table 4: Adverse Reactions in Fully Supplemented Patients Receiving ALIMTA plus Cisplatin in NSCLC[a]

Reaction[b]	ALIMTA/cisplatin (N=839)		Gemcitabine/cisplatin (N=830)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
All Adverse Reactions	90	37	91	53
Laboratory				
Hematologic				
Anemia	33	6	46	10
Neutropenia	29	15	38	27
Leukopenia	18	5	21	8
Thrombocytopenia	10	4	27	13
Renal				
Creatinine elevation	10	1	7	1
Clinical				
Constitutional Symptoms				
Fatigue	43	7	45	5
Gastrointestinal				
Nausea	56	7	53	4
Vomiting	40	6	36	6
Anorexia	27	2	24	1
Constipation	21	1	20	0
Stomatitis/Pharyngitis	14	1	12	0
Diarrhea	12	1	13	2
Dyspepsia/Heartburn	5	0	6	0
Neurology				
Neuropathy-sensory	9	0	12	1
Taste disturbance	8	0[c]	9	0[c]
Dermatology/Skin				
Alopecia	12	0[c]	21	1[c]
Rash/Desquamation	7	0	8	1

[a] For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA.

[b] Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity.

[c] According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

No clinically relevant differences in adverse reactions were seen in patients based on histology.

In addition to the lower incidence of hematologic toxicity on the ALIMTA and cisplatin arm, use of transfusions (RBC and platelet) and hematopoietic growth factors was lower in the ALIMTA and cisplatin arm compared to the gemcitabine and cisplatin arm.

The following additional adverse reactions were observed in patients with non-small cell lung cancer randomly assigned to receive ALIMTA plus cisplatin.

Incidence 1% to 5%

Body as a Whole — febrile neutropenia, infection, pyrexia

General Disorders — dehydration

Metabolism and Nutrition — increased AST, increased ALT
Renal — creatinine clearance decrease, renal failure
Special Senses — conjunctivitis

Incidence Less than 1%

Cardiovascular — arrhythmia
General Disorders — chest pain
Metabolism and Nutrition — increased GGT
Neurology — motor neuropathy

Non-Small Cell Lung Cancer (NSCLC) — Single-Agent

Table 5 provides the frequency and severity of adverse reactions that have been reported in >5% of 265 patients randomly assigned to receive single-agent ALIMTA with folic acid and vitamin B_{12} supplementation and 276 patients randomly assigned to receive single-agent docetaxel. All patients were diagnosed with locally advanced or metastatic NSCLC and received prior chemotherapy.

Table 5: Adverse Reactions in Fully Supplemented Patients Receiving ALIMTA versus Docetaxel in NSCLC[a]

Reaction[b]	ALIMTA (N=265)		Docetaxel (N=276)	
	All Grades Toxicity (%)	Grades 3-4 Toxicity (%)	All Grades Toxicity (%)	Grades 3-4 Toxicity (%)
Laboratory				
Hematologic				
Anemia	19	4	22	4
Leukopenia	12	4	34	27
Neutropenia	11	5	45	40
Thrombocytopenia	8	2	1	0
Hepatic				
Increased ALT	8	2	1	0
Increased AST	7	1	1	0
Clinical				
Gastrointestinal				
Nausea	31	3	17	2
Anorexia	22	2	24	3
Vomiting	16	2	12	1
Stomatitis/Pharyngitis	15	1	17	1
Diarrhea	13	0	24	3
Constipation	6	0	4	0
Constitutional Symptoms				
Fatigue	34	5	36	5
Fever	8	0	8	0
Dermatology/Skin				
Rash/Desquamation	14	0	6	0
Pruritis	7	0	2	0
Alopecia	6	1[c]	38	2[c]

[a] For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA.

[b] Refer to NCI CTC Criteria for lab values for each Grade of toxicity (version 2.0).

[c] According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

No clinically relevant differences in adverse reactions were seen in patients based on histology.

Clinically relevant adverse reactions occurring in <5% of patients that received ALIMTA treatment but >5% of patients that received docetaxel include CTC Grade 3/4 febrile neutropenia (1.9% ALIMTA, 12.7% docetaxel).

The following additional adverse reactions were observed in patients with non-small cell lung cancer randomly assigned to receive ALIMTA.

Incidence 1% to 5%

Body as a Whole — abdominal pain, allergic reaction/hypersensitivity, febrile neutropenia, infection
Dermatology/Skin — erythema multiforme
Neurology — motor neuropathy, sensory neuropathy
Renal — increased creatinine

Incidence Less than 1%

Cardiovascular — supraventricular arrhythmias

Malignant Pleural Mesothelioma (MPM)

Table 6 provides the frequency and severity of adverse reactions that have been reported in >5% of 168 patients with mesothelioma who were randomly assigned to receive cisplatin and ALIMTA and 163 patients with mesothelioma randomly assigned to receive single-agent cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin B_{12}.

Table 6: Adverse Reactions in Fully Supplemented Patients Receiving ALIMTA plus Cisplatin in MPM[a]

Reaction[b]	ALIMTA/cisplatin (N=168)		Cisplatin (N=163)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
Laboratory				
Hematologic				
Neutropenia	56	23	13	3
Leukopenia	53	15	17	1
Anemia	26	4	10	0
Thrombocytopenia	23	5	9	0
Renal				
Creatinine elevation	11	1	10	1
Creatinine clearance decreased	16	1	18	2
Clinical				
Eye Disorder				
Conjunctivitis	5	0	1	0
Gastrointestinal				
Nausea	82	12	77	6
Vomiting	57	11	50	4
Stomatitis/Pharyngitis	23	3	6	0
Anorexia	20	1	14	1
Diarrhea	17	4	8	0
Constipation	12	1	7	1
Dyspepsia	5	1	1	0
Constitutional Symptoms				
Fatigue	48	10	42	9
Metabolism and Nutrition				
Dehydration	7	4	1	1
Neurology				
Neuropathy-sensory	10	0	10	1
Taste Disturbance	8	0[c]	6	0[c]
Dermatology/Skin				
Rash	16	1	5	0
Alopecia	11	0[c]	6	0[c]

[a] For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA.

[b] Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity except the term “creatinine clearance decreased” which is derived from the CTC term “renal/genitourinary-other”.

[c] According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

The following additional adverse reactions were observed in patients with malignant pleural mesothelioma randomly assigned to receive ALIMTA plus cisplatin.

Incidence 1% to 5%

Body as a Whole — febrile neutropenia, infection, pyrexia

Dermatology/Skin — urticaria

General Disorders — chest pain

Metabolism and Nutrition — increased AST, increased ALT, increased GGT

Renal — renal failure

Incidence Less than 1%

Cardiovascular — arrhythmia

Neurology — motor neuropathy

Effects of Vitamin Supplementations

Table 7 compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients who received vitamin supplementation with daily folic acid and vitamin B_{12} from the time of enrollment in the study (fully supplemented) with the incidence in patients who never received vitamin supplementation (never supplemented) during the study in the ALIMTA plus cisplatin arm.

Table 7: Selected Grade 3/4 Adverse Events Comparing Fully Supplemented versus Never Supplemented Patients in the ALIMTA plus Cisplatin arm (% incidence)

Adverse Event[a] (%)	**Fully Supplemented Patients** (N=168)	**Never Supplemented Patients** (N=32)
Neutropenia/granulocytopenia	23	38
Thrombocytopenia	5	9
Vomiting	11	31
Febrile neutropenia	1	9
Infection with Grade 3/4 neutropenia	0	6
Diarrhea	4	9

[a] Refer to NCI CTC criteria for lab and non-laboratory values for each grade of toxicity (Version 2.0).

The following adverse events were greater in the fully supplemented group compared to the never supplemented group: hypertension (11%, 3%), chest pain (8%, 6%), and thrombosis/embolism (6%, 3%).

Subpopulations

No relevant effect for ALIMTA safety due to gender or race was identified, except an increased incidence of rash in men (24%) compared to women (16%).

Phase 2 Studies

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single-agent ALIMTA studies (N=164) and the Phase 3 single-agent ALIMTA study described above, with the exception of neutropenia (12.8% versus 5.3%, respectively) and alanine transaminase elevation (15.2% versus 1.9%, respectively). These differences were likely due to differences in the patient population, since the Phase 2 studies included chemonaive and heavily pretreated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of ALIMTA. 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.

These reactions have occurred with ALIMTA when used as a single-agent and in combination therapies.

Gastrointestinal — colitis

Injury, poisoning, and procedural complications — Radiation recall has been reported in patients who have previously received radiotherapy.

Respiratory — interstitial pneumonitis.

7 DRUG INTERACTIONS

7.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Ibuprofen

Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with ALIMTA in patients with normal renal function (creatinine clearance ≥80 mL/min). Caution should be used when administering ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min) *[see Clinical Pharmacology (12.3)]*.

Other NSAIDs

Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of ALIMTA.

In the absence of data regarding potential interaction between ALIMTA and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following ALIMTA administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

7.2 Nephrotoxic Drugs

ALIMTA is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of ALIMTA. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of ALIMTA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects — Pregnancy Category D *[see Warnings and Precautions (5.6)]*

Based on its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. There are no adequate and well controlled studies of ALIMTA in pregnant women. Pemetrexed was embryotoxic, fetotoxic and teratogenic in mice. In mice, repeated intraperitoneal doses of pemetrexed when given during organogenesis caused fetal malformations (incomplete ossification of talus and skull bone; about 1/833rd the recommended intravenous human dose on a mg/m^2 basis), and cleft palate (1/33rd the recommended intravenous human dose on a mg/m^2 basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced litter sizes. If ALIMTA 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. Women of childbearing potential should be advised to use effective contraceptive measures to prevent pregnancy during the treatment with ALIMTA.

8.3 Nursing Mothers

It is not known whether ALIMTA or its metabolites are 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 ALIMTA, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

8.4 Pediatric Use

The safety and effectiveness of ALIMTA in pediatric patients have not been established.

8.5 Geriatric Use

ALIMTA is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Renal function monitoring is recommended with administration of ALIMTA. No dose reductions other than those recommended for all patients are necessary for patients 65 years of age or older *[see Dosage and Administration (2.4)]*.

In the initial treatment non-small cell lung cancer clinical trial, 37.7% of patients treated with ALIMTA plus cisplatin were ≥65 years and Grade 3/4 neutropenia was greater as compared to patients <65 years (19.9% versus 12.2%). For patients <65 years, the HR for overall survival was 0.96 (95% CI: 0.83, 1.10) and for patients ≥65 years the HR was 0.88 (95% CI: 0.74, 1.06) in the intent to treat population.

In the previously treated non-small cell lung cancer trial, 29.7% patients treated with ALIMTA were ≥65 years and Grade 3/4 hypertension was greater as compared to patients <65 years. For patients <65 years, the HR for overall survival was 0.95 (95% CI: 0.76, 1.19), and for patients ≥65 years the HR was 1.15 (95% CI: 0.79, 1.68) in the intent to treat population.

The mesothelioma trial included 36.7% patients treated with ALIMTA plus cisplatin that were ≥65 years, and Grade 3/4 fatigue, leukopenia, neutropenia, and thrombocytopenia were greater as compared to patients <65 years. For patients <65 years, the HR for overall survival was 0.71(95% CI: 0.53, 0.96) and for patients ≥65 years, the HR was 0.85 (95% CI: 0.59, 1.22) in the intent to treat population.

8.6 Patients with Hepatic Impairment

There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed *[see Clinical Pharmacology (12.3)]*.

Dose adjustments based on hepatic impairment experienced during treatment with ALIMTA are provided in Table 2 *[see Dosage and Administration (2.4)]*.

8.7 Patients with Renal Impairment

ALIMTA is known to be primarily excreted by the kidneys. Decreased renal function will result in reduced clearance and greater exposure (AUC) to ALIMTA compared with patients with normal renal function *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*. Cisplatin coadministration with ALIMTA has not been studied in patients with moderate renal impairment.

8.8 Gender

In the previously untreated non-small cell lung cancer trial, 70% of patients were males and 30% females. For males the HR for overall survival was 0.97 (95% CI: 0.85, 1.10 and for females the HR was 0.86 (95% CI: 0.70, 1.06 in the intent to treat population.

In the previously treated non-small cell lung cancer trial, 72% of patients were males and 28% females. For males the HR for overall survival was 0.95 (95% CI: 0.76, 1.19) and for females the HR was 1.28 (95% CI: 0.86, 1.91) in the intent to treat population.

In the mesothelioma trial, 82% of patients were males and 18% females. For males the HR for overall survival was 0.85 (95% CI: 0.66, 1.09) and for females the HR was 0.48 (95% CI: 0.27, 0.85) in the intent to treat population.

8.9 Race

In the previously untreated non-small cell lung cancer trial, 78% of patients were Caucasians, 13% East/Southeast Asians, and 9% others. For Caucasians, the HR for overall survival was 0.92 (95% CI: 0.82, 1.04), for East/Southeast Asians the HR was 0.86 (95% CI: 0.61, 1.21), and for others the HR was 1.24 (95% CI: 0.84, 1.84) in the intent to treat population.

In the previously treated non-small cell lung cancer trial, 71% of patients were Caucasians and 29% others. For Caucasians the HR for overall survival was 0.91 (95% CI: 0.73, 1.15) and for others the HR was 1.27 (95% CI: 0.87, 1.87) in the intent to treat population.

In the mesothelioma trial, 92% of patients were Caucasians and 8% others. For Caucasians, the HR for overall survival was 0.77 (95% CI: 0.61, 0.97) and for others the HR was 0.86 (95% CI: 0.39, 1.90) in the intent to treat population.

10 OVERDOSAGE

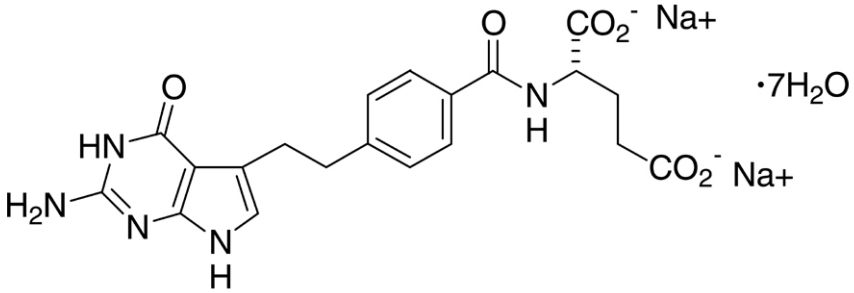
There have been few cases of ALIMTA overdose. Reported toxicities included neutropenia, anemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia, and anemia. In addition, infection with or without fever, diarrhea, and mucositis may be seen. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician.

In clinical trials, leucovorin was permitted for CTC Grade 4 leukopenia lasting ≥3 days, CTC Grade 4 neutropenia lasting ≥3 days, and immediately for CTC Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis. The following intravenous doses and schedules of leucovorin were recommended for intravenous use: 100 mg/m^2, intravenously once, followed by leucovorin, 50 mg/m^2, intravenously every 6 hours for 8 days.

The ability of ALIMTA to be dialyzed is unknown.

11 DESCRIPTION

Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It is a white to almost-white solid with a molecular formula of $C_{20}H_{19}N_5Na_2O_6 \cdot 7H_2O$ and a molecular weight of 597.49. The structural formula is as follows:



ALIMTA is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each 100-mg or 500-mg vial of ALIMTA contains pemetrexed disodium equivalent to 100 mg pemetrexed and 106 mg mannitol or 500 mg pemetrexed and 500 mg mannitol, respectively. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ALIMTA, pemetrexed for injection, is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as the reduced folate carrier, membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, is thought to occur to a lesser extent, in normal tissues. Polyglutamated metabolites are thought to have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

12.2 Pharmacodynamics

Preclinical studies have shown that pemetrexed inhibits the in vitro growth of mesothelioma cell lines (MSTO-211H, NCI-H2052). Studies with the MSTO-211H mesothelioma cell line showed synergistic effects when pemetrexed was combined concurrently with cisplatin.

Absolute neutrophil counts (ANC) following single-agent administration of ALIMTA to patients not receiving folic acid and vitamin B_{12} supplementation were characterized using population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the depth of the ANC nadir, correlates with the systemic exposure, or area under the curve (AUC) of pemetrexed. It was also observed that lower ANC nadirs occurred in patients with elevated baseline cystathionine or homocysteine concentrations. The levels of these substances can be reduced by folic acid and vitamin B_{12} supplementation. There is no cumulative effect of pemetrexed exposure on ANC nadir over multiple treatment cycles.

Time to ANC nadir with pemetrexed systemic exposure (AUC), varied between 8 to 9.6 days over a range of exposures from 38.3 to 316.8 mcg•hr/mL. Return to baseline ANC occurred 4.2 to 7.5 days after the nadir over the same range of exposures.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of ALIMTA administered as a single-agent in doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increase proportionally with dose. The pharmacokinetics of pemetrexed do not change over multiple treatment cycles.

Distribution

Pemetrexed has a steady-state volume of distribution of 16.1 liters. In vitro studies indicate that pemetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

Metabolism and Excretion

Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. The clearance decreases, and exposure (AUC) increases, as renal function decreases. The total systemic clearance of pemetrexed is 91.8 mL/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min).

The pharmacokinetics of pemetrexed in special populations were examined in about 400 patients in controlled and single arm studies.

Effect of Age

No effect of age on the pharmacokinetics of pemetrexed was observed over a range of 26 to 80 years.

Effect of Gender

The pharmacokinetics of pemetrexed were not different in male and female patients.

Effect of Race

The pharmacokinetics of pemetrexed were similar in Caucasians and patients of African descent. Insufficient data are available to compare pharmacokinetics for other ethnic groups.

Effect of Hepatic Insufficiency

There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed. However, studies of hepatically impaired patients have not been conducted *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

Effect of Renal Insufficiency

Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed decreases as renal function decreases, with a resultant increase in systemic exposure. Patients with creatinine clearances of 45, 50, and 80 mL/min had 65%, 54%, and 13% increases, respectively in pemetrexed total systemic exposure (AUC) compared to patients with creatinine clearance of 100 mL/min *[see Warnings and Precautions (5.4) and Dosage and Administration (2.4)]*.

Pediatric

Pediatric patients were not included in clinical trials.

Effect of Ibuprofen

Ibuprofen doses of 400 mg four times a day reduce pemetrexed's clearance by about 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater doses of ibuprofen on pemetrexed pharmacokinetics is unknown *[see Drug Interactions (7.1)]*.

Effect of Aspirin

Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed. The effect of greater doses of aspirin on pemetrexed pharmacokinetics is unknown.

Effect of Cisplatin

Cisplatin does not affect the pharmacokinetics of pemetrexed and the pharmacokinetics of total platinum are unaltered by pemetrexed.

Effect of Vitamins

Coadministration of oral folic acid or intramuscular vitamin B_{12} does not affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes

Results from in vitro studies with human liver microsomes predict that pemetrexed would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic in the in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple in vitro tests (Ames assay, CHO cell assay). Pemetrexed administered at i.v. doses of 0.1 mg/kg/day or greater to male mice (about 1/1666 the recommended human dose on a mg/m^2 basis) resulted in reduced fertility, hypospermia, and testicular atrophy.

14 CLINICAL STUDIES

14.1 Non-Small Cell Lung Cancer (NSCLC) — Combination with Cisplatin

A multi-center, randomized, open-label study in 1725 chemonaive patients with stage IIIb/IV NSCLC was conducted to compare the overall survival following treatment with ALIMTA in combination with cisplatin (AC) versus gemcitabine in combination with cisplatin (GC). ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m^2 with cisplatin administered intravenously at a dose of 75 mg/m^2 after ALIMTA administration, on Day 1 of each 21-day cycle. Gemcitabine was administered at a dose of 1250 mg/m^2 on Day 1 and Day 8, and cisplatin was administered intravenously at a dose of 75 mg/m^2 after administration of gemcitabine, on Day 1 of each 21-day cycle. Treatment was administered up to a total of 6 cycles, and patients in both treatment arms received folic acid, vitamin B_{12}, and dexamethasone *[see Dosage and Administration (2.3)]*.

Patient demographics of the intent to treat (ITT) population are shown in Table 8. The demographics and disease characteristics were well balanced.

Table 8: Summary of Patient Characteristics in Study of NSCLC — Combination with Cisplatin

Patient characteristic	ALIMTA plus Cisplatin (AC) (N=862)	Gemcitabine plus Cisplatin (GC) (N=863)
Age (yrs)		
Median (range)	61.1 (28.8-83.2)	61.0 (26.4-79.4)
Gender (%)		
Male/Female	70.2/29.8	70.1/29.9
Origin		
Caucasian	669 (77.6%)	680 (78.8%)
Hispanic	27 (3.1%)	23 (2.7%)
Asian	146 (16.9%)	141 (16.3%)
African descent	18 (2.1%)	18 (2.1%)
Stage at Entry (%)		
IIIb/IV	23.8/76.2	24.3/75.7
Histology (%)		
Nonsquamous NSCLC[a]	618 (71.7)	634 (73.5)
Adenocarcinoma	436 (50.6)	411 (47.6)
Large cell	76 (8.8)	77 (8.9)
Other[b]	106 (12.3)	146 (16.9)
Squamous	244 (28.3)	229 (26.5)
ECOG PS[c] (%)[d]		
0/1	35.4/64.6	35.6/64.3
Smoking History (%)[e]		
Ever/never smoker	83.1/16.9	83.9/16.1

[a] Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.

[b] The subgroup of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

[c] Eastern Cooperative Oncology Group Performance Status.

[d] ECOG PS was not reported for all randomized patients. Percentages are representative of N=861 for the ALIMTA plus cisplatin arm, and N=861 for the gemcitabine plus cisplatin arm.

[e] Smoking history was collected for 88% of randomized patients (N=757 for the ALIMTA plus cisplatin arm and N=759 for the gemcitabine plus cisplatin arm).

Patients received a median of 5 cycles of treatment in both study arms. Patients treated with ALIMTA plus cisplatin received a relative dose intensity of 94.8% of the protocol-specified ALIMTA dose intensity and 95.0% of the protocol-specified cisplatin dose intensity. Patients treated with gemcitabine plus cisplatin received a relative dose intensity of 85.8% of the protocol-specified gemcitabine dose intensity and 93.5% of the protocol-specified cisplatin dose intensity.

The primary endpoint in this study was overall survival. The median survival time was 10.3 months in the ALIMTA plus cisplatin treatment arm and 10.3 months in the gemcitabine plus cisplatin arm, with an adjusted hazard ratio of 0.94.

Table 9: Efficacy of ALIMTA plus Cisplatin versus Gemcitabine plus Cisplatin in First-line NSCLC — ITT Population

	ALIMTA plus Cisplatin (N=862)	Gemcitabine plus Cisplatin (N=863)
Median overall survival (95% CI)	10.3 mos (9.8-11.2)	10.3 mos (9.6-10.9)
Adjusted hazard ratio (HR)[a,b] (95% CI)	0.94 (0.84-1.05)	
Median progression-free survival (95% CI)	4.8 mos (4.6-5.3)	5.1 mos (4.6-5.5)
Adjusted hazard ratio (HR)[a,b] (95% CI)	1.04 (0.94-1.15)	
Overall response rate (95% CI)	27.1% (24.2-30.1)	24.7% (21.8-27.6)

[a] Adjusted for gender, stage, basis of diagnosis, and performance status.

[b] A HR that is less than 1.0 indicates that survival is better in the AC arm than in the GC arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the GC arm than in the AC arm.

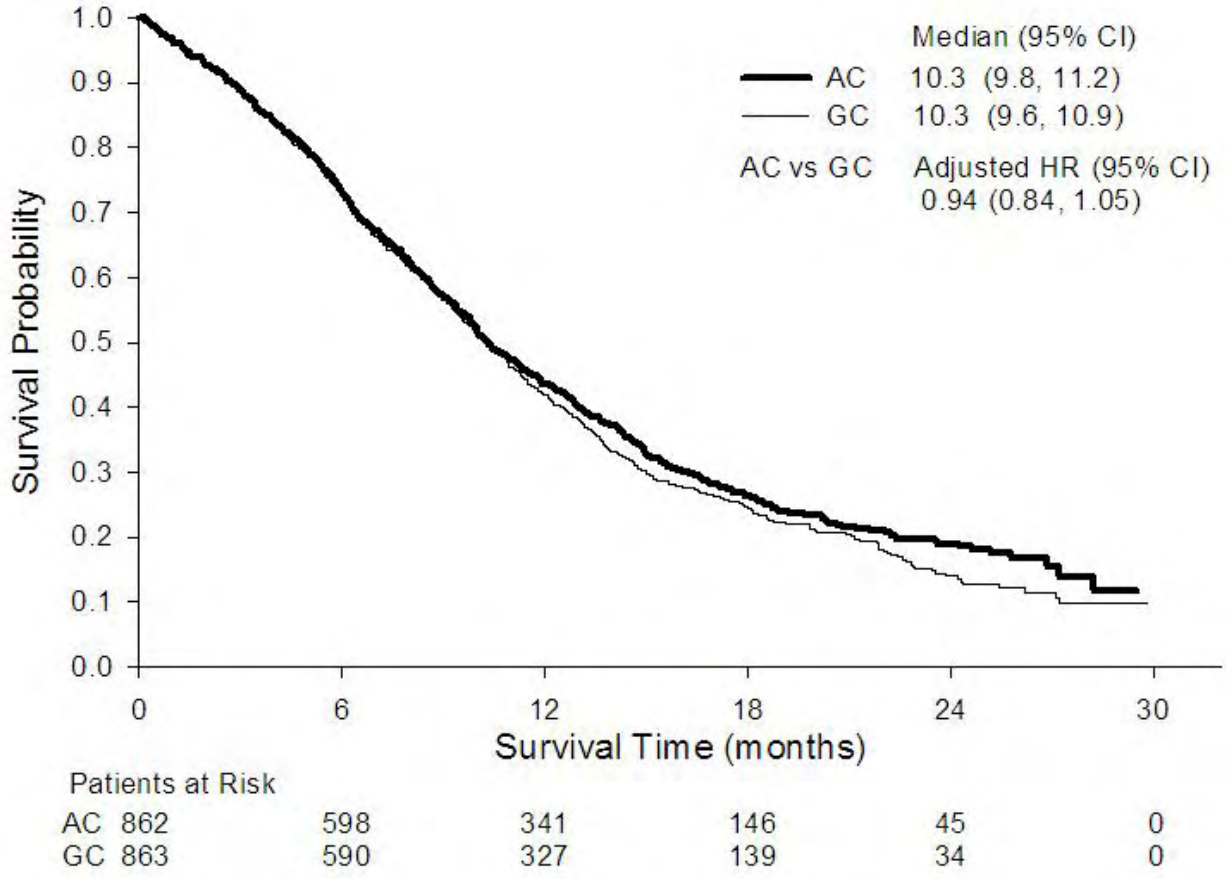


Figure 1: Kaplan-Meier Curves for Overall Survival ALIMTA plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in NSCLC — ITT Population

A pre-specified analysis of the impact of NSCLC histology on overall survival was examined. Clinically relevant differences in survival according to histology were observed and are shown in Table 10. This difference in treatment effect for ALIMTA based on histology was also observed in the single-agent, second-line study *[see Clinical Studies (14.2)]*.

Table 10: Overall Survival of ALIMTA plus Cisplatin versus Gemcitabine plus Cisplatin in NSCLC — Histologic Subgroups, ITT Population

Histology Subgroup	Median Overall Survival in Months (95% CI)				Unadjusted Hazard Ratio (HR)[a,b] (95% CI)	Adjusted Hazard Ratio (HR)[a,b,c] (95% CI)
	ALIMTA plus Cisplatin		Gemcitabine plus Cisplatin			
Nonsquamous NSCLC[d] (N=1252)	11.0 (10.1–12.5)	N=618	10.1 (9.3–10.9)	N=634	0.84 (0.74–0.96)	0.84 (0.74–0.96)
Adenocarcinoma (N=847)	12.6 (10.7-13.6)	N=436	10.9 (10.2-11.9)	N=411	0.84 (0.71-0.98)	0.84 (0.71-0.99)
Large Cell (N=153)	10.4 (8.6-14.1)	N=76	6.7 (5.5-9.0)	N=77	0.68 (0.48-0.97)	0.67 (0.48-0.96)
Other[e] (N=252)	8.6 (6.8-10.2)	N=106	9.2 (8.1-10.6)	N=146	1.12 (0.84-1.49)	1.08 (0.81-1.45)
Squamous Cell (N=473)	9.4 (8.4-10.2)	N=244	10.8 (9.5-12.1)	N=229	1.22 (0.99-1.50)	1.23 (1.00-1.51)

[a] A HR that is less than 1.0 indicates that survival is better in the AC arm than in the GC arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the GC arm than in the AC arm.

[b] Unadjusted for multiple comparisons.

[c] HRs adjusted for ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).
[d] Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.
[e] The subgroup of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

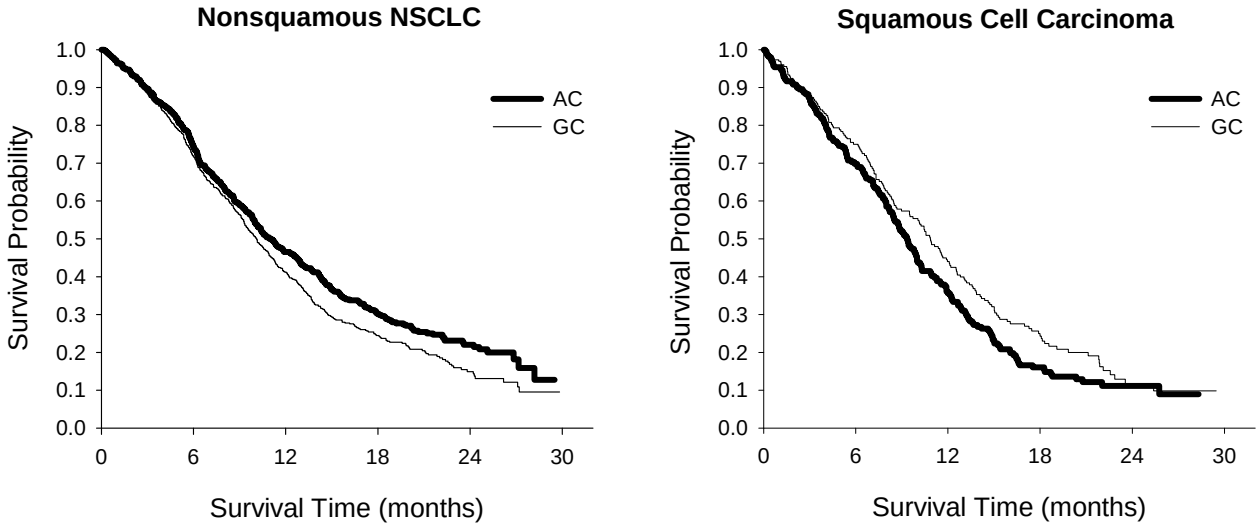


Figure 2: Kaplan-Meier Curves for Overall Survival ALIMTA plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in NSCLC — Nonsquamous NSCLC and Squamous Cell Carcinoma

14.2 Non-Small Cell Lung Cancer — Single-Agent Use

A multi-center, randomized, open label study was conducted in patients with Stage III or IV NSCLC after prior chemotherapy to compare the overall survival following treatment with ALIMTA versus docetaxel. ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m^2 and docetaxel was administered at 75 mg/m^2 as a 1-hour intravenous infusion. Both drugs were given on Day 1 of each 21-day cycle. All patients treated with ALIMTA received vitamin supplementation with folic acid and vitamin B_{12}. The study was intended to show either an overall survival superiority or non-inferiority of ALIMTA to docetaxel. Patient demographics of the intent to treat (ITT) population are shown in Table 11.

Table 11: Summary of Patient Characteristics in NSCLC Study

Patient characteristic	**ALIMTA** (N=283)	**Docetaxel** (N=288)
Age (yrs)		
Median (range)	59 (22-81)	57 (28-87)
Gender (%)		
Male/Female	68.6/31.4	75.3/24.7
Stage at Entry (%)		
III/IV	25.1/74.9	25.3/74.7
Diagnosis/Histology (%)		
Adenocarcinoma	154 (54.4)	142 (49.3)
Squamous	78 (27.6)	94 (32.6)
Bronchoalveolar	4 (1.4)	1 (0.3)
Other	47 (16.6)	51 (17.7)
Performance Status (%)[a]		
0-1	234 (88.6)	240 (87.6)
2	30 (11.4)	34 (12.4)

[a] Performance status was not reported for all randomized patients. Percentages are representative of N=264 for the ALIMTA and N=274 for the docetaxel arm.

The primary endpoint in this study was overall survival. The median survival time was 8.3 months in the ALIMTA treatment arm and 7.9 months in the docetaxel arm, with a hazard ratio of 0.99 (*see* Table 12). The study did not show an overall survival superiority of ALIMTA.

Table 12: Efficacy of ALIMTA versus Docetaxel in Non-Small Cell Lung Cancer — ITT Population

	ALIMTA (N=283)	Docetaxel (N=288)
Median overall survival (95% CI)	8.3 mos (7.0-9.4)	7.9 mos (6.3-9.2)
Hazard ratio (HR) (95% CI)	0.99 (0.82-1.20)	
Median progression-free survival (95% CI)	2.9 mos (2.4-3.1)	2.9 mos (2.7-3.4)
Hazard ratio (HR) (95% CI)	0.97 (0.82-1.16)	
Overall response rate (95% CI)	8.5% (5.2-11.7)	8.3% (5.1-11.5)

A retrospective analysis of the impact of NSCLC histology on overall survival was examined. Clinically relevant differences in survival according to histology were observed and are shown in Table 13. This difference in treatment effect for ALIMTA based on histology was also observed in the first-line combination study *[see Clinical Studies (14.1)]*.

Table 13: Overall Survival of ALIMTA versus Docetaxel in NSCLC — Histologic Subgroups, ITT Population

Histology Subgroup	**Median Overall Survival in Months (95% CI)**				**Unadjusted Hazard Ratio (HR)[a,b] (95% CI)**	**Adjusted Hazard Ratio (HR)[a,b,c] (95% CI)**
	ALIMTA		Docetaxel			
Nonsquamous NSCLC[d] (N=399)	9.3 (7.8–9.7)	N=205	8.0 (6.3–9.3)	N=194	0.89 (0.71–1.13)	0.78 (0.61–1.00)
Adenocarcinoma (N=301)	9.0 (7.6-9.6)	N=158	9.2 (7.5-11.3)	N=143	1.09 (0.83-1.44)	0.92 (0.69-1.22)
Large Cell (N=47)	12.8 (5.8-14.0)	N=18	4.5 (2.3-9.1)	N=29	0.38 (0.18-0.78)	0.27 (0.11-0.63)
Other[e] (N=51)	9.4 (6.0-10.1)	N=29	7.9 (4.0-8.9)	N=22	0.62 (0.32-1.23)	0.57 (0.27-1.20)
Squamous Cell (N=172)	6.2 (4.9-8.0)	N=78	7.4 (5.6-9.5)	N=94	1.32 (0.93-1.86)	1.56 (1.08-2.26)

[a] A HR that is less than 1.0 indicates that survival is better in the ALIMTA arm than in the docetaxel arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the docetaxel arm than in the ALIMTA arm.

[b] Unadjusted for multiple comparisons.

[c] HRs adjusted for ECOG PS, time since prior chemotherapy, disease stage, and gender.

[d] Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.

[e] The subgroup of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

14.3 Malignant Pleural Mesothelioma

A multi-center, randomized, single-blind study in 448 chemonaive patients with malignant pleural mesothelioma (MPM) compared survival in patients treated with ALIMTA in combination with cisplatin to survival in patients receiving cisplatin alone. ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m^2 and cisplatin was administered intravenously over 2 hours at a dose of 75 mg/m^2 beginning approximately 30 minutes after the end of administration of ALIMTA. Both drugs were given on Day 1 of each 21-day cycle. After 117 patients were treated, white cell and GI toxicity led to a change in protocol whereby all patients were given folic acid and vitamin B_{12} supplementation.

The primary analysis of this study was performed on the population of all patients randomly assigned to treatment who received study drug (randomized and treated). An analysis was also performed on patients who received folic acid and vitamin B_{12} supplementation during the entire course of study therapy (fully supplemented), as supplementation is recommended *[see Dosage and Administration (2.3)]*. Results in all patients and those fully supplemented were similar. Patient demographics are shown in Table 14.

Table 14: Summary of Patient Characteristics in MPM Study

Patient characteristic	**Randomized and Treated Patients**		**Fully Supplemented Patients**	
	ALIMTA/cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (N=168)	Cisplatin (N=163)
Age (yrs)				
Median (range)	61 (29-85)	60 (19-84)	60 (29-85)	60 (19-82)
Gender (%)				
Male	184 (81.4)	181 (81.5)	136 (81.0)	134 (82.2)
Female	42 (18.6)	41 (18.5)	32 (19.0)	29 (17.8)

Origin (%)				
Caucasian	204 (90.3)	206 (92.8)	150 (89.3)	153 (93.9)
Hispanic	11 (4.9)	12 (5.4)	10 (6.0)	7 (4.3)
Asian	10 (4.4)	4 (1.9)	7 (4.2)	3 (1.8)
African descent	1 (0.4)	0	1 (0.6)	0
Stage at Entry (%)				
I	16 (7.1)	14 (6.3)	15 (8.9)	12 (7.4)
II	35 (15.6)	33 (15.0)	27 (16.2)	27 (16.8)
III	73 (32.4)	68 (30.6)	51 (30.5)	49 (30.4)
IV	101 (44.9)	105 (47.2)	74 (44.3)	73 (45.3)
Unspecified	1 (0.4)	2 (0.9)	1 (0.6)	2 (1.2)
Diagnosis/Histology[a] (%)				
Epithelial	154 (68.1)	152 (68.5)	117 (69.6)	113 (69.3)
Mixed	37 (16.4)	36 (16.2)	25 (14.9)	25 (15.3)
Sarcomatoid	18 (8.0)	25 (11.3)	14 (8.3)	17 (10.4)
Other	17 (7.5)	9 (4.1)	12 (7.1)	8 (4.9)
Baseline KPS[b] (%)				
70-80	109 (48.2)	97 (43.7)	83 (49.4)	69 (42.3)
90-100	117 (51.8)	125 (56.3)	85 (50.6)	94 (57.7)

[a] Only 67% of the patients had the histologic diagnosis of malignant mesothelioma confirmed by independent review.
[b] Karnofsky Performance Scale.

Table 15 summarizes the survival results for all randomized and treated patients regardless of vitamin supplementation status and those patients receiving vitamin supplementation from the time of enrollment in the trial.

Table 15: Efficacy of ALIMTA plus Cisplatin versus Cisplatin in Malignant Pleural Mesothelioma

Efficacy Parameter	**Randomized and Treated Patients**		**Fully Supplemented Patients**	
	ALIMTA/cis (N=226)	Cisplatin (N=222)	ALIMTA/cis (N=168)	Cisplatin (N=163)
Median overall survival (95% CI)	12.1 mos (10.0-14.4)	9.3 mos (7.8-10.7)	13.3 mos (11.4-14.9)	10.0 mos (8.4-11.9)
Hazard ratio	0.77		0.75	
Log rank p-value[a]	0.020		0.051	

[a] p-value refers to comparison between arms.

Similar results were seen in the analysis of patients (N=303) with confirmed histologic diagnosis of malignant pleural mesothelioma. There were too few non-white patients to assess possible ethnic differences. The effect in women (median survival 15.7 months with the combination versus 7.5 months on cisplatin alone), however, was larger than the effect in males (median survival 11 versus 9.4 respectively). As with any exploratory analysis, it is not clear whether this difference is real or is a chance finding.

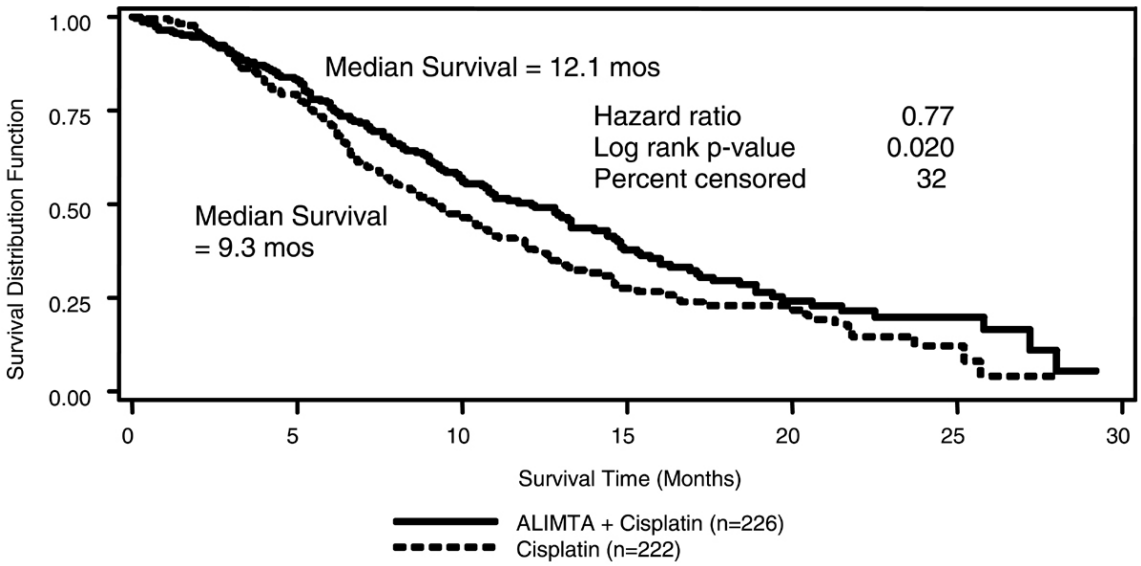


Figure 3: Kaplan-Meier Estimates of Survival Time for ALIMTA plus Cisplatin and Cisplatin Alone in all Randomized and Treated Patients.

Objective tumor response for malignant pleural mesothelioma is difficult to measure and response criteria are not universally agreed upon. However, based upon prospectively defined criteria, the objective tumor response rate for ALIMTA plus cisplatin was greater than the objective tumor response rate for cisplatin alone. There was also improvement in lung function (forced vital capacity) in the ALIMTA plus cisplatin arm compared to the control arm.

Patients who received full supplementation with folic acid and vitamin B_{12} during study therapy received a median of 6 and 4 cycles in the ALIMTA/cisplatin (N=168) and cisplatin (N=163) arms, respectively. Patients who never received folic acid and vitamin B_{12} during study therapy received a median of 2 cycles in both treatment arms (N=32 and N=38 for the ALIMTA/cisplatin and cisplatin arm, respectively). Patients receiving ALIMTA in the fully supplemented group received a relative dose intensity of 93% of the protocol specified ALIMTA dose intensity; patients treated with cisplatin in the same group received 94% of the projected dose intensity. Patients treated with cisplatin alone had a dose intensity of 96%.

15 REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. 2006;63:1172-1193.
4. Polovich, M., White, J. M., & Kelleher, L. O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ALIMTA, pemetrexed for injection is available in sterile single-use vials containing 100 mg pemetrexed.
NDC 0002-7640-01 (VL7640): single-use vial with ivory flip-off cap individually packaged in a carton.
ALIMTA, pemetrexed for injection is available in sterile single-use vials containing 500 mg pemetrexed.
NDC 0002-7623-01 (VL7623): single-use vial with ivory flip-off cap individually packaged in a carton.

16.2 Storage and Handling

ALIMTA, pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Chemical and physical stability of reconstituted and infusion solutions of ALIMTA were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. When prepared as directed, reconstituted and infusion solutions of ALIMTA contain no antimicrobial preservatives. Discard unused portion.

ALIMTA is not light sensitive.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

17.1 Need for Folic Acid and Vitamin B_{12}

Patients treated with ALIMTA must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related hematologic and gastrointestinal toxicity *[see Dosage and Administration (2.3)]*.

17.2 Low Blood Cell Counts

Patients should be adequately informed of the risk of low blood cell counts and instructed to immediately contact their physician should any sign of infection develop including fever. Patients should also contact their physician if bleeding or symptoms of anemia occur.

17.3 Gastrointestinal Effects

Patients should be instructed to contact their physician if persistent vomiting, diarrhea, or signs of dehydration appear.

17.4 Concomitant Medications

Patients should be instructed to inform the physician if they are taking any concomitant prescription or over-the-counter medications including those for pain or inflammation such as non-steroidal anti-inflammatory drugs *[see Drug Interactions (7.1)]*.

17.5 FDA Approved Patient Labeling

Patients should be instructed to read the patient package insert carefully.

Literature revised September 26, 2008

Eli Lilly and Company

Indianapolis, IN 46285, USA

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INFORMATION FOR PATIENTS AND CAREGIVERS

ALIMTA® (uh-LIM-tuh)

(pemetrexed for injection)

Read the Patient Information that comes with ALIMTA before you start treatment and each time you get treated with ALIMTA. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about ALIMTA.

What is ALIMTA?

ALIMTA is a treatment for:

- **Malignant pleural mesothelioma.** This cancer affects the inside lining of the chest cavity. ALIMTA is given with cisplatin, another anti-cancer medicine (chemotherapy).
- **Non-small cell lung cancer.** This cancer is a disease in which malignant (cancer) cells form in the tissues of the lung. If this is the first time you have been treated for your lung cancer, ALIMTA may be given with another anti-cancer drug called cisplatin. If you are being treated because your cancer has come back or you had trouble tolerating a prior treatment, ALIMTA may be given alone. Your doctor will speak to you about whether ALIMTA is appropriate for your specific type of non-small cell lung cancer.

To lower your chances of side effects of ALIMTA, you must also take folic acid and vitamin B_{12} prior to and during your treatment with ALIMTA. Your doctor will prescribe a medicine called a "corticosteroid" to take for 3 days during your treatment with ALIMTA. Corticosteroid medicines lower your chances of getting skin reactions with ALIMTA.

ALIMTA has not been studied in children.

What should I tell my doctor before taking ALIMTA?

Tell your doctor about all of your medical conditions, including if you:

- **are pregnant or planning to become pregnant.** ALIMTA may harm your unborn baby.
- **are breastfeeding.** It is not known if ALIMTA passes into breast milk. You should stop breastfeeding once you start treatment with ALIMTA.
- **are taking other medicines,** including prescription and nonprescription medicines, vitamins, and herbal supplements. ALIMTA and other medicines may affect each other causing serious side effects. Especially, tell your doctor if you are taking medicines called "nonsteroidal anti-inflammatory drugs" (NSAIDs) for pain or swelling. There are many NSAID medicines. If you are not sure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

How is ALIMTA given?

- ALIMTA is slowly infused (injected) into a vein. The injection or infusion will last about 10 minutes. You will usually receive ALIMTA once every 21 days (3 weeks).
- If you are being treated with ALIMTA and cisplatin for the initial treatment of either mesothelioma or non-small cell lung cancer, ALIMTA will be given first as a 10 minute infusion into your vein and cisplatin (another anti-cancer drug) will also be given through your vein starting about 30 minutes after ALIMTA and ending about 2 hours later.
- If you are being treated because your non-small cell lung cancer has returned, you may receive ALIMTA alone, given as a 10 minute infusion into your vein.
- Your doctor will prescribe a medicine called a "corticosteroid" to take for 3 days during your treatment with ALIMTA. Corticosteroid medicines lower your chances for getting skin reactions with ALIMTA.
- **It is very important to take folic acid and vitamin B_{12} during your treatment with ALIMTA to lower your chances of harmful side effects.** You must start taking 350-1000 micrograms of folic acid every day for at least 5 days out of the 7 days before your first dose of ALIMTA. You must keep taking folic acid every day during the time you are getting treatment with ALIMTA, and for 21 days after your last treatment. You can get folic acid vitamins over-the-counter. Folic acid is also found in many multivitamin pills. Ask your doctor or pharmacist for help if you are not sure how to choose a folic acid product. Your doctor will give you vitamin B_{12} injections while you are getting treatment with ALIMTA. You will get your first vitamin B_{12} injection during the week before your first dose of ALIMTA, and then about every 9 weeks during treatment.
- You will have regular blood tests before and during your treatment with ALIMTA. Your doctor may adjust your dose of ALIMTA or delay treatment based on the results of your blood tests and on your general condition.

What should I avoid while taking ALIMTA?

- **Women who can become pregnant should not become pregnant during treatment with ALIMTA.** ALIMTA may harm the unborn baby.
- **Ask your doctor before taking medicines called NSAIDs.** There are many NSAID medicines. If you are not sure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

What are the possible side effects of ALIMTA?

Most patients taking ALIMTA will have side effects. Sometimes it is not always possible to tell whether ALIMTA, another medicine, or the cancer itself is causing these side effects. **Call your doctor right away if you have a fever, chills, diarrhea, or mouth sores.** These symptoms could mean you have an infection.

The most common side effects of ALIMTA when given alone or in combination with cisplatin are:

- **Stomach upset, including nausea, vomiting, and diarrhea.** You can obtain medicines to help control some of these symptoms. Call your doctor if you get any of these symptoms.
- **Low blood cell counts:**
  - **Low red blood cells.** Low red blood cells may make you feel tired, get tired easily, appear pale, and become short of breath.
  - **Low white blood cells.** Low white blood cells may give you a greater chance for infection. If you have a fever (temperature above 100.4°F) or other signs of infection, call your doctor right away.
  - **Low platelets.** Low platelets give you a greater chance for bleeding. Your doctor will do blood tests to check your blood counts before and during treatment with ALIMTA.
- **Tiredness.** You may feel tired or weak for a few days after your ALIMTA treatments. If you have severe weakness or tiredness, call your doctor.
- **Mouth, throat, or lip sores** (stomatitis, pharyngitis). You may get redness or sores in your mouth, throat, or on your lips. These symptoms may happen a few days after ALIMTA treatment. Talk with your doctor about proper mouth and throat care.
- **Loss of appetite.** You may lose your appetite and lose weight during your treatment. Talk to your doctor if this is a problem for you.
- **Rash.** You may get a rash or itching during treatment. These usually appear between treatments with ALIMTA and usually go away before the next treatment. Call your doctor if you get a severe rash or itching.

Talk with your doctor, nurse or pharmacist about any side effect that bothers you or that doesn't go away.

These are not all the side effects of ALIMTA. For more information, ask your doctor, nurse or pharmacist.

General information about ALIMTA

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. ALIMTA was prescribed for your medical condition.

This leaflet summarizes the most important information about ALIMTA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ALIMTA that is written for health professionals. You can also call 1-800-LILLY-RX (1-800-545-5979) or visit www.ALIMTA.com.

Patient information revised September 26, 2008

Eli Lilly and Company

Indianapolis, IN 46285, USA

www.ALIMTA.com

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	9/26/08
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review/CDTL Review
NDA/BLA # **Supplement #**	21-642 015
Applicant Name	Eli Lilly and Company
Date of Submission	8/28/08
PDUFA Goal Date	9/28/08 (due to major amendment)
Proprietary Name / **Established (USAN) Name**	ALIMTA® Pemetrexed disodium
Dosage Forms / Strength	Lyophilized powder in sterile single-use vials containing 100 mg or 500 mg of pemetrexed
Proposed Indication(s)	ALIMTA is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer. ALIMTA is not indicated for treatment of patients with squamous cell non-small cell lung cancer.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	X
Statistical Review	3 statistical reviews
Pharmacology Toxicology Review	N/A
CMC Review/OBP Review	X
Microbiology Review	N/A
Clinical Pharmacology Review	X
DDMAC	X
DSI	N/A
CDTL Review	This review serves as the CDTL Review.
OSE/DMETS	N/A
OSE/DDRE	N/A
OSE/DSRCS	N/A
Other	Statistical (2) and clinical (1) consultant reports

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This efficacy supplement seeks approval of ALIMTA for the following indication.

> ALIMTA is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer. ALIMTA is not indicated for treatment of patients with squamous cell non-small cell lung cancer.

The supplement also seeks revision of the following currently approved indication.

> ALIMTA is indicated as a single-agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

The revised indication will read as follows.

> ALIMTA is indicated as a single-agent for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy. ALIMTA is not indicated for treatment of patients with squamous cell non-small cell lung cancer.

This review will summarize the efficacy and safety data that support approval of the new indication and revision of the currently approved NSCLC indication. It will also highlight and discuss the differences of opinion regarding approvability of the application.

2. Background

Pemetrexed received regular approval for the following indication on 2/4/04: "ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery."

Pemetrexed received accelerated approval for the following indication on 8/19/04:

> ALIMTA as a single-agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy. The effectiveness of ALIMTA in second-line NSCLC was based on the surrogate endpoint, response rate. There are no controlled trials demonstrating a clinical benefit, such as a favorable survival effect or improvement in disease-related symptoms.

As part of their subpart H post-marketing study commitments, the applicant agreed to submit studies JMBD and JMEN. Study JMBD is the subject of this efficacy supplement. During the

review of this application, the FDA requested that a report on study JMEN be submitted to this supplement in support of the treatment by histology interaction described below. This study report did not include the datasets but was considered a major amendment.

3. CMC/Device

The Chemistry Review of 6/18/08 noted that annotated draft labeling and a claim for categorical exclusion from the requirement for an Environmental Assessment were provided to support the new indication. The review concluded that "The information and data provided in the supplement are adequate to support the proposed changes. Approval is recommended."

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review of 5/20/08 noted that there were no changes to the Clinical Pharmacology/Pharmacokinetics section of the labeling and stated that the supplement is acceptable from the clinical pharmacology perspective.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

A single study (JMBD) was submitted in support of this efficacy supplement. The study design, demographics, and efficacy results are summarized in the following excerpt from the final labeling.

> A multi-center, randomized, open-label study in 1725 chemonaive patients with stage IIIb/IV NSCLC was conducted to compare the overall survival following treatment with ALIMTA in combination with cisplatin (AC) versus gemcitabine in combination with cisplatin (GC). ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m^2 with cisplatin administered intravenously at a dose of 75 mg/m^2 after ALIMTA administration, on Day 1 of each 21-day cycle. Gemcitabine was administered at a dose of 1250 mg/m^2 on Day 1 and Day 8, and cisplatin was administered intravenously at a dose of 75 mg/m^2 after administration of gemcitabine, on Day 1 of each 21-day cycle. Treatment was administered up to a total of 6 cycles, and patients in both treatment arms received folic acid, vitamin B_{12}, and dexamethasone.

Patient demographics of the intent to treat (ITT) population are shown in Table 8. The demographics and disease characteristics were well balanced.

Table 8: Summary of Patient Characteristics in Study of NSCLC — Combination with Cisplatin

Patient characteristic	**ALIMTA plus Cisplatin (AC) (N=862)**	**Gemcitabine plus Cisplatin (GC) (N=863)**
Age (yrs)		
Median (range)	61.1 (28.8-83.2)	61.0 (26.4-79.4)
Gender (%)		
Male/Female	70.2/29.8	70.1/29.9
Origin		
Caucasian	669 (77.6%)	680 (78.8%)
Hispanic	27 (3.1%)	23 (2.7%)
Asian	146 (16.9%)	141 (16.3%)
African descent	18 (2.1%)	18 (2.1%)
Stage at Entry (%)		
IIIb/IV	23.8/76.2	24.3/75.7
Histology (%)		
Nonsquamous NSCLC[a]	618 (71.7)	634 (73.5)
Adenocarcinoma	436 (50.6)	411 (47.6)
Large cell	76 (8.8)	77 (8.9)
Other[b]	106 (12.3)	146 (16.9)
Squamous	244 (28.3)	229 (26.5)
ECOG PS[c] (%)[d]		
0/1	35.4/64.6	35.6/64.3
Smoking History (%)[e]		
Ever/never smoker	83.1/16.9	83.9/16.1

[a] Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.

[b] The subgroup of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

[c] Eastern Cooperative Oncology Group Performance Status.

[d] ECOG PS was not reported for all randomized patients. Percentages are representative of N=861 for the ALIMTA plus cisplatin arm, and N=861 for the gemcitabine plus cisplatin arm.

[e] Smoking history was collected for 88% of randomized patients (N=757 for the ALIMTA plus cisplatin arm and N=759 for the gemcitabine plus cisplatin arm).

Patients received a median of 5 cycles of treatment in both study arms. Patients treated with ALIMTA plus cisplatin received a relative dose intensity of 94.8% of the protocol-specified ALIMTA dose intensity and 95.0% of the protocol-specified cisplatin dose intensity. Patients treated with gemcitabine plus cisplatin received a relative dose intensity of 85.8% of the protocol-specified gemcitabine dose intensity and 93.5% of the protocol-specified cisplatin dose intensity.

The primary endpoint in this study was overall survival. The median survival time was 10.3 months in the ALIMTA plus cisplatin treatment arm and 10.3 months in the gemcitabine plus cisplatin arm, with an adjusted hazard ratio of 0.94.

Table 9: Efficacy of ALIMTA plus Cisplatin versus Gemcitabine plus Cisplatin in First-line NSCLC — ITT Population

	ALIMTA plus Cisplatin (N=862)	Gemcitabine plus Cisplatin (N=863)
Median overall survival (95% CI)	10.3 mos (9.8-11.2)	10.3 mos (9.6-10.9)
Adjusted hazard ratio (HR)[a,b] (95% CI)	0.94 (0.84-1.05)	
Median progression-free survival (95% CI)	4.8 mos (4.6-5.3)	5.1 mos (4.6-5.5)
Adjusted hazard ratio (HR)[a,b] (95% CI)	1.04 (0.94-1.15)	
Overall response rate (95% CI)	27.1% (24.2-30.1)	24.7% (21.8-27.6)

[a] Adjusted for gender, stage, basis of diagnosis, and performance status.

[b] A HR that is less than 1.0 indicates that survival is better in the AC arm than in the GC arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the GC arm than in the AC arm.

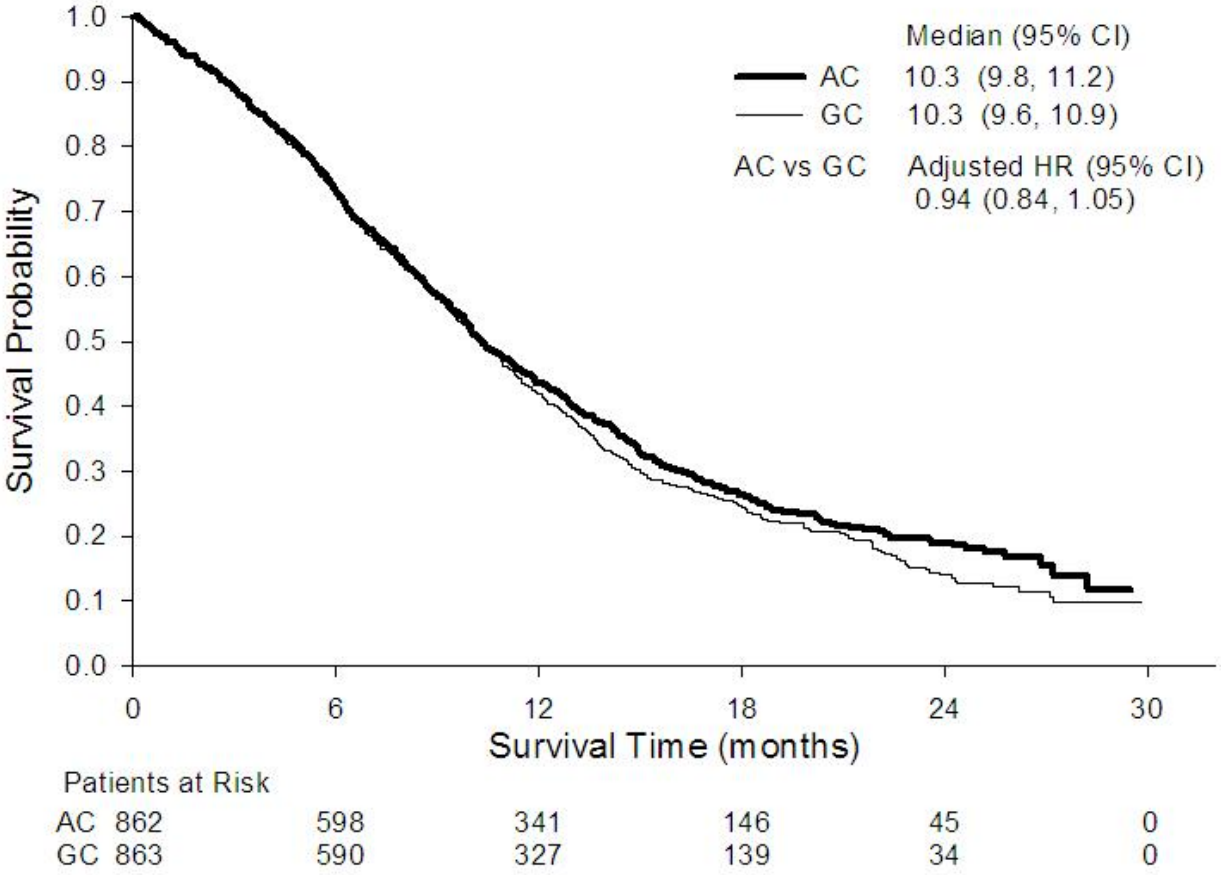

Figure 1: Kaplan-Meier Curves for Overall Survival ALIMTA plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in NSCLC — ITT Population

A pre-specified analysis of the impact of NSCLC histology on overall survival was examined. Clinically relevant differences in survival according to histology were

observed and are shown in Table 10. This difference in treatment effect for ALIMTA based on histology was also observed in the single-agent, second-line study.

Table 10: Overall Survival of ALIMTA plus Cisplatin versus Gemcitabine plus Cisplatin in NSCLC — Histologic Subgroups, ITT Population

Histology Subgroup	Median Overall Survival in Months (95% CI)				Unadjusted Hazard Ratio (HR)[a,b] (95% CI)	Adjusted Hazard Ratio (HR)[a,b,c] (95% CI)
	ALIMTA plus Cisplatin		Gemcitabine plus Cisplatin			
Nonsquamous NSCLC[d] (N=1252)	11.0 (10.1–12.5)	N=618	10.1 (9.3–10.9)	N=634	0.84 (0.74–0.96)	0.84 (0.74–0.96)
Adenocarcinoma (N=847)	12.6 (10.7-13.6)	N=436	10.9 (10.2-11.9)	N=411	0.84 (0.71-0.98)	0.84 (0.71-0.99)
Large Cell (N=153)	10.4 (8.6-14.1)	N=76	6.7 (5.5-9.0)	N=77	0.68 (0.48-0.97)	0.67 (0.48-0.96)
Other[e] (N=252)	8.6 (6.8-10.2)	N=106	9.2 (8.1-10.6)	N=146	1.12 (0.84-1.49)	1.08 (0.81-1.45)
Squamous Cell (N=473)	9.4 (8.4-10.2)	N=244	10.8 (9.5-12.1)	N=229	1.22 (0.99-1.50)	1.23 (1.00-1.51)

[a] A HR that is less than 1.0 indicates that survival is better in the AC arm than in the GC arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the GC arm than in the AC arm.

[b] Unadjusted for multiple comparisons.

[c] HRs adjusted for ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).

[d] Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.

[e] The subgroup of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

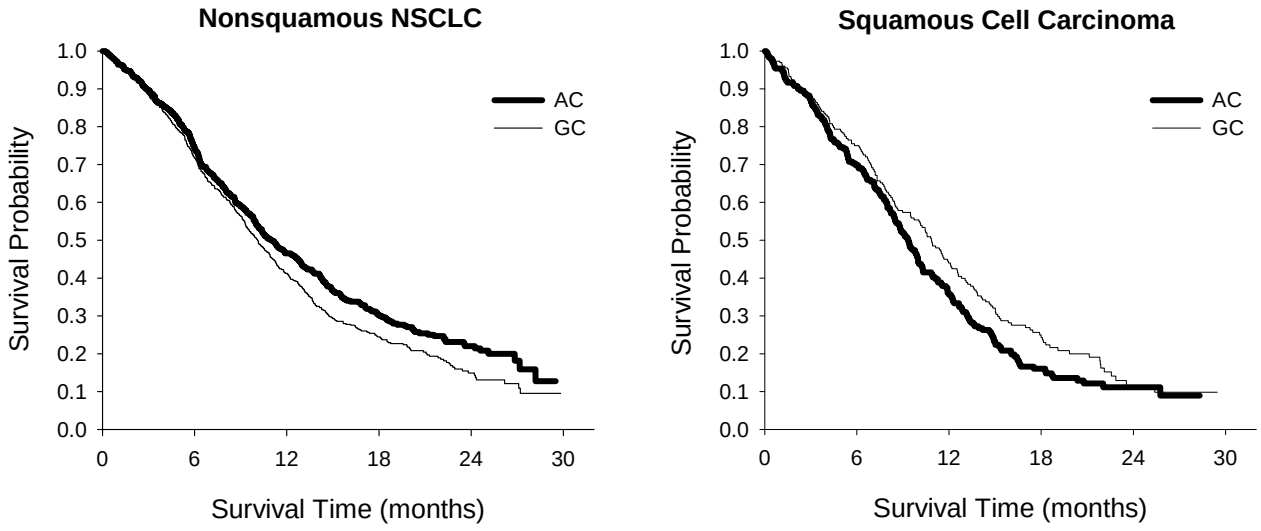

Figure 2: Kaplan-Meier Curves for Overall Survival ALIMTA plus Cisplatin (AC) versus Gemcitabine plus Cisplatin (GC) in NSCLC — Nonsquamous NSCLC and Squamous Cell Carcinoma

Study JMEI was previously submitted and reviewed and was used to support the accelerated approval of pemetrexed for the indication for use as a single agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy. In this submission the applicant provided a retrospective analysis of efficacy by histology to show that the adverse effect of pemetrexed in the squamous cell lung cancer population was consistent across studies and to justify restriction of the indication to patients with non-squamous histologies. The updated description of this study and the new analyses from the final labeling are excerpted below.

> A multi-center, randomized, open label study was conducted in patients with Stage III or IV NSCLC after prior chemotherapy to compare the overall survival following treatment with ALIMTA versus docetaxel. ALIMTA was administered intravenously over 10 minutes at a dose of 500 mg/m^2 and docetaxel was administered at 75 mg/m^2 as a 1-hour intravenous infusion. Both drugs were given on Day 1 of each 21-day cycle. All patients treated with ALIMTA received vitamin supplementation with folic acid and vitamin B_{12}. The study was intended to show either an overall survival superiority or non-inferiority of ALIMTA to docetaxel. Patient demographics of the intent to treat (ITT) population are shown in Table 11.

Table 11: Summary of Patient Characteristics in NSCLC Study

Patient characteristic	**ALIMTA** (N=283)	**Docetaxel** (N=288)
Age (yrs)		
Median (range)	59 (22-81)	57 (28-87)
Gender (%)		
Male/Female	68.6/31.4	75.3/24.7
Stage at Entry (%)		
III/IV	25.1/74.9	25.3/74.7
Diagnosis/Histology (%)		
Adenocarcinoma	154 (54.4)	142 (49.3)
Squamous	78 (27.6)	94 (32.6)
Bronchoalveolar	4 (1.4)	1 (0.3)
Other	47 (16.6)	51 (17.7)
Performance Status (%)[a]		
0-1	234 (88.6)	240 (87.6)
2	30 (11.4)	34 (12.4)

[a] Performance status was not reported for all randomized patients. Percentages are representative of N=264 for the ALIMTA and N=274 for the docetaxel arm.

> The primary endpoint in this study was overall survival. The median survival time was 8.3 months in the ALIMTA treatment arm and 7.9 months in the docetaxel arm, with a hazard ratio of 0.99 (*see* Table 12). The study did not show an overall survival superiority of ALIMTA.

Table 12: Efficacy of ALIMTA versus Docetaxel in Non-Small Cell Lung Cancer — ITT Population

	ALIMTA (N=283)	Docetaxel (N=288)
Median overall survival (95% CI)	8.3 mos (7.0-9.4)	7.9 mos (6.3-9.2)
Hazard ratio (HR) (95% CI)	0.99 (0.82-1.20)	
Median progression-free survival (95% CI)	2.9 mos (2.4-3.1)	2.9 mos (2.7-3.4)
Hazard ratio (HR) (95% CI)	0.97 (0.82-1.16)	
Overall response rate (95% CI)	8.5% (5.2-11.7)	8.3% (5.1-11.5)

A retrospective analysis of the impact of NSCLC histology on overall survival was examined. Clinically relevant differences in survival according to histology were observed and are shown in Table 13. This difference in treatment effect for ALIMTA based on histology was also observed in the first-line combination study.

Table 13: Overall Survival of ALIMTA versus Docetaxel in NSCLC — Histologic Subgroups, ITT Population

Histology Subgroup	**Median Overall Survival in Months (95% CI)**				**Unadjusted Hazard Ratio (HR)[a,b] (95% CI)**	**Adjusted Hazard Ratio (HR)[a,b,c] (95% CI)**
	ALIMTA		Docetaxel			
Nonsquamous NSCLC[d] (N=399)	9.3 (7.8–9.7)	N=205	8.0 (6.3–9.3)	N=194	0.89 (0.71–1.13)	0.78 (0.61–1.00)
Adenocarcinoma (N=301)	9.0 (7.6-9.6)	N=158	9.2 (7.5-11.3)	N=143	1.09 (0.83-1.44)	0.92 (0.69-1.22)
Large Cell (N=47)	12.8 (5.8-14.0)	N=18	4.5 (2.3-9.1)	N=29	0.38 (0.18-0.78)	0.27 (0.11-0.63)
Other[e] (N=51)	9.4 (6.0-10.1)	N=29	7.9 (4.0-8.9)	N=22	0.62 (0.32-1.23)	0.57 (0.27-1.20)
Squamous Cell (N=172)	6.2 (4.9-8.0)	N=78	7.4 (5.6-9.5)	N=94	1.32 (0.93-1.86)	1.56 (1.08-2.26)

[a] A HR that is less than 1.0 indicates that survival is better in the ALIMTA arm than in the docetaxel arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the docetaxel arm than in the ALIMTA arm.

[b] Unadjusted for multiple comparisons.

[c] HRs adjusted for ECOG PS, time since prior chemotherapy, disease stage, and gender.

[d] Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.

[e] The subgroup of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

Clinical Review

The Clinical Review was completed on 9/15/08. This issues associated with this application are summarized in the following Executive Summary of the review.

The initial proposed indication (draft labeling August 27, 2007) was [redacted] (b) (4) " The revised proposed labeling (June 17, 2008) is "Alimta is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology."

A total of 1,725 patients were randomized to receive either Alimta® (pemetrexed) + cisplatin (AC, 862 patients) or gemcitabine plus cisplatin (GC, 863 patients) between July 2004 and January 2006. AC patients received pemetrexed 500 mg/m^2 as a 10-minute intravenous infusion followed by cisplatin 75 mg/m^2 on day 1, every 21 days. GC patients received gemcitabine 1250 mg/m^2 as a 30 to 60-minute intravenous infusion on days 1 and 8 plus cisplatin 75 mg/m^2 on day 1, every 21 days. All patients received folic acid and vitamin B-12 supplementation and dexamethasone premedication. The primary efficacy endpoint was overall survival.

Baseline patient and disease characteristics were well balanced between the treatment arms as was therapy administered after disease progression (17% of AC patients received post-progression gemcitabine and 13% of GC patients received pemetrexed). Docetaxel was administered to about 25% of both AC and GC treated patients). Median survival was 10.28 months for both treatment arms. The 1 and 2-year survival rates were 43.48% and 18.94%, respectively, for the AC arm and 41.94% and 13.98%, respectively, for the GC arm.

Several issues arose in review of this NDA. The first concerns the GC schedule. In the study that led to approval of GC a four week schedule was used. In this application a 3 week schedule was used. However, when looking at the regimens the dose intensity of treatment is comparable for the two schedules and therapeutic results appear to be better for the 3 week schedule setting the non-inferiority bar somewhat higher. Moreover the 4 week GC schedule is not well tolerated. The reviewer believes that these points are valid. If so, there are 12 published first-line randomized studies that enrolled 3,254 patients to the every 21 day GC schedule. Those studies can be used to estimate the control effect size.

The second issue in evaluating this NDA involves the non-inferiority survival analysis. The sponsor used two non-inferiority tests, the fixed margin method and the Rothmann percent retention analysis. Using the Cox regression adjusted fixed margin analysis the non-inferiority test was statistically significant (one-sided $p<0.001$), with the primary cofactor adjusted survival hazard ratio (HR) estimated to be 0.94 (95% CI: 0.84 to 1.05), with the entire confidence interval for HR well below the 1.17645 non-inferiority margin. The confidence interval for the survival HR implies that the risk of death for the AC arm was 16% lower than that for the GC arm in the best-case scenario, and 5% higher in the worst-case scenario. In addition, the Rothmann percent retention analysis showed that AC retained 120% of GC's survival benefit over single-agent cisplatin, with a 95% confidence interval of 83% to 190% (that is, at least 83% of the benefit of GC over single-agent cisplatin was retained by AC).

One problem impeding demonstration of non-inferiority of survival was the administration of post-discontinuation cytotoxic and targeted chemotherapy. Approximately 50% of patients on each arm received such therapy. Among patients initially treated with pemetrexed 16.7% crossed over to receive gemcitabine and among patients initially treated with gemcitabine 13.4% crossed over to receive pemetrexed. Also approximately 26% of patients on each study arm received post-discontinuation docetaxel. Other drugs were administered fairly uniformly to study patients.

A third issue affecting a non-inferiority claim is the observed difference in the treatment effect of Alimta based on NSCLC histology with the efficacy benefits of Alimta demonstrated primarily in patients with non-squamous NSCLC. There is a biochemical rationale for this observation in that higher levels of thymidylate synethetase have been demonstrated in squamous than in adenocarcinoma/large cell anaplastic carcinoma cells.

The reviewer's opinion is that while non-inferiority cannot be conclusively demonstrated there is substantial evidence that Alimta is active in non-squamous NSCLC. In 2 randomized Alimta NSCLC studies reviewed by the Agency, JMDB and JMEI and from preliminary results of the maintenance study, JMEN, the treatment by histology interaction test significantly favored Alimta treatment for both overall survival and progression free survival.

Regarding safety, a median of 5 cycles of therapy was administered to patients in both arms. Dose adjustments (delays, reductions, and omissions) were less frequent in patients treated with AC compared to patients treated with GC. Most pemetrexed dose reductions were attributed to neutropenia only, while gemcitabine and cisplatin dose reductions were mainly attributed to neutropenia, thrombocytopenia, febrile neutropenia, and leukopenia. The dose intensity for pemetrexed and cisplatin was 94.8% and 95.0%, compared with 85.8% and 93.5% for gemcitabine and cisplatin, respectively. Overall, the number of deaths reported by investigators to be possibly due to study-drug toxicity was low on both arms; 9 deaths (1.1%) in the AC arm and 6 deaths (0.7%) in the GC arm. The number of patients experiencing possibly study-drug related treatment emergent adverse events (TEAEs) or

serious adverse events (SAEs) was similar between treatment arms. Patients on the AC arm experienced statistically significantly lower incidences of febrile neutropenia than patients on the GC arm (9 cases [1.1%] versus 25 cases [3.0%], p=0.005), but statistically higher incidences of renal failure (6 cases [0.7%] versus 0 cases, p=0.031). Statistically significantly more patients in the GC arm than in the AC arm experienced possibly study-drug related Grade 3 and 4 laboratory toxicity (39.9% versus 22.6%, p<0.001) including. anemia (9.9% versus 5.6%, p<0.001), leukopenia (7.6% versus 4.8%, p<0.001), neutropenia (26.7% versus 15.1%, p<0.001), and thrombocytopenia (12.7% versus 4.1%, p<0.001). Possibly study-drug related Grade 3/4 febrile neutropenia occurred in significantly more patients on the GC arm than on the AC arm (3.7% versus 1.3%, p=0.002)

Patients in the AC arm experienced significantly more possibly study-drug related Grade 3/4 anorexia (2.4% versus 0.7%, p=0.009) and Grade 3/4 nausea (7.2% versus 3.9%, p=0.004) than patients on the GC arm, although the incidences of Grade 3/4 vomiting (6.1% versus 6.1%, p=1.000), Grade 3/4 weight loss (0 versus 0.1%, p=0.497),and Grade 3/4 dehydration (1.2% versus 0.7%, p=0.452) were similar between arms.

There was no significant difference in the number of hospitalizations observed between treatment arms. There were significantly fewer patients with red blood cell and platelet transfusions administered to patients on the AC arm as compared to the GC arm.

The review made the following recommendation on regulatory action.

The reviewing medical officer recommends that AC receive full approval for initial treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology (b) (4) who meet the eligibility criteria of study JMDB.

The review did not recommend any post-marketing action.

Statistical Reviews

The Statistical Review and Evaluation of study JMDB was completed on 6/11/08. The review had the following conclusions and recommendations.

In this submission, the sponsor submitted a Phase IV commitment Study JMDB as a part of requirement for the accelerated approval of pemetrexed (Alimta) as a single agent for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004. This is a multicenter, randomized, Phase III trial study to compare the efficacy and safety of pemetrexed in combination with cisplatin (AC) with that of gemcitabine in combination with cisplatin (GC) in patients with locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer. In this study, the primary efficacy measure was the overall survival. The non-inferiority analysis of the treatment efficacy was conducted using Cox proportional hazards model. The survival distribution was displayed using Kaplan-Meier estimator. The percent retention analysis was also conducted to support the efficacy results.

Although the statistical analyses suggested that the AC treatment arm was non-inferior to the GC treatment arm in the reduction of the risk of death in patients with locally advanced or metastatic NSCLC, such a statement seems to be problematic. First, the active control effect size was not well established; second, the non-inferiority margin was not well established; third, there were 50% post-discontinuation therapy and the statistically significant post-discontinuation crossover therapy; finally, there was a statistically significant interaction between treatment arm and patient histology categories These factors together compromised the statistical findings of this non-inferiority study and greatly reduced the credibility of the findings of the statistical analyses. This also makes the non-inferiority results hard to interpret. From a statistical perspective the data and analyses do not support the sponsor's non-inferiority claim for Alimta in the treatment of patients with locally advanced or metastatic NSCLC who have not received prior chemotherapy.

Because of the treatment by histology interaction in a prospective analysis of study JMDB and in a retrospective analysis of study JMEI, the applicant was asked to submit the study report for study JMEN which was reported to show a similar interaction. The Statistical Review and Evaluation of the study report was completed on 9/23/08. The review had the following conclusions and recommendations.

Pemetrexed (as a single agent, Alimta) received an accelerated approval for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004 based on the randomized study JMEI comparing pemetrexed monotherapy with docetaxel (Please see the statistical review for this study by Dr. Yong-cheng Wang, dated August 11, 2004). As a condition of this approval, as per Subpart H, further studies (JMDB and JMEN) were required to confirm and describe the clinical benefit of pemetrexed.

Study JMDB was a multicenter, randomized, Phase III trial comparing the efficacy and safety of Alimta + cisplatin (AC) with that of gemcitabine + cisplatin (GC) in patients with a diagnosis of locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer. First patient was enrolled on July 6, 2004 and the database was locked on January 25, 2007. In August 2007, the sponsor submitted the study JMDB. Please see the statistical review for this study by Dr. Fanhui Kong, dated June 11, 2008.

When the sponsor submitted Study JMDB, study JMEN was on going. Study JMEN was a Phase III trial comparing the efficacy and safety of pemetrexed + best supportive care versus best supportive care as a maintenance treatment for advanced NSCLC.

On June 23, 2008 FDA requested the final study report for Study JMEN be submitted as an amendment to the pending 1st line application. The sponsor submitted the report on June 24, 2008 without datasets. Therefore, this reviewer will review the submitted analyses without confirming the results.

In February 2007, the primary objective for Study JMEN was changed from overall survival (OS) to progression free survival (PFS). The submitted JMEN study report included the final PFS analysis and an interim analysis for OS. As indicated in the FDA End of Phase 2 (EOP2) meeting minutes and the January 11, 2007 meeting minutes, OS should be the primary efficacy endpoint.

Results from previous randomized, Phase 3 studies in advanced NSCLC (Study JMEI and Study JMDB) indicated that for patients treated with pemetrexed, those with nonsquamous histology (adenocarcinoma, large cell carcinoma, and other or unknown histology) tend to have better overall survival and progression-free survival compared to patients with squamous histology. Patients with squamous-cell NSCLC had worse survival with Alimta compared to control arm. In the JMEN study report, the sponsor also performed analyses for such interactions. Although the analyses of JMEN showed a trend toward the same interaction as

Study JMEI and Study JMDB did, the p-values from interaction and subgroup analyses were not interpretable because no alpha (type-I error) was allocated for the interaction test or any subgroup analyses in the statistical analysis plan for Study JMEN. The OS results should also be interpreted with caution since the submitted OS results were from an interim analysis with a total of 300 deaths,

Nevertheless, the sponsor analyses of JMEN appear to show a trend toward the same interactions for OS and PFS as Study JMEI and Study JMDB did.

The progression-free survival and overall survival results by histology in this study are shown below in Table 6 from the review.

Table 6. Progression-Free Survival and Overall Survival by Histologic Subgroups All Randomized Patients Study JMEN

	Final PFS		Preliminary OS	
	Pemetrexed (N = 441) median mos	Placebo (N = 222) median mos	Pemetrexed (N = 441) median mos	Placebo (N = 222) median mos
Histologic Subgroup	HR (95% CI) p-Value		HR (95% CI) p-Value	
Nonsquamous (n = 482)	4.50	2.60	14.36	9.43
	0.44 (0.36-0.55)		0.66 (0.49-0.88)	
	< 0.00001		0.005	
Adenocarcinoma (n = 329)	4.73	2.60	16.39	11.73
	0.45 (0.35-0.59)		0.73 (0.50-1.05)	
	< 0.00001		0.091	
Large Cell (n = 20)	3.48	2.09	9.13	5.45
	0.40 (0.13-1.22)		0.42 (0.13-1.38)	
	0.109		0.154	
Other/Indeterminate (n = 133)	4.21	2.79	11.27	7.03
	0.43 (0.28-0.670)		0.47 (0.28-0.80)	
	0.0002		0.005	
Squamous (n = 181)	2.79	2.60	9.63	11.86
	0.69 (0.49-0.98)		1.28 (0.85-1.93)	
	0.039		0.231	

Abbreviations: CI = confidence interval; HR = hazard ratio; mos = months; N = number of randomized patients; n = number of patients in category; OS = overall survival; PFS = progression-free survival.

Statistical Team Leader Memo

The Statistical Team Leader's Memo was completed on 9/24/08 and reached the following conclusion.

One well-controlled Phase IV commitment study JMDB was submitted to compare the efficacy and safety of AC with that of GC in patients with locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer. In this study, the primary efficacy measure was the overall survival. The study was designed as a non-inferiority study using fixed margin approach. Even though the choice of the control does not lend to NI analysis, control treatment as administered was in itself not of concern.

Although the confidence interval for HR is below the protocol specified fixed non-inferiority margin, (a) highly significant treatment by histology interaction effect, (b) almost 50% of patients receiving post-discontinuation therapy, and (c) the lack of historical study(ies) to estimate effect size of GC, make the interpretation of the study results problematic. The treatment by histology interaction observed in Study JMEI in which Alimta was administered as monotherapy for the treatment of second-line NSCLC can not be considered confirmatory due to the retrospective post-hoc analyses and observed imbalances between treatment groups within each histology subgroup. Interim results of Study JMEN in which Alimta was administered as a maintenance therapy, appear to suggest similar results which needs further follow-up data with the final overall survival analysis.

The memo made the following recommendation.

This application is seeking approval of Alimta in combination with cisplatin for the first-line treatment of patients with non-squamous NSCLC based on the results of Study JMDB. Because of treatment cross-over in nearly 50% of patients and a highly statistically significant qualitative treatment-histology interaction, the primary hypothesis of non-inferiority with respect overall survival can not be concluded based on this study. The results of JMDB generates the hypotheses that (1) patients with non-squamous NSCLC benefit with the treatment of Alimta in combination with cisplatin, and (2) Alimta plus cisplatin harms the patients with squamous cell NSCLC when compared to gemcitabine plus cisplatin.

Retrospective analyses of Study JMEI where Alimta was administered as monotherapy in the second-line treatment of NSCLC, confirms that Alimta compared to docetaxel harms the patients with squamous cell NSCLC. In this study, majority of the patients with non-squamous histology were those with adeno carcinoma. The advantage of Alimta over docetaxel is not obvious in the

adeno carcinoma group and therefore, benefit of Alimta over docetaxel as treatment for patients with non-squamous NSCLC can not be concluded. Furthermore, post-hoc subgroup analyses with observed imbalances in patient characteristics between treatment arms make the inference of these analyses problematic.

Interim analyses of Study JMEN where Alimta was compared to placebo as maintenance therapy after patients had received platinum containing doublet chemotherapy, confirms that Alimta should not be used in patients with squamous cell NSCLC as the survival in the Alimta treated group is worse than placebo in this subgroup of patients. Although the interim results suggest that Alimta may be beneficial in patients with non-squamous NSCLC, the null hypothesis of no difference between Alimta and placebo in the ITT population could not be rejected based on the pre-specified type I error rate allocation. These results need be confirmed with the verification of the data and final overall survival analyses.

For the above reasons, the data submitted in this application does not provide adequate support to the sponsor's claim that Alimta in combination with cisplatin has demonstrated benefit in the first-line treatment of patients with non-squamous NSCLC. The data presented provides the evidence that Alimta should not be used in patients with squamous cell NSCLC.

8. Safety

The safety of pemetrexed in combination with cisplatin in the first-line treatmement of NSCLC is summarized in the following excerpt from the final labeling.

Table 4 provides the frequency and severity of adverse reactions that have been reported in >5% of 839 patients with NSCLC who were randomized to study and received ALIMTA plus cisplatin and 830 patients with NSCLC who were randomized to study and received gemcitabine plus cisplatin. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin B_{12}.

Table 4: Adverse Reactions in Fully Supplemented Patients Receiving ALIMTA plus Cisplatin in NSCLC[a]

Reaction[b]	ALIMTA/cisplatin (N=839)		Gemcitabine/cisplatin (N=830)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
All Adverse Reactions	90	37	91	53
Laboratory				
Hematologic				
Anemia	33	6	46	10
Neutropenia	29	15	38	27
Leukopenia	18	5	21	8
Thrombocytopenia	10	4	27	13
Renal				
Creatinine elevation	10	1	7	1
Clinical				
Constitutional Symptoms				
Fatigue	43	7	45	5

Gastrointestinal				
Nausea	56	7	53	4
Vomiting	40	6	36	6
Anorexia	27	2	24	1
Constipation	21	1	20	0
Stomatitis/Pharyngitis	14	1	12	0
Diarrhea	12	1	13	2
Dyspepsia/Heartburn	5	0	6	0
Neurology				
Neuropathy-sensory	9	0	12	1
Taste disturbance	8	0[c]	9	0[c]
Dermatology/Skin				
Alopecia	12	0[c]	21	1[c]
Rash/Desquamation	7	0	8	1

[a] For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA.

[b] Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity.

[c] According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

No clinically relevant differences in adverse reactions were seen in patients based on histology.

In addition to the lower incidence of hematologic toxicity on the ALIMTA and cisplatin arm, use of transfusions (RBC and platelet) and hematopoietic growth factors was lower in the ALIMTA and cisplatin arm compared to the gemcitabine and cisplatin arm.

The following additional adverse reactions were observed in patients with non-small cell lung cancer randomly assigned to receive ALIMTA plus cisplatin.

Incidence 1% to 5%

Body as a Whole — febrile neutropenia, infection, pyrexia
General Disorders — dehydration
Metabolism and Nutrition — increased AST, increased ALT
Renal — creatinine clearance decrease, renal failure
Special Senses — conjunctivitis

Incidence Less than 1%

Cardiovascular — arrhythmia
General Disorders — chest pain
Metabolism and Nutrition — increased GGT
Neurology — motor neuropathy

9. Advisory Committee Meeting

Although this application was not referred to an Advisory Committee, advice was requested individually from two statistical consultants (Drs. David Harrington and Tom Fleming) and one clinical consultant (Dr. David Johnson).

Dr. Johnson provided the following answers to our questions regarding this application.

1. Do you believe that every 3 week schedule of gemcitabine plus cisplatin, rather than the every 4 week approved schedule is an acceptable comparator regimen?

YES. I think the extant data in the literature coupled with my own experience suggests the every 3 week scheduled is a reasonable comparator regimen.

2. Do you believe that the combination of Alimta plus cisplatin has demonstrated to be non-inferior to the combination of gemcitabine and cisplatin?

YES. Although I share the concerns of the FDA reviewer vis-à-vis the proposed margin and analysis I believe these data coupled with other data in the literature [or recently presented at ASCO 2008] support the claim of non-inferiority.

3. Given the results of study JMDB and the results from JMEI and JMEN studies, do you believe that Alimta has demonstrated efficacy in adenocarcinoma and large cell lung cancer?

YES. These data and other studies sponsored by Lilly strongly suggest pemetrexed exerts a differential effect on adenocarcinomas and large cell carcinomas as compared with squamous carcinomas.

Dr. David Harrington provided the following answers to the FDA questions.

1. Do you believe that every 3 week schedule of gemcitabine plus cisplatin, rather than the every 4 week approved schedule is an acceptable comparator regimen?

Yes, it is my opinion that the 4 week schedule used in the Sandler GC vs C trial can be used to establish the GC effect over platinum alone. There is sufficient data to support the claim that a 3 week schedule of GC would have equivalent or better efficacy than a 4 week schedule, when compared to platinum alone. The three week regimen also seems to be more tolerable.

2. Do you believe that the combination of Alimta plus cisplatin has demonstrated to be non-inferior to the combination of gemcitabine and cisplatin?

No, not across all histologies. The primary analysis of AC vs GC seems to support a claim of non-inferiority, whether one uses the fixed non-inferiority margin of 15% or a `percent retention margin' of 50%, but the strong evidence of a qualitative interaction in squamous vs non-squamous histology makes the overall analysis of non-inferiority difficult to interpret. Specifically, the AC regimen seems to be superior in the non-squamous histologies and inferior in squamous cell histology. Several aspects of the interaction make it credible: statistical tests for interactions typically have low power, and the test in the JMDB study is highly significant; the retrospective analysis of JMEI found the same interaction, confirming the result in JMDB; although the analysis of JMEN is preliminary, there is also a trend toward the same interaction. Because of the significant interaction, I would support a more limited labeling for use in adeno and large cell NSCLC, rather than the broad labeling of NI presented in the briefing document.

The analysis presented in the briefing document does have some aspects that may weaken the evidence for the interaction, but in my opinion these are not serious enough to invalidate the analysis. The adjusted analysis presented for the JMEI study uses a variable (sex) that was not a stratification factor in the randomization, but sex has been shown to significantly associated with outcome in this disease in other studies. The JMEI study shows superiority in large cell but not adeno carcinoma, while the JMDB shows superiority in both subsets.

3. Given the results of study JMDB and the results from JMEI and JMEN studies, do you believe that Alimta has demonstrated efficacy in adenocarcinoma and large cell lung cancer?

Yes, I do believe Alimta has demonstrated efficacy in these subsets; it has certainly demonstrated NI in these subsets. As noted in the briefing document, a large subset of patients received additional therapy after finishing AC or GC treatment. Even though these additional treatments may obscure the `pure effect` of Alimta on survival, I believe they reflect the practice of treating end-stage NSCLC patients, the large majority of whom fail several therapies. As was noted in the briefing document, cross-over therapy after receiving treatment in a randomized trial may dilute treatment differences. If the indication for AC is limited to non-squamous histology, however, the estimated treatment effect is positive for patients with these histologies, so the cross-overs may be masking an even larger treatment effect in this subgroup.

General comments

The briefing document reports a number of unplanned subgroup analyses done by the sponsor, largely in response to the unexpected and statistically significant interaction between treatment and histology. Because the interaction is a qualitative one (treatment effects in opposite directions in two subsets defined by histology), is highly significant, and appears confirmed in two of three studies, I believe the subgroup analyses are warranted.

AC seems no less tolerable than GC, so there does not seem to be a reason to deny the indication based on side-effects.

It is not clear whether the labeling should include the claim that AC is superior to GC as initial therapy in non-squamous, NSCLC histology, or the more conservative claim that AC is at least as effective as GC in this setting. Had the JMDB trial been designed as an NI trial in this subset of NSCLC, the outcome of the trial may well have supported a claim of superiority because of the confidence interval estimate of the AC vs GC effect. The interaction of treatment by histology appears to have been unexpected, however, and appears not to be present in the adeno-carcinoma subset in JMEI. I would favor the more conservative labeling of `at least as effective' in the non-squamous histology.

Dr. Tom Fleming provided extensive comments which are attached as Appendix 2 to the Statistical Team Leader's Memo. His brief concluding assessment is quoted below.

Based on the JMDB, JMEI and JMEN trials, it appears that the large cell patients provide the only setting where substantial evidence for efficacy could emerge when complete data are available from all three trials. Post-hoc pooling of large cell and adenocarcinoma (i.e., excluding squamous cell patients) would be inappropriate and contradicts the JMDB SAP which clearly specifies on p 3293 that the three cell types would be considered separately. Hence, the evidence for efficacy in adenocarcinoma patients is inconsistent, and is especially problematic in the JMEI trial where the estimate of the pemetrexed to docetaxel hazard ratio is 1.07 and where the justification of any NI margin greater than 1.1 is weak, (e.g., see Fleming, *Statistics in Medicine* 27: 317-332,2008). Finally, the evidence that pemetrexed has a harmful effect on overall survival in squamous cell patients is similarly persuasive to the evidence for benefit in large cell patients. This deserves proper attention in any decisions about approval and labeling.

10. Pediatrics

The applicant has previously been given a waiver for pediatric studies for this population since NSCLC does not occur in pediatric patients.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

There are no unresolved labeling issues.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  I have considered the recommendations of the statistical and clinical reviewers and consultants. It is clear that everyone agrees that pemetrexed should not be approved for use in patients with NSCLC of squamous cell histology because of the unfavorable results with pemetrexed in this subgroup in three studies of different designs (JMBD, JMEI, and JMEN). The applicant has agreed to limit both the first-line and second-line indications to patients with non-squamous histologies and to make it clear that pemetrexed is not indicated in patients with squamous cell lung cancer. What is less clear is how to interpret the results of the JMBD study given the statistically significant interaction in this subgroup. I

believe that the rationale for approval was best expressed by Dr. Harrington's answer to question 3 and his general comments. I concur with the recommendation for approval made by the clinical reviewer and with the recommendations of Drs. Harrington and Johnson.

- Recommendation for Postmarketing Risk Management Activities

  None

- Recommendation for other Postmarketing Study Commitments

  No new postmarketing study commitments are recommended.

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/s/

Robert Justice
9/26/2008 06:27:39 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 21-462

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Hathaway, Steve
Zhou, Liang
Lee Ham, Doo Y
Verbois, Leigh
Tang, Shengui
Sridhara, Raji
Cohen, Martin
Justice, Robert

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

MEDICAL REVIEW(S)

Clinical Review of an NDA Submission

Application Type	NDA 21-462
Submission Number	SE1-015
Letter Date	8/27/07
Stamp Date	8/27/07
Reviewer Name	Martin H. Cohen, M.D.
Review Completion Date	5/21/08
Established Name	Pemetrexed
Trade Name	Alimta®
Therapeutic Class	Antifolate
Sponsor	Eli Lilly and Company.
Priority Designation	S

Formulation:
Pemetrexed for injection is a white to either light-yellow or green-yellow lyophilized powder available in sterile single-use vials containing 500 mg pemetrexed.

Dosing Regimen:
Pemetrexed 500 mg/m^2 is administered i.v. on Day 1 of each 21-day cycle in combination with cisplatin 75 mg/m^2 i.v. beginning 30 minutes after pemetrexed administration.

Dosage Forms And Strengths:
500 mg vial for injection

Proposed Indication
The initial proposed indication (August 27, 2007) was "(b) (4) " The revised proposed labeling (June 17, 2008) is "Alimta is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology."

Other Indication(s)

- Pemetrexed is indicated for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy.
- Pemetrexed in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

Intended Population
See proposed indication

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1.0 EXECUTIVE SUMMARY

The initial proposed indication (draft labeling August 27, 2007) was "(b) (4) ." The revised proposed labeling (June 17, 2008) is "Alimta is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology."

A total of 1,725 patients were randomized to receive either Alimta® (pemetrexed) + cisplatin (AC, 862 patients) or gemcitabine plus cisplatin (GC, 863 patients) between July 2004 and January 2006. AC patients received pemetrexed 500 mg/m^2 as a 10-minute intravenous infusion followed by cisplatin 75 mg/m^2 on day 1, every 21 days. GC patients received gemcitabine 1250 mg/m^2 as a 30 to 60-minute intravenous infusion on days 1 and 8 plus cisplatin 75 mg/m^2 on day 1, every 21 days. All patients received folic acid and vitamin B-12 supplementation and dexamethasone premedication. The primary efficacy endpoint was overall survival.

Baseline patient and disease characteristics were well balanced between the treatment arms as was therapy administered after disease progression (17% of AC patients received post-progression gemcitabine and 13% of GC patients received pemetrexed). Docetaxel was administered to about 25% of both AC and GC treated patients). Median survival was 10.28 months for both treatment arms. The 1 and 2-year survival rates were 43.48% and 18.94%, respectively, for the AC arm and 41.94% and 13.98%, respectively, for the GC arm.

Several issues arose in review of this NDA. The first concerns the GC schedule. In the study that led to approval of GC a four week schedule was used. In this application a 3 week schedule was used. However, when looking at the regimens the dose intensity of treatment is comparable for the two schedules and therapeutic results appear to be better for the 3 week schedule setting the non-inferiority bar somewhat higher. Moreover the 4 week GC schedule is not well tolerated. The reviewer believes that these points are valid. If so, there are 12 published first-line randomized studies that enrolled 3,254 patients to the every 21 day GC schedule. Those studies can be used to estimate the control effect size.

The second issue in evaluating this NDA involves the non-inferiority survival analysis. The sponsor used two non-inferiority tests, the fixed margin method and the Rothmann percent retention analysis. Using the Cox regression adjusted fixed margin analysis the non-inferiority test was statistically significant (one-sided $p<0.001$), with the primary cofactor adjusted survival hazard ratio (HR) estimated to be 0.94 (95% CI: 0.84 to 1.05), with the entire confidence interval for HR well below the 1.17645 non-inferiority margin. The confidence interval for the survival HR implies that the risk of death for the AC arm was 16% lower than that for the GC arm in the best-case scenario, and 5% higher in the worst-case scenario. In addition, the Rothmann percent retention analysis showed that AC retained 120% of GC's survival benefit over single-agent cisplatin, with a 95% confidence interval of 83% to 190% (that is, at least 83% of the benefit of GC over single-agent cisplatin was retained by AC).

One problem impeding demonstration of non-inferiority of survival was the administration of post-discontinuation cytotoxic and targeted chemotherapy. Approximately 50% of patients on each arm received such therapy. Among patients initially treated with pemetrexed 16.7% crossed over to receive gemcitabine and among patients initially treated with gemcitabine 13.4% crossed over to receive pemetrexed. Also approximately 26% of patients on each study arm received post-discontinuation docetaxel. Other drugs were administered fairly uniformly to study patients.

A third issue affecting a non-inferiority claim is the observed difference in the treatment effect of Alimta based on NSCLC histology with the efficacy benefits of Alimta demonstrated primarily in patients with non-squamous NSCLC. There is a biochemical rationale for this observation in that higher levels of thymidylate synethetase have been demonstrated in squamous than in adenocarcinoma/large cell anaplastic carcinoma cells.

The reviewer's opinion is that while non-inferiority cannot be conclusively demonstrated there is substantial evidence that Alimta is active in non-squamous NSCLC. In 2 randomized Alimta NSCLC studies reviewed by the Agency, JMDB and JMEI and from preliminary results of the maintenance study, JMEN, the treatment by histology interaction test significantly favored Alimta treatment for both overall survival and progression free survival.

Regarding safety, a median of 5 cycles of therapy was administered to patients in both arms. Dose adjustments (delays, reductions, and omissions) were less frequent in patients treated with AC compared to patients treated with GC. Most pemetrexed dose reductions were attributed to neutropenia only, while gemcitabine and cisplatin dose reductions were mainly attributed to neutropenia, thrombocytopenia, febrile neutropenia, and leukopenia. The dose intensity for pemetrexed and cisplatin was 94.8% and 95.0%, compared with 85.8% and 93.5% for gemcitabine and cisplatin, respectively. Overall, the number of deaths reported by investigators to be possibly due to study-drug toxicity was low on both arms; 9 deaths (1.1%) in the AC arm and 6 deaths (0.7%) in the GC arm. The number of patients experiencing possibly study-drug related treatment emergent adverse events (TEAEs) or

serious adverse events (SAEs) was similar between treatment arms. Patients on the AC arm experienced statistically significantly lower incidences of febrile neutropenia than patients on the GC arm (9 cases [1.1%] versus 25 cases [3.0%], p=0.005), but statistically higher incidences of renal failure (6 cases [0.7%] versus 0 cases, p=0.031). Statistically significantly more patients in the GC arm than in the AC arm experienced possibly study-drug related Grade 3 and 4 laboratory toxicity (39.9% versus 22.6%, p<0.001) including. anemia (9.9% versus 5.6%, p<0.001), leukopenia (7.6% versus 4.8%, p<0.001), neutropenia (26.7% versus 15.1%, p<0.001), and thrombocytopenia (12.7% versus 4.1%, p<0.001). Possibly study-drug related Grade 3/4 febrile neutropenia occurred in significantly more patients on the GC arm than on the AC arm (3.7% versus 1.3%, p=0.002)

Patients in the AC arm experienced significantly more possibly study-drug related Grade 3/4 anorexia (2.4% versus 0.7%, p=0.009) and Grade 3/4 nausea (7.2% versus 3.9%, p=0.004) than patients on the GC arm, although the incidences of Grade 3/4 vomiting (6.1% versus 6.1%, p=1.000), Grade 3/4 weight loss (0 versus 0.1%, p=0.497),and Grade 3/4 dehydration (1.2% versus 0.7%, p=0.452) were similar between arms.

There was no significant difference in the number of hospitalizations observed between treatment arms. There were significantly fewer patients with red blood cell and platelet transfusions administered to patients on the AC arm as compared to the GC arm.

1.1 Recommendation On Regulatory Action

The reviewing medical officer recommends that AC receive full approval for initial treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology (adenocarcinoma and large cell anaplastic carcinoma) who meet the eligibility criteria of study JMDB.

1.2 Recommendation On Post-marketing Actions

None at this time.

1.2.1 Risk Management Activity

Continue surveillance of AE's.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None at this time.

1.3 Summary Of Clinical Findings

1.3.1 Overview of Clinical Program

Study JMDB, the pivotal trial, was a multicenter (177 study centers in 26 countries/ regions), randomized, open-label, Phase 3 study for first-line treatment of patients with Stage IIIB (not amenable to curative treatment) or Stage IV NSCLC. Patients were to be randomly assigned to receive pemetrexed plus cisplatin (AC) or gemcitabine plus cisplatin (GC), both regimens administered as a 21 day cycle. The primary efficacy objective was overall survival. Secondary objectives were to compare the following between treatment arms: progression-free survival time (PFS); time-to-progressive disease (TtPD); objective tumor response; duration of tumor response (DoR); time-to-treatment failure (TtTF); toxicities; and risk/benefit (relative to survival). Patients enrolled in this study were men or women at least 18 years of age with adequate bone marrow reserve, hepatic and renal function, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Prior radiation therapy was allowed to <25% of the bone marrow if it was completed at least 4 weeks before study enrollment and all toxicities had resolved. The randomized population included 1725 patients (AC arm = 862 patients; GC arm = 863 patients). The first patient was enrolled on 06 July 2004 and the last patient visit (data cut-off) was 25 January 2007.

A Cox proportional hazard model (adjusted for prognostic factors) was used to compare noninferiority between treatment arms for all time-to-event variables. The protocol-defined noninferiority margin, determined by the fixed margin method, was set at 1.17645. The Kaplan-Meier method was used to estimate parameters (medians, quartiles, and point estimates) for time-to-event endpoints. The primary analysis was also interpreted relative to the historical benefit for GC treatment using the percent retention Rothmann method. Tumor response rates were compared between treatment arms based on an unadjusted, normal-distribution approximation for the difference in rates. Log-rank statistics were calculated to compare unadjusted covariates for time-to-event endpoints, and the Fisher's Exact test was used to compare treatments for categorical variables. Tests were conducted as follows: noninferiority tests at one-sided alpha (α)=0.025 level, superiority tests at α=0.05 level; two-sided confidence intervals (CI) at 95%. In addition, a limited independent central review of the dates of objective progressive disease was conducted on a subset of 333 randomly selected patients. The purpose of this independent review was to look for any evidence of a systematic bias in investigator assessments of progressive disease that would favor one treatment arm with respect to PFS. As prespecified in the analysis plan, if the 2 estimates for HR were found to be similar, then there would be no significant bias from investigator-assessed data. The sample size and determination of the fixed margin was based on a one-sided test, assuming a true value of HR=1.0, with 80% probability of rejecting H_0: HR $\geq$1.17645; this corresponds to GC having a 15% lower hazard (risk of death) than AC (that is, AC has 15% higher risk of death than GC). These assumptions required at least 1190 deaths of patients randomized for treatment for the final analyses. After 1190 death events were known and confirmed by Lilly, the database was locked. After the time of validation and final datalock, the total number of deaths was 1270.

1.3.2 Efficacy

The baseline patient, disease characteristics, and prognostic factors were well balanced between the treatment arms, and are generally reflective of the overall population of patients with NSCLC. The median age was 61 years on both treatment arms, and the majority of patients were Caucasian (78.2%), male (70.1%), and reported ever using tobacco (73.4%). Most patients in this study had Stage IV disease (75.9%) and ECOG performance status of 1 (64.3%). In both treatment arms, adenocarcinoma was the predominant histological type (50.6% in the AC arm and 47.6% in the GC arm), followed by squamous cell carcinoma (28.3% in the AC arm and 26.5% in the GC arm).

Overall survival time, the primary outcome of this study, was 10.28 months for both treatment arms. Using the Cox regression adjusted analysis as the primary analysis, the non-inferiority test was statistically significant (1-sided $p<0.001$), with the primary cofactor adjusted survival hazard ratio (HR) estimated to be 0.94 (95% CI: 0.84 to 1.05), with the entire confidence interval for the HR well below the 1.17645 non-inferiority margin. In addition, the Rothmann analysis showed that AC retained 120% of GC's survival benefit over single agent cisplatin, with a 95% confidence interval of 83% to 190%. Therefore, the non-inferiority criteria were met for testing whether AC retained at least 50% of GC's survival benefit over single-agent cisplatin (one-sided, $p=0.005$). For all patients randomized, the results of other time-to-event endpoints were similar between the treatment arms. Using the same methods as described for the primary OS analysis (that is, Cox and Kaplan-Meier estimation), PFS was also statistically significant for non-inferiority. For PFS, the median PFS was 4.83 months in the AC arm and 5.06 months in the GC arm, with a Cox adjusted HR of 1.04 (95% CI: 0.94 to 1.15; non-inferiority $p=0.008$). Results from an independent review of PFS on a subset of randomly selected patients (n=333) were consistent with the investigator-assessed PFS results of the entire study population. Objective tumor response rates were higher for the AC arm compared to the GC arm (30.6% versus 28.2%), ($p=0.312$ for superiority). Duration of response was longer for the GC arm compared to the AC arm (5.09 months versus 4.50 months); this comparison was not statistically significant for non-inferiority ($p=0.362$) or superiority ($p=0.268$).

One issue impeding demonstration of non-inferiority of survival was the administration of post-discontinuation cytotoxic and targeted chemotherapy. Approximately 50% of patients on each arm received such therapy. Among patients initially treated with pemetrexed 16.7% crossed over to receive gemcitabine and among patients initially treated with gemcitabine 13.4% crossed over to receive pemetrexed. Also approximately 26% of patients on each study arm received post-discontinuation docetaxel. Other drugs were administered fairly uniformly to study patients. The reviewer's conclusion is that the administration of post-discontinuation chemotherapy confounds interpretation of the non-inferiority analyses.

There is an apparent differential effect on survival according to NSCLC histology. There was a favorable survival effect for adenocarcinoma and large cell anaplastic carcinoma patients who received AC treatment and favorable survival results of squamous carcinoma patients who received GC treatment. Two additional studies, JMEI, and NS01, also show a

consistent pattern of better efficacy for pemetrexed in nonsquamous histology than for squamous histology. Preliminary results from a fourth study, JMEN, (maintenance pemetrexed plus best supportive care (BSC) versus BSC immediately following induction chemotherapy for NSCLC again indicate that nonsquamous histology is a predictive factor for better efficacy with Alimta. Prespecified tests for treatment-by-histology interactions resulted in statistically significant interactions for PFS (interaction HR = 0.65, p=0.036) and for preliminary OS (interaction HR = 0.52, p=0.011).

1.3.3 Safety

A median of 5 cycles of therapy was administered to patients in both the arms. Dose adjustments (delays, reductions, and omissions) were less frequent in patients treated with AC compared to patients treated with GC. Most pemetrexed dose reductions were attributed to neutropenia, while gemcitabine and cisplatin dose reductions were mainly attributed to neutropenia, thrombocytopenia, febrile neutropenia, and leukopenia. The dose intensity for pemetrexed and cisplatin was 94.8% and 95.0%, compared with 85.8% and 93.5% for gemcitabine and cisplatin, respectively.

Overall, the number of deaths reported by investigators to be possibly due to study-drug toxicity was low on both arms; 9 deaths (1.1%) in the AC arm and 6 deaths (0.7%) in the GC arm. The number of patients experiencing any possibly study-drug related treatment-emergent adverse event (TEAE) or serious adverse event (SAE) was similar between treatment arms. Among the possibly study-drug related SAEs, patients on the AC arm experienced statistically significantly lower incidences of febrile neutropenia than patients on the GC arm (9 cases [1.1%] versus 25 cases [3.0%], p=0.005), but statistically higher incidences of renal failure (6 cases [0.7%] versus 0 cases, p=0.031). There were no significant differences in the numbers of patients who discontinued study treatment due to possibly study-drug related SAEs betweenn treatment arms.

Patients in the GC arm experienced statistically significantly more possibly study-drug related Grade 3 and 4 laboratory toxicities than patients in the AC arm (39.9 % versus 22.6%, p<0.001). The individual toxicities experienced by statistically significantly more patients on the GC arm than in the AC arm were hematologic and included anemia (9.9% versus 5.6%, p<0.001), leukopenia (7.6% versus 4.8%, p<0.001), neutropenia (26.7% versus 15.1%, p<0.001), and thrombocytopenia (12.7% versus 4.1%, p<0.001). Grade 3 and 4 renal and hepatic laboratory toxicities occurred in less than 1% of patients and with similar frequency across study arms. No Grade 3 and 4 laboratory toxicities occurred significantly more often on the AC arm.

Overall, there was no significant difference in the total number of patients experiencing any possibly study-drug related nonlaboratory toxicity between treatment arms. However, patients in the AC arm experienced significantly more possibly study-drug related Grade 3/4 anorexia (2.4% versus 0.7%, p=0.009) and Grade 3/4 nausea (7.2% versus 3.9%, p=0.004) than patients on the GC arm, although the incidences of Grade 3/4 vomiting (6.1% versus 6.1%, p=1.000), Grade 3/4 weight loss (0 versus 0.1%, p=0.497), and Grade 3/4 dehydration

(1.2% versus 0.7%, p=0.452) were similar between arms. Possibly study-drug related Grade 3/4 febrile neutropenia occurred in statistically significantly more patients on the GC arm than on the AC arm (3.7% versus 1.3%, p=0.002), as did Grade 3/4 sensory neuropathy (0.6% versus 0%, p=0.030), Grade 3/4 syncope (0.6% versus 0%, p=0.030), and any grade of alopecia (21.4% versus 11.9%, p<0.001). Other Grade 3 and 4 toxicities occurred with similar frequency on both study arms.

There was no significant difference in the number of hospitalizations observed between treatment arms. There were significantly fewer transfusions (16.4% versus 28.9%, p<0.001), red blood cell transfusions (16.1% versus 27.3%, p<0.001), and platelet transfusions (1.8% versus 4.5%, p=0.002) administered to patients on the AC arm as compared to the GC arm. Also, there was significantly lower administration of erythropoietin/darbopoietin, iron preparations, and G-CSF/GM-CSF to patients on the AC arm as compared to the GC arm. These differences are consistent with the lower rates of Grade 3/4 hematologic toxicity and Grade 3/4 febrile neutropenia observed in patients treated with AC as compared to GC.

1.3.4 Dosing Regimen and Administration

Combination Use With Cisplatin

Non-Small Cell Lung Cancer and Malignant Pleural Mesothelioma
The recommended dose of pemetrexed is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours beginning approximately 30 minutes after the end of pemetrexed administration. Patients should receive appropriate hydration prior to and/or after receiving cisplatin.

Single-Agent Use

Non-Small Cell Lung Cancer
The recommended dose of pemetrexed is 500 mg/m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

Premedication Regimen

Vitamin Supplementation
To reduce toxicity, patients treated with pemetrexed are instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed; and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive one (1) intramuscular injection of vitamin B-12 during the week preceding the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B-12 injections may be given the same day as pemetrexed. In clinical trials, the dose of folic acid studied ranged from 350 to 1000 mcg, and the dose of

vitamin B-12 was 1000 mcg. The most commonly used dose of oral folic acid in clinical trials was 400 mcg.

Corticosteroid
Skin rash has been reported more frequently in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after pemetrexed administration

1.3.5 Drug-Drug Interactions

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Ibuprofen: Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with pemetrexed in patients with normal renal function (creatinine clearance ≥80 mL/min). Caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min).

Other NSAIDs: Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of pemetrexed.

In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

Nephrotoxic Drugs: Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of pemetrexed. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of pemetrexed.

1.3.6 Special Populations

Pregnancy - Category D
Nursing Mothers - It is not known whether pemetrexed or its metabolites are 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 pemetrexed, it is recommended that nursing be discontinued if the mother is treated with pemetrexed.
Pediatric Use - The safety and effectiveness of pemetrexed in pediatric patients have not been established.

Geriatric Use - Pemetrexed is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Renal function monitoring is recommended with administration of pemetrexed. No dose reductions other than those recommended for all patients are necessary for patients 65 years of age or older.

In the initial treatment lung cancer randomized clinical trial 62.3 % patients treated with pemetrexed plus cisplatin were <65 years and 37.7% patients were ≥65 years, in the previously treated lung cancer trial 70.3% patients were <65 years and 29.7% patients were ≥65 years. The mesothelioma trial included 63.3% patients treated with pemetrexed plus cisplatin that were <65 years and 36.7% patients were ≥65 years. The incidence of CTC Grade 3/4 hypertension and Grade 3/4 neutropenia was greater in patients 65 years or older as compared to patients younger than 65 years in the previously treated lung cancer trial and initial treatment lung cancer trial, respectively. In the mesothelioma trial, the incidence of CTC Grade 3/4 fatigue, leukopenia, neutropenia, and thrombocytopenia were greater in patients 65 years or older as compared to patients younger than 65 years. No differences in effectiveness were seen in patients above and below 65 years in the lung cancer or mesothelioma studies.

Patients with Hepatic Impairment - Patients with bilirubin >1.5 times the upper limit of normal were excluded from clinical trials of pemetrexed. Patients with transaminase >3.0 times the upper limit of normal were routinely excluded from clinical trials if they had no evidence of hepatic metastases. Patients with transaminase from 3 to 5 times the upper limit of normal were included in the clinical trial of pemetrexed if they had hepatic metastases.

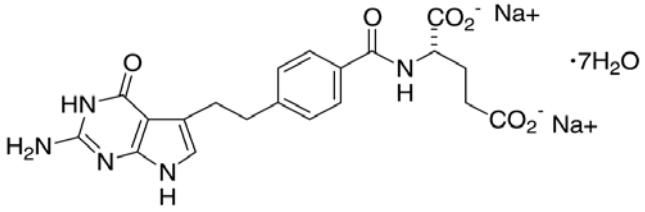
Patients with Renal Impairment - Pemetrexed is known to be primarily excreted by the kidney. Decreased renal function will result in reduced clearance and greater exposure (AUC) to pemetrexed compared with patients with normal renal function. Cisplatin coadministration with pemetrexed has not been studied in patients with moderate renal impairment.

2.0 INTRODUCTION AND BACKGROUND

2.1 Product Information

Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It is a white to almost-white solid with a molecular formula of $C_{20}H_{19}N_5Na_2O_6 \bullet 7H_2O$ and a molecular weight of 597.49. The structural formula is as follows:

Figure 1: Pemetrexed Structural Formula



Pemetrexed is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each 500-mg vial of pemetrexed contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

Dosing Regimen

Dosage Forms And Strengths: Single-dose 500 mg vial for intravenous administration

Proposed Indication(s)

Pemetrexed in combination with cisplatin is indicated for the initial treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)

2.2 Currently Available Treatment For Proposed Indication

Several platinum-based doublet combination regimens have been approved for the initial treatment of locally advanced and metastatic NSCLC in the United States in the past decade. The FDA approvals for both vinorelbine (1994) and gemcitabine (1998) were based on demonstration of a superior survival advantage when combined with cisplatin compared to cisplatin alone. The approval of paclitaxel in combination with cisplatin (1998) was based on improved time to progressive disease and response rate with supportive (but not statistically significant) improvements in survival as compared to etoposide plus cisplatin. The most recent FDA approval, docetaxel (2002), was based on demonstration of noninferiority of docetaxel plus cisplatin compared to vinorelbine plus cisplatin.

The most recent NCCN Oncology Practice Guidelines list platinum-based chemotherapy combined with gemcitabine, vinorelbine, or taxanes (paclitaxel or docetaxel) as standard first-line treatment for patients with Stage IV NSCLC. These combinations offer similar efficacy to patients.

Table 1 presents efficacy results from 4 Phase 3 studies that are representative of regimens commonly used in clinical practice. Efficacy outcomes include overall response rates ranging from 17% to 32%, median overall survival (OS) ranging from 7.4 months to 11.3 months, and 1-year survival of 31% to 46% with comparable safety profiles.

Table 1: Results of Phase 3 Studies of First-Line NSCLC Regimens

Study	Drugs	Pts.	Stage IV (%)	ORR (%)	OS (mo)	1-Yr. (%)
Kelly et al.	vin/cis	202	89	28	8.1	36
SWOG 9503	pac/cb	208	88	25	8.6	38
Schiller et al.	pac/cis	292	89	21	7.8	31
ECOG 1594	gem/cis	288	86	22	8.1	36
	doc/cis	293	86	17	7.4	31
	pac/cb	290	86	17	8.1	34
Scagliotti et al.	vin/cis	201	81	30	9.5	37
ILCP	gem/cis	205	81	30	9.8	37
	pac/cb	201	82	32	9.9	43
Fosella et al.	vin/cis	404	67	25	10.1	41
TAX326	doc/cis	408	67	32	11.3	46
	doc/cb	402	67	24	9.4	38

Abbreviations: 1-Yr. = 1-year survival; cb = carboplatin; cis = cisplatin; doc = docetaxel; ECOG = Eastern Cooperative Oncology Group; gem = gemcitabine; ILCP = Italian Lung Cancer Project; ORR = overall response rate; OS = overall survival; pac = paclitaxel; Pts. = number of patients; SWOG = Southwest Oncology Group; vin = vinorelbine.

In the Fosella study approximately 33 percent of patients in each treatment arm had Stage IIIB disease, which likely explains the consistently higher median OS for each treatment arm when compared to the median OS in the other studies.

Randomized trials have not demonstrated that adding a third cytotoxic agent is beneficial in terms of median survival and have shown increased toxicity compared to the standard platinum-based doublets. The addition of a third, noncytotoxic agent, bevacizumab, to paclitaxel and carboplatin showed a significant survival benefit for patients in the experimental arm, with median survival of 12.3 months versus 10.3 months for the control arm and the bevacizumab regimen was recently approved in the United States.

2.3 Availability of Proposed Active Ingredient in the United States

Pemetrexed is currently approved and available in the U.S.

2.4 Important Issues With Pharmacologically Related Products

Not applicable

2.5 Presubmission Regulatory Activity

Pemetrexed received regular approval for the indication, pemetrexed in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma (MPM) whose disease is either unresectable or who are otherwise not candidates for curative surgery by the FDA on February 4, 2004.

Pemetrexed (as a single agent) received an accelerated approval for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004. As a condition of this approval, as per Subpart H, further studies (JMDB and JMEN) were required to confirm and describe the clinical benefit of pemetrexed.

The currently submitted sNDA was discussed during 2 pre-NDA meetings with the FDA. At the January 11, 2007 meeting, Lilly and the FDA discussed the status of the 2 ongoing Phase IV commitment studies in support of converting the second-line NSCLC accelerated approval of pemetrexed to regular approval. The FDA advised Lilly that since the studies (Study JMDB and Study JMEN) seek different indications, each should be submitted as a separate sNDA. The FDA agreed to meet and discuss the results of Study JMDB, "A Multicenter, Randomized Phase III Trial of Alimta and Cisplatin Versus Gemzar and Cisplatin in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer," once results were available. The FDA also requested that the minutes from the Data Monitoring Committee (DMC) be included in the sNDA for Study JMDB.

On June 6, 2007, Lilly met with the FDA to review the results of Study JMDB and discuss plans for submission of the sNDA to confirm the benefit of pemetrexed (for conversion from accelerated approval to regular approval) and to support the proposed indication for use of pemetrexed plus cisplatin for the initial treatment of patients with locally advanced or metastatic NSCLC. At this meeting, the FDA agreed that Lilly would submit the JMDB study results in an sNDA as a Phase IV Commitment. The FDA advised Lilly that a direct comparison of the Sandler study with the 28-day gemcitabine schedule was not acceptable for use in the noninferiority analysis of a 21-day gemcitabine plus cisplatin regimen. Lilly proposed the inclusion of additional data to support the 21-day schedule used in the control arm of Study JMDB in the sNDA. The FDA also advised Lilly that a preferred approach for noninferiority is the use of a meta-analysis of available studies to estimate the control effect size. Lilly has taken the FDA's advice under consideration and has performed a percent retention analysis based on a meta-analysis of 10 Phase 2 and 3 studies for the initial treatment of NSCLC, where gemcitabine plus cisplatin was compared to cisplatin-based regimens

Table 2 summarizes the key regulatory interactions for Study JMDB.

Table 2: Key U.S. Regulatory Interactions for Study JMDB

Date	Description	Comments
23-Apr-2004	Study JMDB Protocol Submission	Initial Protocol submitted to IND (SN627)
24-May-2004	Study JMDB Protocol Amendment	Submitted Study JMDB(a) to IND (SN637)
19-Aug-2004	FDA Accelerated Approval of Alimta 2nd Line Lung Cancer	Study JMDB listed as Phase IV Commitment study requirement under Subpart H in FDA Approval Letter
02-May-2005	Data Monitoring Board Charter	DMB Charter for Study JMDB submitted to IND (SN747)
13-Oct-2006	Statistical Analysis Plan (SAP)	Study JMDB SAP submitted to IND (SN918)
14-Dec-2006	FDA Comments on SAP	Lilly received FDA comments on Study JMDB SAP
11-Jan-2007	Pre-NDA Meeting	Lilly and FDA met to discuss the current status of Phase IV Commitment studies of Alimta in NSCLC and submission plans
6-June-2007	Pre-NDA Meeting	Lilly and FDA met to discuss key results of Phase IV Commitment Study JMDB and submission plans for first-line indication.

2.6 Other Relevant Background Information

None

3.0 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (And Product Microbiology. If Applicable)

The pharmaceutical and chemical specifications for the drug substance have not changed since the earlier NSCLC submission.

3.2 Animal Pharmacology/Toxicology

An additional safety pharmacology study, a hERG assay, was conducted since the initial indication. Pemetrexed was assessed in vitro in the hERG voltage clamp assay to identify the potential for pharmacological blockade of the cardiac I_{Kr} current and was found to be inactive at concentrations up to 300 μM. Based on these data, unbound plasma concentrations up to at least 300 μM pemetrexed (128.2 μg/mL) or total plasma

concentrations up to at least 650.87 µg/mL (based on human plasma protein binding of approximately 80.3%) would not be expected to produce significant risk of QT interval prolongation. Furthermore, electrocardiograms were also evaluated in conscious beagle dogs at doses up to 25 mg/kg (500 mg/m2) administered intravenously every 3 weeks for 9 months and showed no effects related to treatment. Further, there was no evidence of pemetrexed-induced effects on cardiac conduction seen in the clinical program.

4.0 Data Sources, Review Strategy And Data Integrity

4.1 Sources of Clinical Data

Electronic submission NDA 21-462 N_000 8/27/07

4.2 Table of Clinical Studies

See **Table 3**.

Table 3: Submitted Studies

H3E-MC-JMDB (JMDB) Pivotal Study	**Phase 3 study comparing the efficacy and safety of pemetrexed plus cisplatin with that of gemcitabine plus cisplatin in patients with a diagnosis of locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC who have had no prior systemic chemotherapy for lung cancer**
H3E-MC-JMAY (JMAY) Supportive Study	**Phase 2 study assessing the efficacy and safety of pemetrexed in combination with cisplatin in patients with Stage IIIB or Stage IV NSCLC who have had no prior systemic chemotherapy. (This study was previously submitted to the FDA)**
H3E-MC-JMBZ (JMBZ) supportive Study	**Phase 2 study assessing the efficacy and safety of pemetrexed in combination with cisplatin in patients with Stage IIIB or Stage IV NSCLC who have had no prior systemic chemotherapy. (This study was previously submitted to the FDA**

4.3 Review Strategy

Efficacy data submitted by the sponsor was reviewed. All safety data was reviewed.

4.4 Data Quality and Integrity

The sponsor states that all clinical studies included in this submission have been conducted in compliance with the principles of Good Clinical Practice (GCP). As Studies JMDB, JMAY, and JMBZ are the key studies of pemetrexed plus cisplatin that support the proposed indication for this application, an assessment of the conduct of these studies with respect to their compliance with GCP has been performed. A written list of study compliance violations has been reviewed, including a thorough review of GCP noncompliance on a quarterly basis. Investigator GCP noncompliance information observed from site monitoring and Medical Quality Assurance audits has been summarized. The sponsor concludes that reported protocol violations and associated GCP compliance issues have neither prejudiced

nor compromised the safety of the patients participating in the studies. They have also not adversely affected the data integrity of these studies..

4.5 Compliance With Good Clinical Practices

All studies were conducted, as could best be determined, in full compliance with Good Clinical Practice.

4.6 Financial Disclosures

The sponsor has submitted certification that Eli Lilly has not entered into any financial arrangement with the study clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The sponsor also certifies that each clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the product as defined in 21 CFR 54.2(b) did not disclose any such interests with the following exceptions. The Financial interests and arrangements of clinical investigators form was signed by Allen Melemed, M.D., Medical Director, on 8/6/07.

Listed below are investigators who disclosed funding from Lilly. Of the sites listed only the following sites enrolled greater than 15 patients; site (b) (6), (b) (6) patients ((b) (6)%), site (b) (6) patients ((b) (6)%), site (b) (6) (b) (6) patients ((b) (6)%) and site (b) (6), (b) (6) patients ((b) (6)%)

Investigator Name	Institution Name	Lilly Affiliate	Site Number
(b) (6), MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$32,208.00

(b) (6) MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$53,288.09
Professional Services	$37,500.00
Symposia	$ 8,403.26
Speakers Program	$10,823.30

(b) (6), A/Prof.	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$12,406.94
Speakers Program	$14,584.75
Symposia	$ 6,565.45

(b) (6) MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$43,258.36

(b) (6), Prof.	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$46,220.94
Professional Services	$46,875.00
Speakers Program	$46,646.31
Symposia	$19,783.65

(b) (6), MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$ 5,936.40
Professional Services	$ 2,666.14
Speakers Program	$17,439.33
Symposia	$ 1,269.75

(b) (6), MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Consulting Fees	$29,702.97

(b) (6), Prof.	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$78,757.00

(b) (6), MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Honoraria	$39,600

(b) (6), MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$22,371.24
Speakers Program	$61,477.75
Symposia	$12,194.91

5.0 CLINICAL PHARMACOLOGY

Mechanism of Action

Pemetrexed for injection, is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. In vitro

studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as the reduced folate carrier, membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT.

Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, is thought to occur to a lesser extent, in normal tissues. Polyglutamated metabolites are thought to have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

5.1 Pharmacokinetics

The pharmacokinetics of pemetrexed administered as a single-agent in doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. The total systemic clearance of pemetrexed is 91.8 mL/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min). The clearance decreases, and exposure (AUC) increases, as renal function decreases. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increase proportionally with dose. The pharmacokinetics of pemetrexed do not change over multiple treatment cycles. Pemetrexed has a steady-state volume of distribution of 16.1 liters. In vitro studies indicate that pemetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

Studies have also shown that folic acid and vitamin B-12 coadministration do not affect pemetrexed clearance, whether pemetrexed was given in combination with cisplatin or as a single agent.

Coadministration of pemetrexed with cisplatin showed no clinically significant drug interactions that would necessitate dose adjustment or preclude concomitant administration. Coadministration of pemetrexed with cisplatin did not alter the clearance of either drug.

Consistent with clinical experience and preclinical findings, pharmacodynamic analyses identified pemetrexed overall systemic exposure (AUC), and plasma homocysteine, and cystathionine concentrations as the dominant predictors of neutropenic response to pemetrexed. Increased AUC correlated with lower nadir absolute neutrophil count (ANC). Increases in plasma homocysteine and cystathionine concentrations also were associated with lower nadir ANC. Because high homocysteine and cystathionine

concentrations are associated with poor folate status, these findings support the use of vitamin supplementation to ensure normal vitamin B-12 and folate status to control hematologic toxicity secondary to pemetrexed administration. The results adequately demonstrate there is no change in the effect of pemetrexed on neutrophil response following multiple treatment cycles, indicating the lack of cumulative toxicity due to pemetrexed in presence of vitamin supplementation.

Special Populations

The pharmacokinetics of pemetrexed in special populations were examined in about 400 patients in controlled and single arm studies.

Geriatric - No effect of age on the pharmacokinetics of pemetrexed was observed over a range of 26 to 80 years.

Pediatric - Pediatric patients were not included in clinical trials.

Gender - The pharmacokinetics of pemetrexed were not different in male and female patients.

Race - The pharmacokinetics of pemetrexed were similar in Caucasians and patients of African descent. Insufficient data are available to compare pharmacokinetics for other ethnic groups.

Hepatic Insufficiency - There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed. However, studies of hepatically impaired patients have not been conducted.

Renal Insufficiency - Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed decreases as renal function decreases, with a resultant increase in systemic exposure. Patients with creatinine clearances of 45, 50, and 80 mL/min had 65%, 54%, and 13% increases, respectively in pemetrexed total systemic exposure (AUC) compared to patients with creatinine clearance of 100 mL/min.

Two Phase 1 studies conducted since the last application to FDA (for second-line NSCLC) show that pemetrexed doses up to 1200 mg/m^2 were well tolerated. Study H3E-MC-JMAS (JMAS) was a Phase 1 study conducted in Caucasian patients, and the doses ranged from 600 mg/m2 to 1400 mg/m^2 with folic acid supplementation. The pharmacokinetics were linear since pemetrexed clearance was independent of dose over the entire dose range in the study. Study 1001 was the second dose-ranging, Phase 1 study conducted in Japanese patients at doses ranging from 300 mg/m^2 to 1200 mg/m^2. C_{max} and $AUC_{(0-\infty)}$ were dose proportional over the dose range of 500 mg/m^2 to 1000 mg/m^2. These results supplement the previous finding of dose proportionality for pemetrexed. The tolerated doses in these studies (approximately 1000 mg/m^2) are well beyond the suggested clinical dose of 500 mg/m2. Safety evaluations have not identified clinically significant increases in the occurrence of CTC Grade 3 and 4 adverse events based on renal function within the range of renal function of patients enrolled in other studies (previously submitted to FDA). Thus, BSA-normalized dosing, with no further dose adjustment for renal function, is adequate for patients with renal impairment (GFR or $CrCl_{CG,std}$ 45 to

80 mL/min) (measured GFR or calculated [standard Cockcroft and Gault formula, $CrCl_{CG,std}$]).with the suggested pemetrexed clinical dose of 500 mg/m^2.

The relationship between pemetrexed clearance and renal function has been characterized and supports the use of pemetrexed in patients with CrCl of ≥45 mL/ As there is no apparent drug-drug interaction between cisplatin and pemetrexed disodium, no adjustments in dose for either compound are required. The new results presented in this application support the findings and conclusions in previous applications and apply to all patients with mesothelioma and NSCLC.

5.2 Pharmacodynamics

Preclinical studies have shown that pemetrexed inhibits the in vitro growth of mesothelioma cell lines (MSTO-211H, NCI-H2052). Studies with the MSTO-211H mesothelioma cell line showed synergistic effects when pemetrexed was combined concurrently with cisplatin.

Absolute neutrophil counts (ANC) following single-agent administration of pemetrexed to patients not receiving folic acid and vitamin B-12 supplementation were characterized using population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the depth of the ANC nadir, correlates with the systemic exposure, or area under the curve (AUC) of pemetrexed. It was also observed that lower ANC nadirs occurred in patients with elevated baseline cystathionine or homocysteine concentrations. The levels of these substances can be reduced by folic acid and vitamin B-12 supplementation. There is no cumulative effect of pemetrexed exposure on ANC nadir over multiple treatment cycles. Time to ANC nadir with pemetrexed systemic exposure (AUC), varied between 8 to 9.6 days over a range of exposures from 38.3 to 316.8 mcg•hr/mL. Return to baseline ANC occurred 4.2 to 7.5 days after the nadir over the same range of exposures.

5.3 Exposure-Response Relationships

Pemetrexed doses of 500 to 900 mg/m^2 every 21 days have been studied. The 500 mg/m^2 dose appears optimal.

6.0 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Pemetrexed in combination with cisplatin is indicated for the initial treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)

6.1.1 Methods

Clinical information concerning the phase 3 randomized trial (JMDB) and from the two phase 2 studes (JMAY and JMBZ), using an every 3 week AC schedule but without vitamin supplementation,were reviewed.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint for the phase 3 randomized trial (JMDB) is overall survival. Efficacy endpoints have been discussed with the FDA.

6.1.4 Efficacy Findings

Study sites and principal investigators are listed in **Table 4.**

Table 4: Investigators

Investigator 001 Claudia I. Bagnes, MD Argentina	Investigator 002 Daniel Maldonado, MD Argentina	Investigator 005 Alejandro Ferro, MD Argentina
Investigator 006 Daniel S. Lewi, MD Argentina	Investigator 010 Michael Boyer, MD Australia	Investigator 011 Maree Colosimo, MD Australia
Investigator 012 Phil R. Clingan, MD Australia	Investigator 014 Michael Byrne, MD Australia	Investigator 015 Ivon W. Burns, MD Australia
Investigator 016 Paul Mainwaring, MD Australia	Investigator 017 Chris S. Karapetis, MD Australia	Investigator 018 Nick Pavlakis, MD Australia
Investigator 020 Gavin Marx, MD Australia	Investigator 031 Ernest Ulsperger, MD Austria	Investigator 032 Josef Eckmayr, MD Austria
Investigator 033 Hellmut Samonigg, MD Austria	Investigator 034 Wolfgang Hilbe, MD Austria	Investigator 035 Kurt Aigner, MD Austria
Investigator 036 Wolfgang Pohl, MD Austria	Investigator 037 Martin Flicker, MD Austria	Investigator 038 Prof. Peter Balcke Austria
Investigator 050 Johan Vansteenkiste, MD Belgium	Investigator 051 Frederique Bustin, MD Belgium	Investigator 052 Zita Mekinda, MD Belgium
Investigator 070 José Rodrigues Pereira, MD Brazil	Investigator 071 Mauro Zukin, MD Brazil	Investigator 072 Carlos H. Barrios, MD Brazil
Investigator 073 Clarissa Mathias, MD Brazil	Investigator 074 Yeni Neron, MD Brazil	Investigator 200 Paul Klimo, MD Canada
Investigator 201 Ronald L. Burkes, MD Canada	Investigator 202 Bruno Raby, MD Canada	Investigator 205 Stephen Reingold, MD Canada
Investigator 130 Anders Mellemgaard, MD Denmark	Investigator 131 Peter Soerensen, MD Denmark	Investigator 140 Aija Knuuttila, MD Finland
Investigator 142 Antti Ojala, MD Finland	Investigator 143 Eira Ritanen, MD Finland	Investigator 300 Prof. Jean-Yves Douillard France

Investigator 301 Bernard Milleron, MD France	Investigator 302 A/Prof. Elisabeth Quoix France	Investigator 303 Prof. Philippe Astoul France
Investigator 304 Denis Moro-Sibilot, MD France	Investigator 305 Francois Guichard, MD France	Investigator 306 Prof. Jean-Louis Pujol France
Investigator 307 Yves Martinet, MD France	Investigator 400 Prof. Peter Drings Germany	Investigator 401 Ulrich Gatzemeier, MD Germany
Investigator 402 Bernhard Heinrich, MD Germany	Investigator 403 Joachim Von Pawel, MD Germany	Investigator 404 Elke Jaeger, MD Germany
Investigator 405 Prof. R. Loddenkemper Germany	Investigator 406 Thomas Müller, MD Germany	Investigator 407 A/Prof. Werner Georg Digel Germany
Investigator 408 Wilfried Eberhardt, MD Germany	Investigator 409 Lutz Freitag, MD Germany	Investigator 410 A/Prof. Frank Griesinger Germany
Investigator 411 Martin Hetzel, MD Germany	Investigator 412 Meinolf Karthaus, MD Germany	Investigator 413 Jörg Mezger, MD Germany
Investigator 414 Prof. Eckhard Kaukel Germany	Investigator 415 Wolfgang Schuette, MD Germany	Investigator 416 Cornelius S. F. Kortsik, MD Germany
Investigator 417 Claus Steppert, MD Germany	Investigator 418 A/Prof. Cristiana Sessa Switzerland (Germany)	Investigator 419 Prof. Christian Manegold Germany
Investigator 150 Dimosthenis Skarlos, MD Greece	Investigator 151 A/Prof. Vassilios Georgoulias Greece	Investigator 153 Prof. Konstantinos Syrigos Greece
Investigator 154 A/Prof. C. Alexopoulos Greece	Investigator 155 A/Prof. C. Kalofonos Greece	Investigator 170 Zoltan Baliko, MD Hungary
Investigator 171 Agnes Devai, MD Hungary	Investigator 172 Beatrix Balint, MD Hungary	Investigator 700 Poonamalle P. Bapsy, MD India
Investigator 701 Sunil Gupta, MD India	Investigator 702 Dinesh C. Doval, MD India	Investigator 704 Digumarti Raghunadharao, MD India
Investigator 705 Shekar Patil, MD India	Investigator 706 Keechilat Pavithran, MD India	Investigator 707 Shona Nag, MD India
Investigator 708 Purvish M. Parikh, MD India	Investigator 180 Ofer Merimsky, MD Israel	Investigator 181 Maya Gottfried, MD Israel

Investigator 182 Biran Haim, MD Israel	Investigator 500 Prof. Giorgio V. Scagliotti Italy	Investigator 501 Francesco Ferraù, MD Italy
Investigator 502 Alfredo Falcone, MD Italy	Investigator 503 Pier Franco Conte, MD Italy	Investigator 504 Prof. Alba Brandes Italy
Investigator 505 Flippo De Marinis, MD Italy	Investigator 506 Roberto Labianca, MD Italy	Investigator 507 Prof. Stefano Cascinu Italy
Investigator 508 Prof. Alberto Sobrero Italy	Investigator 509 Anna Ceribelli, MD Italy	Investigator 510 Dino Amadori, MD Italy
Investigator 190 Keunchil Park, MD Korea	Investigator 191 Sr. Jin Soo Lee Korea	Investigator 250 Daniel Capdeville Garcia, MD Mexico
Investigator 251 Celia Soto Collins, MD Mexico	Investigator 253 Alicia Acosta, MD Mexico	Investigator 254 Ana Laura Rodriguez, MD Mexico
Investigator 255 Oscar Arrieta, MD Mexico	Investigator 259 Laura Perez Michel, MD Mexico	Investigator 800 Bonne Biesma, MD Netherlands
Investigator 801 Hans J. M. Smit, MD Netherlands	Investigator 803 Gert-Jan Timmers, MD Netherlands	Investigator 804 B.E.E.M. van den Borne, MD Netherlands
Investigator 805 Frank L. J. Custers, MD Netherlands	Investigator 806 Egbert F. Smit, MD Netherlands	Investigator 807 Sjm Gans, MD Netherlands
Investigator 808 Aart Welling, MD Netherlands	Investigator 350 Piotr Serwatowski, MD Poland	Investigator 351 Janusz Rolski, MD Poland
Investigator 352 Maria Blasinska-Morawiec, MD Poland	Investigator 353 Maciej Krzakowski, MD Poland	Investigator 360 Antonio Araujo, MD Portugal
Investigator 361 Francisco Pimentel, MD Portugal	Investigator 362 Fernando Barata, MD Portugal	Investigator 363 Encarnação Teixeira, MD Portugal
Investigator 364 Jorge Santos-Dionisio, MD Portugal	Investigator 600 Rafael Rosell, MD Spain	Investigator 601 Enriqueta Felip, MD Spain
Investigator 602 Jesús Montesinos, MD Spain	Investigator 604 Ana Montes Borinaga, MD Spain	Investigator 605 Luis Pazares Rodriguez, MD Spain
Investigator 606 Dolores Isla Casado, MD Spain	Investigator 607 Mr. Jose Maria Lopez Picazo Spain	Investigator 609 Marta López Brea, MD Spain

Investigator 612 Jose Enrique Ales Martinez, MD Spain	Investigator 613 Prof. Pilar Garrido Lopez Spain	Investigator 614 Ramon Garcia Gomez, MD Spain
Investigator 615 Jose L. Gonzalez-Larriba, MD Spain	Investigator 616 Bartomeu Massuti Sureda, Spain	Investigator 550 Lars Ek, MD Sweden
Investigator 551 Signe Friesland, MD Sweden	Investigator 552 Bengt Bergman, MD Sweden	Investigator 560 Chih-Hsin Yang, MD Taiwan
Investigator 561 Gee-Chen Chang, MD Taiwan	Investigator 562 Te-Chun Hsia, MD Taiwan	Investigator 563 Prof. Chun-Ming Tsai Taiwan
Investigator 564 Meng-Chih Lin, MD Taiwan	Investigator 565 Kuo Han-Pin, MD Taiwan	Investigator 650 Murat Kiyik, MD Turkey
Investigator 651 Prof. Tuncay Goksel Turkey	Investigator 652 Ugur Yilmaz, MD Turkey	Investigator 653 Meral Gulhan, MD Turkey
Investigator 654 Hakan Bozcuk, MD Turkey	Investigator 751 Marianne Nicolson, MD United Kingdom	Investigator 752 A/Prof. Neville Davidson United Kingdom
Investigator 753 N. S. Stuart, MD United Kingdom	Investigator 754 Tim Eisen, MD United Kingdom	Investigator 755 Mary E. O'Brien, MD United Kingdom
Investigator 756 Francis Daniel, MD United Kingdom	Investigator 757 Michael Seckl, MD United Kingdom	Investigator 100 Afshin Farr Dowlati, MD United States
Investigator 101 Susanne Arnold, MD United States	Investigator 102 Harry Harper, MD United States	Investigator 103 John Adams, MD United States
Investigator 104 Renato G. Martins, MD United States	Investigator 105 William Thomas Purcell, MD United States	Investigator 106 Richard Orlowski, MD United States
Investigator 107 Fred J. Kudrik, MD United States	Investigator 108 Tanya Repka, MD United States	Investigator 109 Thomas Marsland, MD United States
Investigator 110 Luis Baez, MD United States	Investigator 111 John R. Eckardt, MD United States	Investigator 112 Joseph T. Beck, MD United States
Investigator 113 Alan Sandler, MD United States	Investigator 114 Alex Makalinao, MD United States	Investigator 115 David R. Gandara, MD United States
Investigator 116 R. Brian Mitchell, MD United States	Investigator 117 Walter Urba, MD United States	Investigator 118 Daniel M. Hayes, MD United States

Investigator 119 Shaker Dakhil, MD United States	Investigator 121 Frederick Schnell, MD United States	Investigator 123 Edward R. Arrowsmith, MD United States

Investigational sites enrolling more than 15 patients are listed in **Table 5**.

Table 5: Investigators enrolling ≥ 15 patients

Site	PI	A/C(N=862)	G/C(N=863)	ALL(N=1725)
708	Parikh	18 (2.1)	22 (2.5)	40 (2.3)
403	Von Pawel	18 (2.1)	18 (2.1)	36 (2.1)
500	Scagliotti	20 (2.3)	16 (1.9)	36 (2.1)
800	Biesma	18 (2.1)	18 (2.1)	36 (2.1)
50	Vansteenkiste	13 (1.5)	22 (2.5)	35 (2.0)
350	Serwatowski	16 (1.9)	15 (1.7)	31 (1.8)
400	Drings	16 (1.9)	14 (1.6)	30 (1.7)
401	Gatzemeier	15 (1.7)	15 (1.7)	30 (1.7)
704	Raghunadhrao	12 (1.4)	16 (1.9)	28 (1.6)
71	Zukin	14 (1.6)	13 (1.5)	27 (1.6)
130	Mellemgaard	9 (1.0)	18 (2.1)	27 (1.6)
190	Park	12 (1.4)	15 (1.7)	27 (1.6)
191	Lee	16 (1.9)	11 (1.3)	27 (1.6)
202	Raby	13 (1.5)	14 (1.6)	27(1.6)
351	Rolski	13 (1.5)	12 (1.4)	25 (1.4)
705	Patil	14 (1.6)	11 (1.3)	25 (1.4)
651	Goksel	11 (1.3)	13 (1.5)	24 (1.4)
153	Syrigos	12 (1.4)	11 (1.3)	23 (1.3)
505	De Marinis	13 (1.5)	9 (1.0)	22 (1.3)
807	Gans	12 (1.4)	9 (1.0)	21 (1.2)
104	Martins	10 (1.2)	9 (1.0)	19 (1.1)
107	Kudrik	7 (0.8)	12 (1.4)	19 (1.1)
172	Balint	11 (1.3)	8 (0.9)	19 (1.1)
506	Labianca	12 (1.4)	7 (0.8)	19 (1.1)
700	Bapsy	10 (1.2)	9 (1.0)	19 (1.1)
707	Nag	10 (1.2)	9 (1.0)	19 (1.1)
352	Blasinska-Morawiec	9 (1.0)	9 (1.0)	18 (1.0)
560	Yang	9 (1.0)	9 (1.0)	18 (1.0)
702	Doval	12 (1.4)	6 (0.7)	18 (1.0)
200	Klimo	9 (1.0)	8 (0.9)	17 (1.0)
300	Douillard	9 (1.0)	8 (0.9)	17 (1.0)
14	Byrne	7 (0.8)	9 (1.0)	16 (0.9)
170	Baliko	7 (0.8)	9 (1.0)	16 (0.9)
182	Haim	5 (0.6)	11 (1.3)	16 (0.9)
551	Friesland	7 (0.8)	9 (1.0)	16 (0.9)
801	Smit	9 (1.0)	7 (0.8)	16 (0.9)
70	Pereira	8 (0.9)	7 (0.8)	15 (0.9)
181	Gottfried	6 (0.7)	9 (1.0)	15 (0.9)

409	Freitag	8 (0.9)	7 (0.8)	15 (0.9)
414	Kaukel	10 (1.2)	5 (0.6)	15 (0.9)
507	Cascinu	7 (0.8)	8 (0.9)	15 (0.9)
654	Bozcuk	9 (1.0)	6 (0.7)	15 (0.9)

The organizational responsibilities for the JMDB Study were as follows **(Table 6)**:

Table 6: Organizational Responsibilities

Organization	Role
(b) (4)	Analysis of clinical blood and urine samples and central collection of tumor tissue for pharmacogenomic analyses
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	Central collection of scans and coordination of independent radiologic review
(b) (4)	Analysis of pharmacogenetic samples
(b) (4)	Data analysis
(b) (4)	Analysis of pharmacogenetic samples

Background

The pivotal study JMDB was a randomized, multicenter, open-label, Phase 3 study using a non-inferiority design to assess the efficacy of AC compared to GC for the initial treatment of patients with locally advanced or metastatic NSCLC. The primary objective was to compare the overall survival (OS) of the two treatment groups. Non-inferiority was to be demonstrated by both the fixed margin method (the fixed non-inferiority margin of 1.17647 corresponds to GC having a 15% lower survival hazard (that is, risk of death) than that of AC) and by a percent retention non-inferiority analysis.

An important issue in the evaluation of this study is that a 3 week GC schedule was used instead of the 4 week schedule that led to the approval of GC for treatment of NSCLC. For non-inferiority to be evaluated it must be accepted that results of the every 3 week GC treatment schedule are comparable to results of the every 4 week GC treatment schedule. If so, then there are multiple historical studies (more than 3,000 patients) from which to estimate the survival effect of gemcitabine with precision, to evaluate interstudy variability and to assess constancy.

Secondary objectives included PFS, TtPD, TtTF, duration of tumor response (DoR), objective tumor response rate, risk/benefit, and toxicity. Consistent methods of measurement were used for tumor assessment, and tumor responses were recorded using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

Tumor measurement images for all patients were collected and stored by the sponsor. An independent review of PFS was conducted on a subset of radiological assessments (for approximately 400 patients randomly selected among roughly the first 1000 patients enrolled) by an external vendor without knowledge of treatment assignment. The objective of the independent review was to test for any evidence of a systematic bias in investigator-assessed PFS that favored one treatment arm over the other. **Figure 2** illustrates the study design and **Table 7** indicates treatment doses and schedule.

Figure 2: Study Design

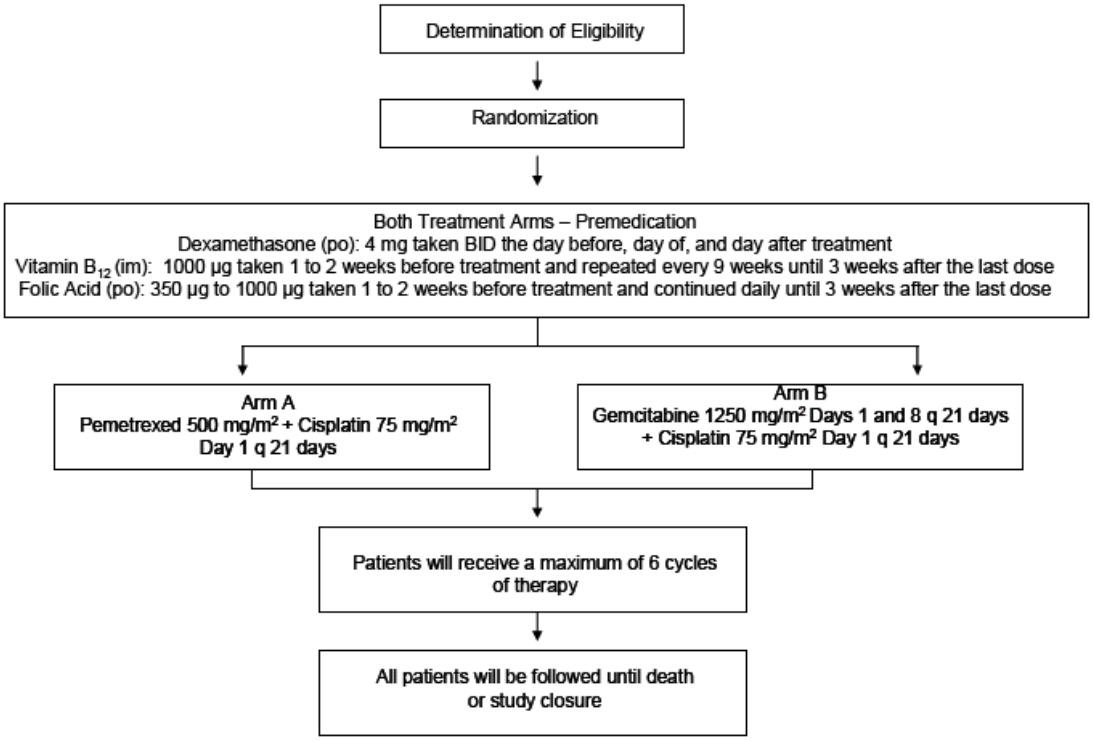


Table 7: Treatment Dose and Schedule

Drug	Dose	Time for Administration
Treatment Arm A (21-Day Cycle)		
Pemetrexed	500 mg/m^2 iv	Approximately 10 minutes on Day 1.
Cisplatin	75 mg/m^2 iv	Administered per local practice on Day 1, approximately 30 minutes after pemetrexed infusion.
Treatment Arm B (21-Day Cycle)		
Gemcitabine	1250 mg/m^2 iv	Approximately 30 to 60 minutes on Day 1 and Day 8.
Cisplatin	75 mg/m^2 iv	Administered per local practice on Day 1, approximately 30 minutes after gemcitabine infusion.
Pretreatment–Both Treatment Arms A and B		
Folic acid	350 µg to 1000 µg	Oral dose daily beginning approximately 1 to 2 weeks before the first dose of study therapy, and continuing daily until 3 weeks after the last dose of study therapy.
Vitamin B12	1000 µg im injection	Approximately 1 to 2 weeks before the first dose of study therapy, and approximately every 9 weeks until 3 weeks after the last dose of study therapy.
Dexamethasone	4 mg, po twice per day (or equivalent)	To be taken on the day before, the day of, and the day after each dose of study therapy. Higher or additional doses were permitted for reasons other than routine rash prophylaxis (for example, antiemetic prophylaxis). Dexamethasone treatment was not required for Day 8 gemcitabine.

Both treatment arms used cisplatin 75 mg/m^2, and patients received up to 6 cycles of assigned treatment (control or experimental). Patients in both treatment arms received folic acid, vitamin B12, and dexamethasone at the same dose and schedule, to avoid creating any potential disadvantage for the control regimen.

Pemetrexed Plus Cisplatin Arm

Data from Study JMAP, prior to vitamin supplementation, established the maximum-tolerated dose (MTD) at 600 mg/m^2 pemetrexed and 100 mg/m^2 cisplatin, with a dose-limiting toxicity (DLT) of thrombocytopenia. However, because of toxicities observed in other single-agent pemetrexed Phase 2 studies, the recommended dose for this combination became 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin. Two Phase 2 clinical studies (JMAY and JMBZ) for the first-line treatment of patients with locally advanced or metastatic NSCLC have evaluated pemetrexed in combination with cisplatin at 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin. Treatment was tolerable and efficacy results compared favorably with standard regimens.

Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 received FDA approval for the treatment of patients with malignant pleural mesothelioma (MPM) whose disease is either unresectable or who are otherwise not candidates for curative surgery on February 4, 2004 and pemetrexed 500 mg/m^2, as a single agent, received an accelerated approval for patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004. Following these approvals pemetrexed with vitamin supplementation was further

investigated to determine if higher doses of pemetrexed would improve efficacy without additional toxicity (studies JMHL,NS01, and JMGX). Study JMHL has shown that higher doses of pemetrexed can be administered with cisplatin (the MTD was 900 mg/m^2, with a recommended dose of 800 mg/m^2; however, randomized Studies NS01 and JMGX have not shown improved efficacy with higher doses of pemetrexed. Given these results there is no clinical justification for administration of doses of pemetrexed higher than 500 mg/m^2 to patients with NSCLC.

Control Arm: Gemcitabine Plus Cisplatin

Gemcitabine in combination with cisplatin received FDA approval for the first-line treatment of locally advanced or metastatic NSCLC in 1998. In a study of 522 patients, gemcitabine 1000 mg/m^2 was administered on Days 1, 8, and 15 of a 28-day cycle, with cisplatin 100 mg/m^2 administered on Day 1 of each cycle. This study compared gemcitabine plus cisplatin to single-agent cisplatin. Median survival time on the gemcitabine plus cisplatin arm was 9.1 months compared to 7.6 months on the single-agent cisplatin arm (HR = 0.73, log-rank p=0.008, two-sided).

Several Phase 2 and 3 clinical studies have confirmed that combination therapy with gemcitabine and cisplatin is an effective regimen for NSCLC Based on a recent meta-analysis of 13 randomized studies of gemcitabine/platinum regimens compared to other platinum-based regimens, gemcitabine-based regimens may provide a statistically significant but slight survival benefit for patients with advanced NSCLC compared to the non-gemcitabine based regimens. (Le Chevalier et al. 2005).

The clinical and statistical background for Study JMDB was based on the Phase 3 study comparing gemcitabine plus cisplatin to single-agent cisplatin both on 28-day regimens (Sandler et al. 2000). In Study JMDB, the control arm received gemcitabine 1250 mg/m^2 on Day 1 and Day 8 plus cisplatin 75 mg/m^2 on Day 1 every 21 days. The rationale for designing the study with a 21-day schedule was based on several factors. First, a randomized Phase 2 study directly comparing 21-day versus 28-day schedules suggested that there was similar efficacy and dose intensity in the 21-day versus the 28-day regimen (Soto Parra et al. 2002,**Table 8**). Relative dose intensity was maintained (589.7 mg/m^2 versus 592.8 mg/m^2, respectively), though the incidence of Grade 3/4 thrombocytopenia was lower on the 21-day schedule (5.5% versus 29.5%, respectively). Toxicity-related dose reductions and omissions are frequently required for Day 15 gemcitabine doses when utilizing a 28-day schedule. This study showed that similar dose intensity could be achieved with the 21-day regimen and could reduce the frequency of dose-limiting toxicities, without compromising efficacy.

Table 8: Phase 2 Gemcitabine/Cisplatin Study Comparing 21 and 28 Day Schedules

	28-Day n=54	21-Day n=53	p-value
ORR	38%	42%	-
Median OS (months)	9.3	12.2	0.49
Dose Intensity	Gem: 592.8	Gem: 589.7	0.89
(mg/week)	Cis: 16.7	Cis: 21.5	0.0001
G3/4 neutropenia	22.5%	27.8%	0.69
G3/4 thrombocytopenia	29.5%	5.5%	0.14

As shown in **Table 9** the GC 21-day schedule has been used in multiple Phase 3 studies, including pivotal registration trials.

Table 9: Phase 3 Gemcitabine/Cisplatin Studies - 21 and 28 Day Schedules

	Pts	ORR	Med TTP	Med OS	1-Yr OS
28-day Regimens/Studies	**(#)**	**(%)**	**(mo)**	**(mo)**	**(%)**
Crino et al. 1999	155	38	5.0	8.6	33
Sandler et al. 2000	260	30	5.6	9.1	39
Schiller et al. 2002	301	22	4.2	8.1	36
Gebbia et al. 2003	138	30	4.0	8.2	20
Total number of pts	854				
21-day Regimens/Studies					
Cardenal et al. 1999	69	41	6.9	8.7	32
Comella et al. 2001	118	28	4.4	8.8	-
Scagliotti et al. 2002	205	30	5.3	9.8	37
Alberola et al. 2003	182	42	6.3	9.3	38
Smit et al. 2003	160	37	5.1	8.9	33
Wachters et al. 2003	119	46	6.0	9.9	45
Zatloukal et al. 2003	87	41	5.9	8.8	33
Giaccone et al. 2004	363	47	6.0	10.9	44
Bissett et al. 2005	181	26	5.5	10.8	38
Paz-Ares et al. 2006	328	35	6.0	10.4	45
Gatzemeier et al. 2007	579	30	5.7	10.2	42
JMDB	863	28	5.4	10.3	42
Total number of pts	3254				

As shown in **Table 10** which compares 3 and 4 week GC schedules of administration patient demographics, percent of patients with G doses decreased or omitted and G percent of planned dose intensity received by patients it appears that the GC 4 week schedule is poorly tolerated requiring day 8 and 15 G dose reductions or omissions so that patients received only 70% and 27% of planned G dose intensity in the two studies that reported such data. By contrast with the 3 week schedule approximately 90% of planned G dose intensity was administered.

Table 10: Gemcitabine (G) 28 or 21 day schedule. G dose received

						Gem dose decreased or omitted (%)		Gem % planned DI*
28-day Regimens/Studies	**Pts (#)**	**Gem dose**	**PT dose**	**Stage III (%)**	**PS 0-1 (%)**	**D 8**	**D15**	
Crino et al. 1999	155	1000 d1,8,15	100 d2	21	95	32	80	70
Sandler et al. 2000	260	"	100 d1	33	80	29	61	27
Schiller et al. 2002	301	"	100 d1	14	95	-	-	-
Gebbia et al. 2003	138	1400 d1,8,	100 d8	46	81	-	-	-
Comella et al. 2001	112	1000 d 1,8,15	100 d1	40	100	-	-	-
Total number of pts	966							
21-day Regimens/Studies								
Cardenal et al. 1999	69	1250 d 1,8	100 d1	48	88	-	-	-
Scagliotti et al. 2002	205	1250 d1,8	75 d2	19	95	18	-	91
Alberola et al. 2003	182	1250 d1,8	100 d1	77	85	7	-	93
Smit et al. 2003	160	1250 d1,8	80 d1	21	89	-	-	95
Wachters et al. 2003	119	1125 d1,8	80 d2	43	86	12	-	92
Zatloukal et al. 2003	87	1200 d1,8	80 d1	41	>69	13	-	94
Giaccone et al. 2004	363	1250 d1,8	80 d1	33	90	-	-	84
Bissett et al. 2005	181	1250 d1,8	75 d1	40	100	4	-	-
Paz-Ares et al. 2006	328	1250 d1,8	80 d1	19	100	15	-	88
Gatzemeier et al. 2007	579	1250 d1,8	80 d1	33	99	-	-	-
JMDB	863	1250 d1,8	75 d1	24	100	10	-	86
Total number of pts	3136							

* DI = dose intensity

Statistical Analysis Plan

Overall survival
For the primary analysis of this study, the OS HR of AC over GC was to be estimated from survival data on all randomized patients using a Cox proportional hazards model including key baseline prognostic cofactors.

If the 95% confidence interval for the OS HR was found to fall entirely below the margin of 1.17647, the null hypothesis H_0 would be rejected at a one-sided 0.025 significance level. (This can be equivalently understood as rejecting the point-null hypothesis "HR = 1.17647" at a two-sided 0.05 significance level.) This fixed non-inferiority margin of 1.17647 corresponds to GC having a 15% lower survival hazard (that is, risk of death) than that of AC. The sponsor chose the 15% margin for the design of this study, as it would allow a sufficient and practical similarity between the 2 treatments, for which a study could be conducted and completed within a reasonable time frame. For example, the sample size required for a 10% non-inferiority margin would be 4000 patients, versus 1700 patients needed for the 15% margin, more than doubling the required sample size and leading to a substantial delay in the completion of the study. At the same time, the addition of this large number of patients would have improved the precision of the estimates of median survival by only 2 weeks. To date, this 1725-patient trial, which was conducted over a period of 2.5 years, is the largest 2-arm trial ever conducted in first-line locally advanced or metastatic NSCLC.

Predefinition of a non-inferiority margin is usually made on the assumption that the toxicity of the 2 treatments will be identical. In addition, based on the historical toxicity profile of pemetrexed, the sponsor expected to demonstrate a clinically relevant improvement in safety and convenience compared to GC; thus, the potential, relatively small, loss in survival benefit should be considered in this context.

Key secondary analyses included Kaplan-Meier and Cox methods applied to PFS, TtPD, and survival without Grade 3/4 toxicity (and survival without Grade 4 toxicity), and comparison of overall response rates. Prespecified subgroup analyses included Kaplan-Meier and Cox survival analyses by smoking status (ever-smokers versus neversmokers), histology (adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, and other), as well as other key baseline characteristics. Toxicity was primarily to be summarized by considering counts and percentages of patients experiencing particular laboratory and nonlaboratory adverse events, by maximum Common Toxicity Criteria (CTC, v2.0) grade, per treatment group.

In addition to the protocol-specified analyses presented, the Sponsor has conducted a percent retention non-inferiority analysis. Retention of 50% of the survival effect of the standard treatment has been used as the minimum requirement for FDA approval in settings where the cancer is advanced and incurable. Further consideration is given to the overall risks and benefits of the new regimen in determining approvability. Examples where percent retention for determining whether a new regimen is non-inferior to a standard regimen as the

basis for approval include capecitabine (for the treatment of colorectal cancer), docetaxel (for the treatment of breast cancer), and docetaxel plus cisplatin (for the treatment of NSCLC).

Two earlier studies (Wozniak et al. 1998; Sandler et al. 2000) showed clear, statistically significant survival advantages for cisplatin-based doublets over C. The survival hazard ratio in the Wozniak trial was estimated to be 0.720, indicating a 28% reduction in the risk of death for the doublet vinorelbine plus cisplatin over C. The Sandler trial estimated the survival hazard ratio to be 0.732, indicating a 27% reduction in the risk of death for the doublet GC over C.

Various methods to determine percent retention of benefit have been used in the FDA's review and approval of the regimens listed above. The percent retention methodology used for capecitabine was published by Rothmann and colleagues (2003) and mirrors the method described by Simon (1999). In the FDA review of docetaxel, the FDA chose a more conservative methodology to address limitations of using a single historical trial to establish the survival benefit of vinorelbine plus cisplatin relative to cisplatin alone. This method is called either the "two confidence interval" or "95-95" method (www.fda.gov) and assumes that the true efficacy of the control regimen is equal to the worst-case 95% confidence bound (the log hazard ratio bound as determined from the historical data). The methodologies described above have been used to interpret the percent benefit retained by pemetrexed relative to the survival effect of gemcitabine. The survival benefit of gemcitabine was demonstrated in a single Phase 3 study, referred to as the Sandler trial (2000).

For this study, the method of Rothmann and colleagues was used to estimate the percentage of the survival benefit for GC over C retained by AC. Rothmann's method is to estimate this "percent retention" directly by combining survival hazard ratio estimates (with standard errors) from both historical data and from the current trial.

The primary statistical analysis was based on the ITT population, defined as all patients randomly assigned to a treatment arm, whether or not they received the assigned study drug, and analyzed according to the randomized therapy. Additional sensitivity analyses were performed on patients in the protocol-qualified (PQ) population, defined as all randomized patients who had eligible study disease, who did not take prohibited anticancer therapy, who had a baseline scan, and who received at least 1 dose of chemotherapy. Patients in the PQ population were analyzed according to the therapy received in the first treatment cycle. Of the 1725 ITT patients, 1666 were qualified for PQ analyses (AC, 838; GC, 828).

Progression-Free Survival

Progression-free survival duration was calculated and analyzed including clinical progressions of disease not based on lesion measurements, and including only objective clinical progressions. In addition, an independent review of PFS was conducted to assess the potential for investigator bias in the determination of progressive disease between treatment arms. Sensitivity analyses were also performed on the PFS results to evaluate the robustness

of the results and to investigate the impact of various event and censoring mechanisms for progressive disease.

Variations between the AC and GC treatment arms were minimized by assessing patients in both arms at regularly scheduled visits, at the same intervals, and during both the treatment and follow-up period. Patients in each arm were assessed clinically every 3 weeks and objectively (with radiographic imaging) every 6 weeks until objective progression or death. Assessments continued to be performed at regular intervals in both treatment arms during the follow-up phase of the study. If a patient experienced progressive disease (PD) based on clinical deterioration, this PD date was captured as the first progression date. Patients with PD based on clinical progression continued to be followed radiographically until objective progression, according to the protocol.

A statistical noninferiority test (using the same 1.17647 HR margin) was performed for secondary time-to-event variables PFS, TtPD, and TtTF. Of these variables only PFS will be considered in this review.

Objective response and duration
Tumor response was assessed according to the RECIST criteria and was calculated, per treatment arm, as the proportion of tumor-response qualified (TRQ) patients having a confirmed best response of partial response (PR) or complete response (CR). Duration of response was also analyzed for the subgroup of patients with PR or CR.

Study Conduct
Following an initial randomization based on whether the investigative center was participating in the companion biomarker study (yes versus no), randomization was adjusted for baseline factors, including investigative site, disease stage (IIIB versus IV), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), history of brain metastases (yes versus no), sex (male versus female), and basis for initial pathological diagnosis (histological versus cytological).

Each patient underwent a treatment period and a follow-up period. The planned treatment period consisted of up to 6 cycles of assigned treatment, and cycles were 21 days in length. The follow-up period included periodic tumor response evaluations until disease progression and follow up for all patients until death or study closure.

The primary objective of Study JMDB was the comparison of OS time between patients treated with pemetrexed plus cisplatin (AC) versus gemcitabine plus cisplatin (GC) as initial treatment for locally advanced or metastatic NSCLC. The study plan included pretreatment supplementation with folic acid, vitamin B_{12}, and dexamethasone for patients on both arms at the same dose and schedule.

Interim Analyses
The study protocol specified a planned interim analysis, with an optional, planned second

interim analysis to occur if requested by the independent Data Monitoring Committee (DMC). The DMC, formed in accordance with Lilly policies and procedures, was responsible for evaluating interim results. The DMC had a membership of qualified personnel, excluding Lilly employees. The DMC reviewed unblinded interim efficacy and safety analyses with results remaining blinded to anyone outside the DMC. The purpose of each interim analysis was to estimate efficacy and safety parameters and consider whether continuation of enrollment was scientifically and ethically appropriate. No other interim analyses were performed. Interim statistical tests of efficacy were performed according to protocol and considered only whether there was inferiority of the pemetrexed plus cisplatin regimen compared to the gemcitabine plus cisplatin regimen; therefore, the interim analyses did not impact the alpha level of the final analysis (noninferiority/superiority of pemetrexed plus cisplatin).

Both interim analyses for this trial were completed and reviewed by the DMC during the study. The first interim analysis included data collected in the first 10 months of enrollment (including data from over 700 patients), and was performed in May 2005. The second interim analysis occurred approximately 4 months after the first interim analysis, in September 2005. During interim analyses, patient accrual continued. Following both interim analyses, the DMC recommended the trial continue as planned per protocol. Because no changes were recommended based on the DMC review, interim results were not disseminated outside of the DMC and were not unblinded to Lilly.

Supporting Phase 2 Studies

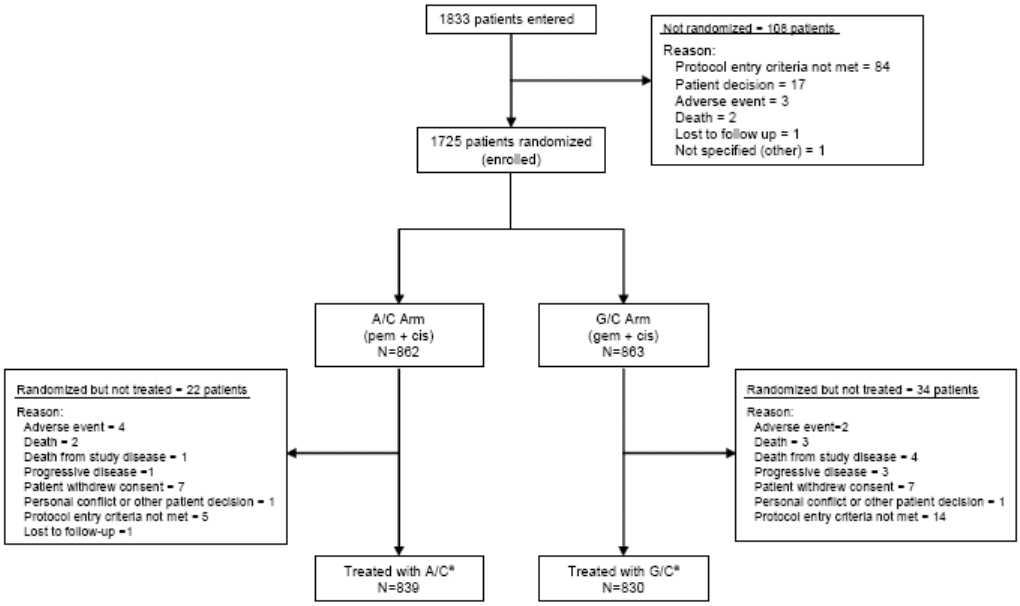
Study JMAY was a single-arm, multicenter, Phase 2 trial of pemetrexed in combination with cisplatin administered intravenously every 21 days as initial treatment for patients with Stage IIIB or IV NSCLC. The primary objective of this study was overall response rate (ORR). The secondary efficacy objectives included overall survival time (OS), time-to-progressive disease (TtPD), time-to-treatment failure (TtTF), and duration of response (DoR) for responding patients. Pemetrexed was administered at 500 mg/m2 followed by cisplatin at 75 mg/m2 over 30 minutes on Day 1 of each 21-day cycle. This study was initiated and completed prior to the programmatic addition of folic acid and vitamin B12 supplementation to pemetrexed studies; but patients did receive prophylactic dexamethasone.

Study JMBZ was a single-arm, multicenter, Phase 2 trial of pemetrexed in combination with cisplatin administered intravenously every 21 days as initial treatment for patients with Stage IIIB or IV NSCLC. The primary objective of this study was ORR. The secondary efficacy objectives included DoR and OS. Pemetrexed was administered at 500 mg/m2 over 10 minutes on Day 1 every 3 weeks followed by cisplatin 75 mg/m2 over 60 minutes on Day 1 every 3 weeks. This study was initiated and completed prior to the programmatic addition of folic acid and vitamin B12 supplementation to pemetrexed studies; but patients did receive prophylactic dexamethasone.

Study Results

Study JMDB was a multicenter study that entered 1833 patients at 177 investigational sites in 26 countries. Of these, 1725 (94.1%) patients were enrolled (randomized): 862 to the AC arm and 863 to the GC arm. Of those enrolled, 839 (97.3%) were treated with AC and 830 (96.2%) were treated with GC. **Figure 3** describes the disposition of patients who entered the trial.

Figure 3: Patient Disposition



Reasons for study discontinuation were similar for patients on the AC and GC arms. Among randomized patients, the 3 most common reasons for discontinuation for both the AC and GC arms were protocol completed (35.4% and 35.3%, respectively), progressive disease (32.5% and 29.3%, respectively), and adverse events (11.5% and 13.6%, respectively).

Baseline demographic and disease characteristics were similar between the 2 treatment arms of the ITT population (**Table 11**). Approximately 70% of the patients were men, reflecting the gender ratio of this disease observed in the general NSCLC patient population. The median age of 61 years with a wide age range (26 years to 83 years) also corresponds with the expected demographics of the general patient population. At study entry, 24% of patients had Stage IIIB disease and approximately 76% of patients had Stage IV disease. Approximately 36% of patients had an ECOG performance status (PS) of 0, and 64% of patients had an ECOG PS of 1. The arms were balanced with respect to these well-established prognostic factors, as well as age, history of tobacco use, and histological classification.

Table 11: Baseline demographic and disease characteristics

Variable		AC N=862	GC N=863

Sex	Male n (%)	605 (70.2)	605 (70.1)
	Female n (%)	257 (29.8)	258 (29.9)
Origin	African Decent n (%)	18 (2.1)	18 (2.1)
	Caucasian n (%)	669 (77.6)	680 (78.8)
	East/Southeast Asian n (%)	116 (13.5)	104 (12.1)
	Hispanic n (%)	27 (3.1)	23 (2.7)
	Western Asian n (%)	30 (3.5)	37 (4.3)
	Other n (%)	2 (0.2)	1 (0.1)
Age Group	Age <65 years n (%)	541 (62.8)	577 (66.9)
	Age ≥65 years n (%)	321 (37.2)	286 (33.1)
	Median Age/Range (years)	61.05 (28.8-83.2)	60.95 (26.4-79.4)
Smoking Status	Ever Smoker n (%)	629 (73.0)	637 (73.8)
	Never Smoker n (%)	128 (14.8)	122 (14.1)
	Unknown	105 (12.2)	104 (12.1)
Performance Status	ECOG PS 0 n (%)	305 (35.4)	307 (35.6)
	ECOG PS 1 n (%)	556 (64.5)	554 (64.2)
	Unknown	1 (0.1)	2 (0.2)
Basis for Diagnosis	Cytological n (%)	289 (33.5)	288 (33.4)
	Histological n (%)	573 (66.5)	575 (66.6)
Stage of Disease	Stage IIIB n (%)	205 (23.8)	210 (24.3)
	Stage IV n (%)	657 (76.2)	653 (75.7)
Histology	Adenocarcinoma n (%)	436 (50.6)	411 (47.6)
	Squamous Cell Carcinoma n (%)	244 (28.3)	229 (26.5)
	Large Cell Carcinoma n (%)	76 (8.8)	77 (8.9)
	Other n (%)	106 (12.3)	146 (16.9)

Table 12 summarizes preexisting (secondary) conditions reported to be present at the time of enrollment in ≥5% of all patients randomized. Seven-hundred eighty-three patients (90.8%) in the AC arm and 795 patients (92.1%) in GC arm reported at least 1 secondary condition. Secondary conditions were well balanced between treatment arms. Among all randomized patients, the most common secondary conditions reported were cough (40.4%), dyspnea (32.6%), hypertension (27.2%), chest pain (21.9%), fatigue (12.6%), chronic obstructive pulmonary disease (10.4%), and anorexia (10.2%). There were no significant differences between AC and GC treated patients.

Table 12: Preexisting conditions

	AC (N=862)	**GC (N=863)**	

Preferred Term	n (%)	n (%)	p-Value*
PATIENTS WITH ≥1 CONDITION	783 (90.8)	795 (92.1)	0.344
Cough	356 (41.3)	341 (39.5)	0.462
Dyspnea	287 (33.3)	275 (31.9)	0.538
Hypertension	227 (26.3)	243 (28.2)	0.417
Chest pain	195 (22.6)	182 (21.1)	0.449
Fatigue	106 (12.3)	112 (13.0)	0.717
Chronic obstructive pulmonary disease	93 (10.8)	86 (10.0)	0.582
Anorexia	96 (11.1)	80 (9.3)	0.204
Weight decreased	81 (9.4)	83 (9.6)	0.935
Hemoptysis	75 (8.7)	69 (8.0)	0.603
Constipation	67 (7.8)	64 (7.4)	0.786
Insomnia	61 (7.1)	68 (7.9)	0.583
Back pain	66 (7.7)	56 (6.5)	0.350
Anemia	56 (6.5)	65 (7.5)	0.451
Dysphonia	54 (6.3)	60 (7.0)	0.628
Hypercholesterolemia	47 (5.5)	57 (6.6)	0.363
Diabetes mellitus	49 (5.7)	51 (5.9)	0.918
Anxiety	34 (3.9)	44 (5.1)	0.297
Productive cough	45 (5.2)	33 (3.8)	0.167

Table 13 provides a summary of reported prior therapies for the diagnosis of NSCLC. Data show that the 2 treatment arms were relatively well balanced with respect to prior therapies.

Table 13: Prior Therapies

	A/C (N=862)	G/C (N=863)	
Patients with Therapy Type	n(%)	n(%)	p-value
Prior Radiotherapy	59 (6.8)	60 (7.0)	1.000
Prior Surgery	73 (8.5)	98 (11.4)	0.053

Table 14 summarizes the results for OS for the ITT and PQ populations. The primary cofactor-adjusted survival hazard ratio in the ITT population was 0.94 (95% CI: 0.84 to 1.05), with a non-inferiority p-value of <0.001 for testing the HR margin of 1.17647. Median OS was 10.28 months for the ITT population on both arms. The 1- and 2-year survival rates in the ITT population were 43.48% and 18.94%, respectively, for the AC arm and 41.94% and 13.98%, respectively, for the GC arm. The unadjusted estimate of the survival HR was 0.93 (95% CI: 0.83 to 1.04), with a non-inferiority p-value of <.0001. Results were similar between the ITT and PQ populations.

Table 14: Overall Survival

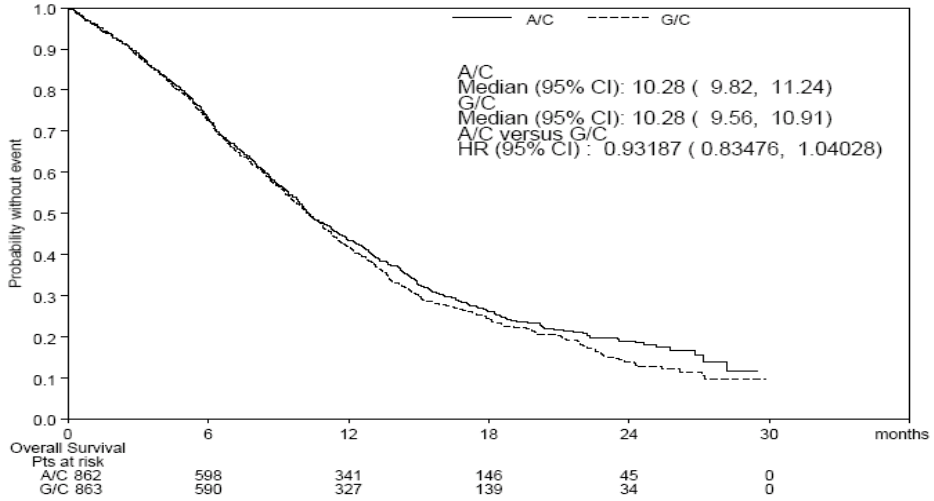
	ITT Patients	**PQ Patients**

	N=1725		N=1666	
	AC (N=862)	**GC** (N=863)	**AC** (N=838)	**GC** (N=828)
Percent censored	27.73	25.03	27.21	24.28
Median	**10.28**	**10.28**	**10.38**	**10.45**
95% CI for median	9.82-11.24	9.56-10.91	9.82-11.30	9.72-11.14
75th percentile	18.53	17.84	18.69	17.91
Maximum	29.50	29.83	29.50	29.83
Percent of patients surviving at least:				
6 months	73.05	72.61	73.79	73.72
12 months	43.48	41.94	43.84	42.52
18 months	26.16	24.56	26.52	24.88
24 months	18.94	13.98	19.20	14.20
Unadjusted Hazard Ratio* (95% CI)	0.93 (0.83 – 1.04)		0.93 (0.84-1.04)	
Unadjusted Noninferiority p-value*	<.0001		<.0001	
Adjusted HR** (95% CI)	0.94 (0.84-1.05)		0.94 (0.84-1.05)	
Adjusted Noninferiority p-value**	<0.001		<0.001	

Abbreviations: AC = pemetrexed plus cisplatin; CI = confidence interval; ECOG PS = Eastern Cooperative Group performance status; GC = gemcitabine plus cisplatin; HR = hazard ratio; ITT = intent to treat; N = number of patients; PQ = protocol qualified.
*Unadjusted HR and p-value from Cox model with treatment as the only cofactor.
**Adjusted HR and p-values from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for initial pathological diagnosis (histological/cytological).

Figure 4 presents the Kaplan-Meier (K-M) survival graph for the ITT population.

Figure 4: Overall survival (ITT Population)



Applying the Rothmann method using the cofactor-adjusted log hazard ratios and their

standard errors as stated in **Table 15**, AC was estimated to retain 120% of GC's survival benefit over C (95% CI: 83% to 190%). The one-sided statistical test of whether AC retained at least 50% of GC's survival benefit over C was statistically significant (p=0.005). If applying the method using the unadjusted log hazard ratios, AC was estimated to retain 123% of GC's survival benefit over C (95% CI: 86% to 193%). The one-sided statistical test of whether AC retained at least 50% of GC's survival benefit over C was statistically significant (p=0.003).

Regardless of whether adjusted or unadjusted is used, AC retains over 80% of the survival effect of GC over C. This analysis demonstrates that the non-inferiority analyses are robust, satisfying the fixed margin criteria, and retaining well over 50% retention.

Table 15: Survival, Percent Retention Analyses (ITT)

Parameter	Hazard Ratio (standard error)
Log HR* for C over GC (standard error)	0.31136 (0.10401)
Log HR* for AC over GC (standard error)	-0.07056 (0.05615)
Adjusted Log HR** for C over GC (standard error)	0.31342 (0.10690)
Adjusted Log HR*** for AC over GC (standard error)	-0.06345 (0.05619)

*Unadjusted log hazard ratio from Cox model with treatment as the only cofactor.
**Adjusted log hazard ratio from Cox model with treatment plus 3 cofactors: ECOG PS, gender, and disease stage.
***Adjusted HR from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).

Subgroup Analyses Defined by Baseline Characteristics

As prespecified in the statistical analysis plan (SAP), subgroup analyses were performed to assess whether the survival results within certain key subgroups were consistent with survival results for the overall study, or whether there is evidence of differential treatment benefit in certain subgroups.

Subgroup analyses of OS were performed using Cox and Kaplan-Meier methods. Subgroups were analyzed separately as defined by the following factors: disease stage, performance status, sex, basis for initial pathological diagnosis, smoking status, age, ethnic origin, and NSCLC histology. Several of these factors are commonly found to be prognostic of OS in advanced NSCLC. Additional rationale for certain subgroup analyses are described further below:

The choice of ever-smoker versus never-smoker is based on the Tarceva (erlotinib) data showing that erlotinib was more effective in patients who had never been smokers than in current or former smokers. In addition, smoking status may be associated with histologic cell type and other patient comorbidities, which may impact patient prognosis.

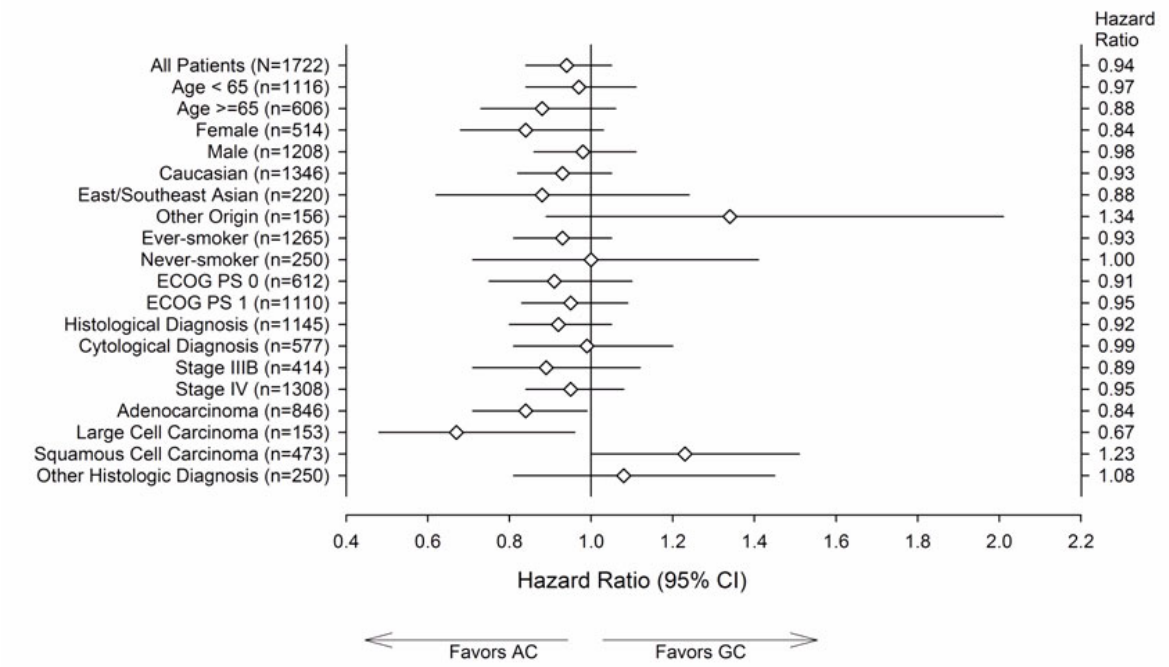
Safety and efficacy analyses by age and origin (as well as sex, included as a randomization factor) are regulatory requirements; the categories for origin were divided into 3 groups

based on a blinded review of Study JMDB baseline data, permitting adequately sized categories for meaningful comparisons.

Histology categories of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the most common NSCLC cell types. Histology has not historically been demonstrated to be prognostic or predictive for chemotherapy outcomes in NSCLC. However, the prospective decision to perform histology subgroup analyses in Study JMDB was based on a retrospective analysis of the Phase 3 study of pemetrexed in previously treated NSCLC (H3E-MC-JMEI [JMEI]) and 2 gemcitabine plus cisplatin NSCLC studies, which suggested a possible correlation between histology and OS. These studies demonstrate that thymidine synthetase (TS) expression was significantly higher in squamous cell carcinoma compared with adenocarcinoma ($p<0.0001$) (Ceppi et al. 2006), and preclinical data has indicated that overexpression of TS correlates with reduced sensitivity to pemetrexed (Sigmond et al. 2003; Giovannetti et al. 2005). These data suggest that pemetrexed may be more effective in patients with NSCLC histology with lower TS expression such as adenocarcinoma, as compared to patients with squamous cell carcinoma whose tumors may be less sensitive due to TS overexpression.

Figure 5 shows a plot of the adjusted hazard ratios (with 95% confidence intervals) for the preplanned subgroup analyses, which evaluated differences in overall survival between treatment arms with respect to baseline patient and disease characteristics.

Figure 5: Survival Hazard Ratio by Subgroup



As shown in **Figure 5**, the effect on survival of AC relative to GC was similar for disease and patient characteristics; however, a differential effect on survival was seen within

histologic groups. The results show that AC patients with adenocarcinoma and large cell carcinoma had significantly better survival than GC patients with these histologies (adenocarcinoma: n=847, 12.6 months versus 10.9 months [adjusted HR 0.84, CI: 0.71 to 0.99, superiority p=0.033]; large cell carcinoma: n=153, 10.4 months versus 6.7 months [adjusted HR 0.67, CI: 0.48 to 0.96, superiority p=0.027]). Patients on the GC arm with squamous histology showed better survival than AC patients with squamous histology (n=473, 10.8 months (GC) versus 9.4 months (AC) [adjusted HR 1.23, CI: 1.00 to 1.51, superiority p=0.050]).

Progression Free Survival

The tumor measurement intervals were similar for both treatment arms. The time from previous lesion assessment (or visit) to objective progression for all randomized patients Is illustrated in **Table 16**.

Table 16: Time from previous lesion assessment (or visit) to objective progression

	Until First Objective Progression		On-Treatment*		Postdiscontinuation of Treatment**		Postdiscontinuation of Treatment*	
	AC	GC	AC	GC	AC	GC	AC	GC
25th Percentile	5.98	5.98	5.98	5.98	4.22	3.68	5.98	5.98
Median	6.67	6.97	6.67	6.97	6.67	6.97	6.62	6.84
75th Percentile	8.66	8.66	7.97	8.10	10.65	10.65	9.40	9.96

*Interval between disease assessment dates (weeks).
**Interval between progression and previous visit date (weeks).

As shown in **Table 17**, the PFS analyses were mainly driven by objective progressions or deaths. Clinical progression accounted for 7 and 6 events, respectively, for AC and GC treatment.

Table 17: Objective and Clinical Progressions per Arm

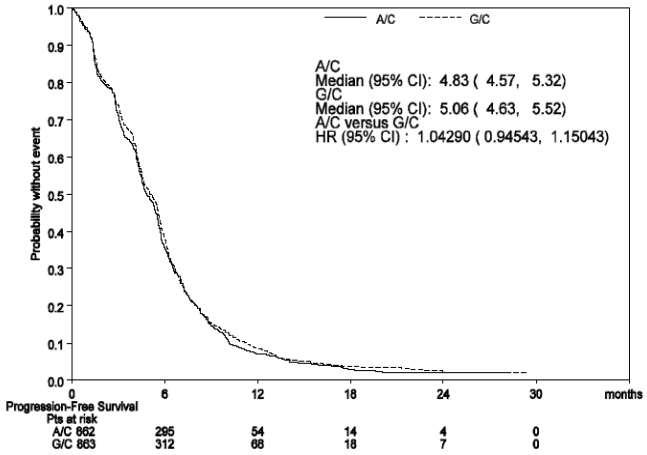
	AC Arm N=862	GC Arm N=863
PFS Events by Type of Analysis	**n (%)**	**n (%)**
All progressions	802 (93.0)	795 (92.1)
Death or objective PD only	795 (92.2)	789 (91.4)
Difference (that is, clinical progressions)	7 (0.8)	6 (0.7)

The median PFS was 4.83 (4.57, 5.32) months for the AC arm and 5.06 (4.63, 5.52) months for the GC arm. Using the Cox regression adjusted model, the non-inferiority test of H_0 versus H_a was statistically significant (one-sided p=0.008), with an adjusted estimate for the HR of 1.04 (95% CI: 0.94 to 1.15), with the entire confidence interval for HR below the 1.17645 non-inferiority margin. These results demonstrate that AC is not inferior to GC

with respect to PFS. The confidence interval for the PFS HR implies that the risk of PD or death on the AC arm is 6% lower than that on the GC arm in the best-case scenario, and 15% higher in the worst-case scenario.

Figure 6 displays the Kaplan-Meier PFS graph for randomized patients by treatment group. The superiority test (log-rank) was not statistically significant (p=0.402).

Figure 6: Progression Free Survival



Analyses of PFS for histologic subgroups were generally consistent with the efficacy results shown for OS. There were trends for AC to perform better than GC in adenocarcinoma and large cell carcinoma. In squamous cell carcinoma, GC tended to perform better than AC (**Table 18**). As was emphasized previously these results should be viewed as hypothesis generating because of missing histology data on 252 study patients and because large cell anaplastic cancer patients, a waste basket classification that includes both anaplastic adenocarcinoma and squamous carcinoma had the most striking survival benefit with AC treatment.

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Table 18: Progression Free Survival Results by Histology

	Median (mo)	Adjusted HR [a] (95% CI)	NI p-Value [a]	Sup. p-Value [a]
Adenocarcinoma (N=847) [b]				
AC (n=436)	5.45	0.90 (0.78–1.03)	<0.001	0.125
GC (n=411)	4.99			
Large Cell (N=153) [b]				
AC (n=76)	4.45	0.89 (0.65-1.24)	0.049	0.499
GC (n=77)	4.21			
Squamous Cell (N=473) [b]				
AC (n=244)	4.40	1.36 (1.12-1.65)	0.933	0.002
GC (n=229)	5.52			

Abbreviations: AC = pemetrexed plus cisplatin; CI = confidence interval; ECOG PS = Eastern Cooperative Group performance status; GC = gemcitabine plus cisplatin; HR = hazard ratio; mo = months; N= number of patients per histologic subgroup; n = number of patients per treatment arm; NI = noninferiority; NSCLC = non-small cell lung cancer; Sup = superiority.

[a] Adjusted HR and superiority and NI p-values from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis histopathological/ cytopathological).

[b] 252 patients had "other" or unknown histology, 106 AC, 146 GC.

Sensitivity analyses were conducted on PFS to investigate whether various event and censoring mechanisms for progressive disease had any impact on the interpretation of the PFS results.

The first sensitivity analysis addressed the potential impact of post-discontinuation anticancer therapy. In the primary PFS analysis, post-discontinuation anticancer therapy use was not considered even if it occurred prior to documentation of progression or death. No impact of post-discontinuation anticancer therapy on the PFS results was observed.

The second sensitivity analysis was performed on PFS using only objectively determined progression, and ignoring (that is, not censoring on) post-discontinuation anticancer therapy. For this analysis, patients who did not have progressive disease were censored back to the date of last tumor measurement (PFS and objectively determined PFS were censored back to the date of last prior contact). The purpose of this analysis is to assess the impact of censoring on last contact date versus censoring on last tumor measurement. The HR and point estimates of this sensitivity analysis are consistent with the primary PFS results.

A third sensitivity analysis (SA3) was performed to ensure the precision of the estimates was not impacted as a result of missing or incomplete assessments. In this analysis, progressions with documentation following a missed or incomplete scheduled assessment were back-dated to the date of the missed or incomplete scheduled assessment. Backdating was used as a conservative approach to determining progression, as the progression may have occurred at the time of the missed assessment. Again, the results show that the

estimates of PFS for each arm were not biased in favor of 1 arm and the overall estimate of PFS is consistent with the findings in the primary analysis.

As shown in **Table 19**, the analysis of PFS, a secondary endpoint in this study, is robust and is supported by the multiple sensitivity analyses. As expected, a more stringent censoring definition that accounts for missing scans results in a lower estimate of median PFS, but the results are consistent between treatment arms, as indicated by the hazard ratio and confidence intervals.

Table 19: PFS Sensitivity Analyses

	Median PFS (95% CI) [a]		Adjusted HR [b]
	AC Arm	GC Arm	(95% CI)
Primary PFS Analysis	4.83 (4.57–5.32)	5.06 (4.63–5.52)	1.04 (0.94–1.15)
PFS Sensitivity Analysis			
1: All progressions, censored at date of PDT anticancer therapy	4.83 (4.57–5.32)	5.19 (4.70–5.52)	1.05 (0.95-1.17)
2: Objective progressions, censored at last tumor measurement	5.06 (4.63–5.39)	5.29 (4.80–5.55)	1.05 (0.95-1.16)
3: Objective progressions, back-dating progression to an earlier visit date (when missing tumor measurements) and censoring at last tumor measurement	4.37 (4.24–4.50)	4.37 (4.21–4.57)	1.04 (0.94–1.15)

[a] Unadjusted summary statistics.
[b] Adjusted HR from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).

Independently-Reviewed Progression-Free Survival
A preplanned limited independent central review of imaging for determination of objective progressive disease was conducted on a subset of 400 patients randomly selected from the first 1000 patients enrolled. The purpose of this independent review was to look for any evidence of a systematic bias in investigator assessments of progressive disease in terms of the relative efficacy of the 2 treatment arms.

Of the 400 patients sampled for review, 333 had reviewable scans. Reasons why scans for 67 patients were missing or were not reviewable were balanced between treatment arms. Baseline patient and disease characteristics for the randomly selected subset of patients was representative of the larger study population. The investigator-assessed median PFS for these 333 patients was 5.59 months on the AC arm and 5.62 months on the GC arm, with the unadjusted HR estimated to be 1.12 (95% CI: 0.90 to 1.40). Independently reviewed median PFS for these 333 patients was 4.37 months on the AC arm and 4.90 months on the GC arm, with the unadjusted HR estimated to be 1.07 (95% CI: 0.86 to 1.34), which is similar to the 1.04 estimate based on investigator assessments for the entire study population. Overall, the independent review confirms the investigator assessment. In

addition, there is no evidence of any systematic bias in the investigator assessments favoring one of the treatment arms.

Tumor Response
The tumor-response qualified (TRQ) population included randomized patients who had eligible study disease, did not take prohibited anticancer therapy, had a baseline scan and at least 1 follow-up scan, and received at least 1 dose of study treatment. A total of 1517 patients were included in the TRQ population: 762 patients in the AC arm and 755 patients in the GC arm.

Table 20 presents a summary of the investigator-determined best tumor response for the TRQ population by treatment arm. The tumor response rate was 30.6% (27.3% to 33.9%) in the AC arm and 28.2% (25.0% to 31.4%) in the GC arm; however, there was no evidence of superiority for either arm with respect to response rate.

Table 20: Response Rate

	A/C (N = 762) n (%)	G/C (N = 755) n (%)
CR	2 (0.3)	3 (0.4)
PR	231 (30.3)	210 (27.8)
Responders (CR+PR) n(%)(95% CI)	233 (30.6) (27.3-33.9)	213 (28.2) (25.0-31.4)

Analyses of response rates for histologic subgroups were generally consistent with the efficacy results shown for OS. There were trends for AC to perform better than GC in adenocarcinoma and large cell carcinoma. In squamous cell carcinoma, GC tended to perform better than AC for response rate (**Table 21**). It should be emphasized, however that 252 patients had unknown histology. Therefore these results must be viewed as tentative and hypothesis generating.

Table 21: Histology and Response

	AC	GC	Sup.

					p-Value [a]
	Responders/ Patients (n)	Response Rate* (95% CI)	Responders/ Patients (n)	Response Rate* (95% CI)	
Histologic Subgroup Populations					
Adenocarcinoma [b]	126/436	28.9 (24.6-33.2)	89/411	21.7 (17.7-25.6)	0.015
Large Cell [b]	21/76	27.6 (17.6-37.7)	21/77	27.3 (17.3-37.2)	0.960
Squamous Cell [b]	57/244	23.4 (18.1-28.7)	72/229	31.4 (25.4-37.5)	0.049

[a] Adjusted HR and superiority and NI p-values from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis histopathological/ cytopathological).
[b] 252 patients had "other" or unknown histology, 106 AC, 146 GC.

Response Duration

A total of 446 patients were considered confirmed responders and were included in the Response duration analysis. Patients in the GC arm experienced a longer median response duration than patients in the AC arm (5.09 months versus 4.50 months); however, the difference was not statistically significant for either non-inferiority or superiority. The Cox adjusted HR was estimated to be 1.14 (95% CI: 0.94 to 1.38).

Post-discontinuation Anticancer Therapy Use

Table 22 provides a summary of the types of post-discontinuation anticancer therapy received among all randomized patients. Approximately 50% of patients received post-discontinuation systemic therapy in each arm.

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Table 22: Post-Discontinuation Therapy

Anticancer Therapy [a]	AC (N=862)	GC (N=863)	p-Value [b]
Radiotherapy	273 (31.7%)	289 (33.5%)	0.441
Surgery	28 (3.2%)	26 (3.0%)	0.784
Any post-discontinuation systemic treatment:	453 (52.6%)	484 (56.1%)	
Chemotherapy [c]:			
Any line	358 (41.5%)	408 (47.3%)	0.018
1 lines	245 (28.4 %)	285 (33.0%)	0.042
2 lines	77 (8.9%)	98 (11.4 %)	0.111
3 or more lines	36 (4.2 %)	25 (2.9 %)	0.154
Targeted therapy [d]	216 (25.1%)	196 (22.7%)	0.259
Other	31 (3.6%)	37 (4.3%)	0.536

a Patients could have received more than 1 type of post-discontinuation therapy
b p-value is from Fisher's Exact test.
c Refer to Table 23 for a list of the types of chemotherapies administered.
d Refer to Table 24 for a list of targeted therapies administered.

Table 23 provides a summary of the types of post-discontinuation chemotherapies for all randomized patients, and **Table 24** provides a summary of post-discontinuation targeted therapy for all randomized patients.

The post-discontinuation systemic anticancer agents received were well balanced between treatment arms, with the exception of post-pemetrexed or post-gemcitabine exposure. A small percentage of patients were reported to receive the same drug (pemetrexed or gemcitabine) post-discontinuation as was received according to randomized study treatment. Other patients crossed over to receive the opposite drug in post-discontinuation treatment (pemetrexed to gemcitabine 16.7%, gemcitabine to pemetrexed 13.4%). Overall, fewer patients on the AC arm received post-discontinuation systemic anticancer treatment (chemotherapy, targeted therapy, or immunotherapy) than patients on the GC arm (52.6% versus 56.1%), and significantly fewer patients on the AC arm received chemotherapy agents post-discontinuation (41.5% versus 47.3%, p=0.018).

Table 23: Post-Discontinuation Chemotherapy

	A/C (N=862)	G/C (N=863)
Drug Name	n(%)	n(%)
5-Fluorouracil	2 (0.2)	3 (0.3)
Adriamycin	1 (0.1)	1 (0.1)
Anthracycline	0 (0.0)	1 (0.1)
Capecitabine	1 (0.1)	4 (0.5)
Carboplatin	73 (8.5)	84 (9.7)
Cisplatinum	53 (6.1)	34 (3.9)
Cyclophosphamide	3 (0.3)	4 (0.5)
Cytosine arabinoside	1 (0.1)	0 (0.0)
Docetaxel	**219 (25.4)**	**238 (27.6)**
Doxorubicin	0 (0.0)	1 (0.1)
Epirubicin	1 (0.1)	2 (0.2)
Etoposide	16 (1.9)	12 (1.4)
Gemcitabine	**144 (16.7)**	**74 (8.6)**
Ifosfamide	3 (0.3)	4 (0.5)
Irinotecan	8 (0.9)	11 (1.3)
Lomustine	1 (0.1)	0 (0.0)
Methotrexate	1 (0.1)	2 (0.2)
Mitomycin	2 (0.2)	9 (1.0)
Mitoxantrone	0 (0.0)	1 (0.1)
Oxaliplatin	1 (0.1)	0 (0.0)
Paclitaxel	42 (4.9)	37 (4.3)
Pemetrexed	**30 (3.5)**	**116 (13.4)**
Taxane	0 (0.0)	1 (0.1)
Temozolomide	2 (0.2)	2 (0.2)
Thalidomide	2 (0.2)	0 (0.0)
Topotecan	5 (0.6)	2 (0.2)
Vinblastine	0 (0.0)	4 (0.5)

Table 24: Post-Discontinuation Targeted Therapy

	A/C (N=862)	G/C (N=863)
Bevacizumab	9 (1.0)	6 (0.7)
Bortezomib	0 (0.0)	1 (0.1)
Cetuximab	1 (0.1)	2 (0.2)
Erlotinib	167 (19.4)	137 (15.9)
Gefitinib	49 (5.7)	58 (6.7)
Imatinib	1 (0.1)	0 (0.0)

Phase 2 Study Results

Table 25 provides a summary of patient demographic and disease characteristics at baseline for Studies JMAY and JMBZ (both studies completed prior to vitamin supplementation). Study JMAY was a multicenter study enrolling 36 patients at 4 study centers: 1 in Austria and 3 in Germany and Study JMBZ was a multicenter study, enrolling 31 patients at 5 study centers in Canada.

Table 25: Demographics-Supporting Phase 2 Studies

	JMAY	JMBZ
Dose (mg/m2)	Pemetrexed: 500 Cisplatin: 75	Pemetrexed: 500 Cisplatin: 75
N (evaluable)	36	31
Sex: n (%) Male Female	 29 (81%) 7 (19%)	 11 (35%) 20 (65%)
Median Age: years (range)	58 (26-73)	60 (35-75)
Performance Status: n (%) 0 1 2	 8 (22%) 27 (75%) 1 (3%)**	 2 (6%) 24 (77%) 5 (16%)
Stage of Disease at Entry: n (%) Stage IIIB Stage IV	 18 (50%) 18 (50%)	 5 (16%) 26 (84%)

In Study JMAY chemonaive patients with NSCLC were treated. Of the 36 patients who entered this study, 14 patients (39%; 95% CI: 0.23 to 0.57) exhibited a PR (as best response) to drug therapy. Stable disease was reported in 18 patients (50.0%). The median survival was 10.9 months (95% CI: 7.7 months to 16.9 months) based on all eligible patients. Side effects were manageable.

In Study JMBZ chemonaive patients with NSCLC were treated. Of the 31 patients who enrolled into this study, 29 patients were eligible for response analysis. Of these, 13 patients had partial response confirmed through independent radiology review for an overall response rate of 44.8%. Stable disease was reported in 11 patients (38%). The median survival was 8.9 months.

6.1.6 Clinical Microbiology

Not applicable

6.1.7 Efficacy Conclusions

Study JMDB was a non-inferiority study designed to compare the efficacy of pemetrexed plus cisplatin (AC) and gemcitabine plus cisplatin (GC) in terms of overall survival (OS) in patients with Stage III and Stage IV NSCLC. A total of 862 patients on the AC arm and 863 patients on the GC arm were included in the OS analysis of randomized patients. Overall survival time, the primary outcome of this study, was 10.28 months for both treatment arms. Using the Cox regression adjusted model as the primary analysis, the non-inferiority test was statistically significant (one-sided $p<0.001$), with the primary cofactor-adjusted survival hazard ratio (HR) estimated to be 0.94 (95% CI: 0.84 to 1.05), with the entire confidence interval well below the 1.17645 non-inferiority margin. A supporting analysis, which used the Rothmann methodology, showed that AC retained 120% of GC's survival benefit over single-agent cisplatin, with a 95% confidence interval of 83% to 190%.

For all randomized patients, the results of another time-to-event endpoint, PFS, was also similar between the treatment arms. For PFS, the median PFS was 4.83 months on the AC arm and 5.06 months on the GC arm, with a Cox adjusted HR of 1.04 (95% CI: 0.94 to 1.15; non-inferiority $p=0.008$). Results from an independent review of PFS on a subset of randomly selected patients (n=333) were consistent with the investigator-assessed PFS results of the entire study population.

Objective tumor response rates were higher for the AC arm compared to the GC arm (30.6% versus 28.2%), although this difference was not statistically significant for superiority ($p=0.312$). Duration of response was longer for the GC arm compared to the AC arm (5.09 months versus 4.50 months); this comparison was not statistically significant for non-inferiority ($p=0.362$) or superiority ($p=0.268$).

Several issues arose in evaluating efficacy results of this NDA. The first concerns the GC schedule. In the study that led to approval of GC a four week schedule was used. In this application a 3 week schedule was used. However, when looking at the regimens the dose intensity of treatment is comparable for the two schedules and therapeutic results appear to be better for the 3 week schedule setting the non-inferiority bar somewhat higher. Moreover the 4 week GC schedule is not well tolerated. The reviewer believes that these points are valid. If so, there are 12 published first-line randomized studies that enrolled 3,254 patients to the every 21 day GC schedule. Those studies can be used to estimate the control effect size.

The second issue in evaluating this NDA involves the non-inferiority survival analysis. One problem impeding demonstration of non-inferiority of survival was the administration of post-discontinuation cytotoxic and targeted chemotherapy. Approximately 50% of patients on each arm received such therapy. Among patients initially treated with pemetrexed 16.7% crossed over to receive gemcitabine and among patients initially treated with gemcitabine 13.4% crossed over to receive pemetrexed. Also approximately 26% of patients on each

study arm received post-discontinuation docetaxel. Other drugs were administered fairly uniformly to study patients.

A third issue affecting a non-inferiority claim is the observed difference in the treatment effect of Alimta based on NSCLC histology with the efficacy benefits of Alimta demonstrated primarily in patients with non-squamous NSCLC.

The reviewer's conclusion is that while non-inferiority cannot be optimally demonstrated there is conclusive evidence that Alimta is active in non-squamous NSCLC. In 3 randomized Alimta NSCLC studies, JMDB, JMEN and JMEI, the treatment by histology interaction test significantly favored Alimta treatment for both overall survival and progression free survival.

In conclusion,

- GC performed as well as expected compared to historical data from Phase 3 studies of both 21-day and 28-day regimens.

- The non-inferiority primary endpoint of survival could not be fully evaluated because of extensive post-discontinuation cytotoxic and targeted chemotherapy in both treatment groups.

- Prespecified analyses showed improved survival for AC compared to GC for patients with adenocarcinoma and large cell anaplastic carcinoma in three randomized studies (see 6.1.8).

- AC should, therefore, be considered an effective treatment option for the initial treatment of patients with locally advanced or metastatic non-squamous NSCLC.

6.1.8 Histologic Subgroups in Studies JMEI, NS01 and JMEN

The favorable effect of pemetrexed on NSCLC non-squamous histology has been demonstrated by retrospective analysis in two additional studies, study JMEI, the study that led to the initial approval of pemetrexed for NSCLC and study NS01. In addition preliminary analysis of study JEMN further supports the above findings.

Pemetrexed was studied in comparison to 75 mg/m2 docetaxel in the JMEI Phase 3 study of previously treated patients with advanced NSCLC. A retrospective analysis of this study assessed whether the efficacy of pemetrexed was higher in patients with non-squamous histology compared to docetaxel. A Cox model of OS was used to test for a significant treatment-by-histology interaction, and subsequent Cox models were used to estimate hazard ratios for OS and PFS in both squamous and non-squamous groups. All models included baseline cofactors for performance status (ECOG PS), time since prior chemotherapy (TSPC), disease stage, and gender. Medians for OS and PFS were derived by the Kaplan-Meier method.

In Study JMEI, the treatment-by-histology interaction test for OS was statistically significant (p=0.001), indicating that patients with non-squamous histology treated with pemetrexed had higher survival compared to all others on study. **Table 26** summarizes histologic diagnoses of study patients and **Table 27** analyzes overall survival by squamous versus non-squamous histology for the ITT population.

Analyzing by non-squamous histology would, if anything, tend to limit differences between groups as it is likely that some patients with predominantly squamous histology would be included in the non-squamous group.

Table 26: Histologic Diagnosis of JMEI study patients

Diagnosis/Histology (%)	Pemetrexed	Docetaxel
Adenocarcinoma	154 (54.4)	142 (49.3)
Squamous	78 (27.6)	94 (32.3)
Bronchoalveolar	4 (1.4)	1 (0.3)
Large cell anaplastic	18 (6.4)	29 (10.1)
Adenoid cyst cancer	0	1 (0.3)
Epidermoid squamous	0	1 (0.3)
Bronchoalveolar adenocarcinoma	1 (0.4)	0
Bronchoalveolar carcinoma	1 (0.4)	1 (0.3)
Other		
Lung, adeno-squamous	4 (1.4)	5 (1.7)
Lung, bronchoalveolar	2 (0.7)	0
Other unspecified	1 (0.4)	0
Poor differentiated	2 (0.7)	1 (0.3)
Sar. pleural mesothelioma	0	1 (0.3)
Lung, NSCLC	2 (0.7)	2 (0.7)
NSCLC	9 (3.2)	6 (2.1)
Undifferentiated carcinoma	1 (0.4)	1 (0.3)
Poor differentiated NSCLC	10 (3.5)	5 (1.7)

Table 27. Survival of Squamous and Non-squamous Subgroups in Study JMEI

	Non-squamous Group		**Squamous Group**	
	Pemetrexed (N=205)	**Docetaxel (N=194)**	**Pemetrexed (N=78)**	**Docetaxel (N=94)**
Median survival, months	9.3	8.0	6.2	7.4
Survival HR (95% CI)	0.778 (0.607-0.997)		1.563 (1.079-2.264)	
Median PFS, months	3.1	3.0	2.3	2.7
PFS HR (95% CI)	0.823 (0.664-1.020)		1.403 (1.006-1.957)	

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; N = number of patients; PFS = progression-free survival.

Recently, an additional study (H3E-JE-NS01 [NS01]) of patients previously treated with 1 to 2 prior chemotherapy regimens for advanced NSCLC was completed (Ichinose et al. 2007). Study NS01 randomized 216 evaluable patients to either 500 mg/m2 or to 900 mg/m2 pemetrexed (each administered once per 3-week cycle). Retrospective subgroup analysis for this study further assessed whether the efficacy of pemetrexed is higher in patients with non-squamous histology, with results presented below for the ITT population. (**Table 28**).

Table28: Survival of Squamous and Non-squamous Subgroups in Study NS01

	Nonsquamous Group		Squamous Group	
	Pem 500 (N=85)	Pem 900 (N=83)	Pem 500 (N=23)	Pem 900 (N=25)
Median survival, months	19.4	14.0	7.9	8.6
Squamous/Non-squamous survival HR (95% CI)	2.01 (1.34–3.02)			
Median PFS, months	3.1	3.1	1.4	1.7
Squamous/Non-squamous PFS HR (95% CI)	2.13 (1.50-3.03)			

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; N = number of patients; Pem = pemetrexed; PFS = progression-free survival.

Preliminary results from a fourth study, JMEN, (maintenance pemetrexed plus best supportive care (BSC) versus BSC immediately following induction chemotherapy for NSCLC again indicate that non-squamous histology is a predictive factor for better efficacy with Alimta (**Table 29)**. Prespecified tests for treatment-by-histology interactions resulted in statistically significant interactions for PFS (interaction HR = 0.65, p=0.036) and for preliminary OS (interaction HR = 0.52, p=0.011).

Table 29: PFS by histology. Study JMEN

	Final PFS	
	Pemetrexed (N = 441) median mos	**Placebo (N = 222) median mos**
Histologic Subgroup	**HR (95% CI) p-Value**	
Non-squamous (n = 482)	4.50	2.60
	0.44 (0.36-0.55)	
	< 0.00001	
Adenocarcinoma (n = 329)	4.73	2.60
	0.45 (0.35-0.59)	
	< 0.00001	
Large Cell (n = 20)	3.48	2.09
	0.40 (0.13-1.22)	
	0.109	
Other/Indeterminate (n = 133)	4.21	2.79
	0.43 (0.28-0.670)	
	0.0002	
Squamous (n = 181)	2.79	2.60
	0.69 (0.49-0.98)	
	0.039	

Preliminary analysis of OS in the submission of June 24, 2008 included a total of 300 events, so that most patients were censored (56.7% of patients in the pemetrexed arm and 50.9% in the placebo arm). According to the statistical gatekeeping and alpha-spending scheme presented in the protocol, the significance level for this preliminary analysis was a one-sided alpha of 0.00001, leaving a nominal level of 0.02499 to be spent for the final analysis of OS, which will take place when 475 events have occurred.

For patients with non-squamous histology, results for preliminary median OS suggest a strong trend favoring the pemetrexed arm with a 5-month advantage for pemetrexed compared to placebo (14.4 months versus 9.4 months; HR = 0.66; p = 0.005). Although not statistically significant, the preliminary OS results in patients with squamous histology suggest a disadvantage for pemetrexed (9.6 months) compared to placebo (11.9 months; HR = 1.28; p = 0.231).

Objective response rate by histology is shown in **Table 30**.

Table 30: Objective response by histology. Study JMEN

	Tumor Response (CR+PR)	
	Pemetrexed (N = 441) %	**Placebo (N = 222) %**
Histologic Subgroup	**p-Value**	
Non-squamous (n = 482)	7.4	1.9
	0.018	
Adenocarcinoma (n = 329)	8.1	2.8
	0.090	
Large Cell (n = 20)	9.1	0.0
	> 0.999	
Other/Indeterminate (n = 133)	5.4	0.0
	0.323	
Squamous (n = 181)	5.2	1.5
	0.425	

Taken together these 4 randomized studies (JMDB, JMEI, NS01 and JMEN) show a consistent pattern of better efficacy for pemetrexed in non-squamous histology than for squamous histology.

7.0 INTEGRATED REVIEW OF SAFETY

7.1 Methods And Findings

Safety assessments consist of evaluating adverse events and serious adverse events, laboratory parameters including hematology, chemistry, vital signs, physical examinations, and documentation of all concomitant medications and/or therapies.

Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, were collected and recorded on the Adverse Event Case Report Form and followed as appropriate.

Extent of Exposure

All patients who received at least 1 dose of pemetrexed, gemcitabine, or cisplatin were evaluated for safety. A total of 1725 patients were randomized in this study: 862 patients were randomized to the AC arm, and 863 patients were randomized to the GC arm. Of these 1725 patients, 839 received at least 1 dose of pemetrexed or cisplatin, and 830 received at least 1 dose of gemcitabine or cisplatin. Thus, the safety population (that is, the randomized and treated population) includes 1669 patients: 839 patients in the AC arm, and 830 patients

in the GC arm. Patients in the safety population are analyzed according to the therapy they received in the first treatment cycle. **Table 31** provides a summary of the number of reasons why patients (22 in the AC arm and 34 in the GC arm) were randomized but did not receive study treatment.

Table 31: Patients Randomized but Not Treated

Reason for Study Discontinuation Prior to Treatment	AC N=22 n	GC N=34 n
Protocol entry criteria not met	5	14
Patient withdrew consent	7	7
Death from study disease	1	4
Adverse event	4	2
Death	2	3
Personal conflict or other patient decision	1	1
Lack of efficacy, progressive disease	1	3
Lost to follow up	1	0

Extent of Exposure

Table 32 provides a summary of the number of cycles given for all patients who received any dose of study drug. A total of 3648 cycles of AC were administered to 839 patients on the AC arm, and 3626 cycles of GC were administered to 830 patients on the GC arm. A median of 5 cycles of therapy was administered to patients in both arms. Approximately 45% of patients in both treatment arms completed at least 6 cycles of study treatment.

Table 32: Cycles of Treatment

	AC		GC	
	A	C	G	C
No. Patients	839	839	830	829
Mean	4.3	4.3	4.4	4.3
Median	5.0	5.0	5.0	5.0
Patients completed at least:				
1 cycle	85 (10.1)	86 (10.3)	87 (10.5)	87 (10.5)
2 cycles	122 (14.5)	121 (14.4)	110 (13.3)	110 (13.3)
3 cycles	42 (5.0)	42 (5.0)	52 (6.3)	54 (6.5)
4 cycles	149 (17.8)	149 (17.8)	147 (17.7)	145 (17.5)
5 cycles	61 (7.3)	63 (7.5)	45 (5.4)	46 (5.5)
6 cycles	379 (45.2)	377 (44.9)	385 (46.4)	383 (46.2)
7 cycles	1 (0.1)	1 (0.1)	3 (0.4)	3 (0.4)
8 cycles	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)

Patients treated with AC received 94.8% and 95.0% of the planned dose intensity for pemetrexed and cisplatin while GC treated patients received 85.8% and 93.5% of the planned dose intensity for gemcitabine and cisplatin.

A total of 815 dose delays were reported on the AC arm, and 929 dose delays were reported on the GC arm. Scheduling conflict was the most commonly reported reason for dose delays in both treatment arms (486 in the AC arm and 514 in the GC arm). In both treatment arms, the most common clinical reasons for dose delays were neutropenia (138 in the AC arm and 188 in the GC arm) and anemia (25 in the AC arm and 43 in the GC arm).

There were more dose reductions on the GC arm than on the AC arm. In the AC arm, 54 dose reductions were reported for pemetrexed, and 64 dose reductions were reported for cisplatin. For both study therapies of the AC arm, the most common reasons for dose reductions were neutropenia (17 for pemetrexed and 17 for cisplatin), fatigue (6 for pemetrexed and 8 for cisplatin), nausea (5 for pemetrexed and 8 for cisplatin), and febrile neutropenia (5 for pemetrexed and 5 for cisplatin). On the GC arm, 362 dose reductions were reported for gemcitabine, and 154 dose reductions were reported for cisplatin. For both study therapies of the GC arm, the most common reasons for dose reductions were neutropenia (184 for gemcitabine and 59 for cisplatin), thrombocytopenia (82 for gemcitabine and 37 for cisplatin), and febrile neutropenia (15 for gemcitabine and 12 for cisplatin).

Dose omissions of Day 8 gemcitabine were provided for in the study protocol based on hematologic toxicities, and as expected, the majority of dose omissions reported during the study occurred in patients receiving gemcitabine, and were attributed to neutropenia (69), thrombocytopenia (26), and fatigue (20). Of the 341 gemcitabine dose omissions, only 2 omissions occurred for Day 1; the remainder were for Day 8. There were few dose omissions for pemetrexed or cisplatin on the AC arm or the GC arm.

Table 33 provides a brief overview of the number of serious adverse events (SAEs), adverse events that resulted in discontinuations, deaths that occurred during the study, and treatment emergent adverse events (TEAEs). There were no relevant differences in SAEs, SURs, deaths, or TEAEs, regardless of causality, between treatment arms.

Table 33: Overview of AEs

	Regardless of Drug Causality	
	AC	**GC**
Adverse Events	**(N=839)**	**(N=830)**
Patients with ≥1 SAE	294 (35.0%)	315 (38.0%)
Discontinuations due to SAE	30 (3.6%)	46 (5.5%)
Deaths (on-study)	63 (7.5%)	53 (6.4%)
Deaths (within 30 days of last dose)	13 (1.5%)	14 (1.7%)
Patients with ≥1 TEAE	812 (96.8%)	807 (97.2%)

Adverse Reactions

Adverse reactions (incidence ≥10%) during therapy with pemetrexed when used in combination with cisplatin included thrombocytopenia, decreased creatinine clearance, constipation, alopecia, creatinine elevation, and sensory neuropathy. **Table 34** provides the frequency and severity of adverse reactions that have been reported in >5% of 839 patients with NSCLC who were randomized to study and received pemetrexed plus cisplatin and 830 patients with NSCLC who were randomized to study and received gemcitabine plus cisplatin.

Table 34: Adverse Reactions

Reaction[b]	Pemetrexed/cisplatin (N=839)		Gemcitabine/cisplatin (N=830)	
	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
All Adverse Reactions	90	37	91	53
Laboratory				
Hematologic				
Anemia	33	6	46	10
Neutropenia	29	15	38	27
Leukopenia	18	5	21	8
Thrombocytopenia	10	4	27	13
Renal				
Creatinine elevation	10	1	7	1
Clinical				
Constitutional Symptoms				
Fatigue	43	7	45	5
Gastrointestinal				
Nausea	56	7	53	4
Vomiting	40	6	36	6
Anorexia	27	2	24	1
Constipation	21	1	20	0
Stomatitis/Pharyngitis	14	1	12	0
Diarrhea	12	1	13	2
Dyspepsia/Heartburn	5	0	6	0
Neurology				
Neuropathy-sensory	9	0	12	1
Taste disturbance	8	0[c]	9	0[c]
Dermatology/Skin				
Alopecia	12	0[c]	21	1[c]
Rash/Desquamation	7	0	8	1

In addition to the lower incidence of hematologic toxicity on the pemetrexed and cisplatin arm, use of RBC and platelet transfusions (**Table 35**) and hematopoietic growth factors was significantly lower in the ALIMTA and cisplatin arm compared to the gemcitabine and cisplatin arm.

Table 35: Transfusions

	P/C N=839		G/C N=830		
Transfusion	n	%	n	%	p-value
Patients With ≥ 1 Transfusion	138	(16.4)	240	(28.9)	<.001
Patients With Packed RBC Transfusions	135	(16.1)	227	(27.3)	<.001
Patients With Platelets Transfusions	15	(1.8)	37	(4.5)	0.002

The following additional adverse reactions were observed in patients with non-small cell lung cancer randomly assigned to receive pemetrexed plus cisplatin.

Incidence 1% to 5%

Body as a Whole — febrile neutropenia, infection, pyrexia
General Disorders — dehydration
Metabolism and Nutrition — increased AST, increased ALT
Renal — creatinine clearance decrease, renal failure
Special Senses — conjunctivitis

Incidence Less than 1%

Cardiovascular — arrhythmia
General Disorders — chest pain
Metabolism and Nutrition — increased GGT
Neurology — motor neuropathy

Subpopulations

No clinically relevant differences in adverse reactions were seen in patients based on gender, ethnicity, or histology.

7.1.1 Deaths

A total of 116 on-therapy deaths were reported; 63 deaths in the AC arm and 53 deaths in the GC arm. In the AC arm, 23 on-therapy deaths were due to study disease as compared to 17 on the GC arm. In the AC and GC arms, respectively 9 and 6 on-therapy deaths were considered by the investigator to be possibly due to study-drug toxicity There were 61 cases of deaths due to other causes, 31 on the AC arm and 30 on the GC arm. Overall, the most commonly reported reasons for deaths due to other causes were pulmonary events (including pulmonary embolism, respiratory distress, respiratory failure, pneumonia, hemoptysis and pulmonary edema) and cardiac events (including myocardial infarction, cardiac arrest, cardiac failure, and cardiogenic shock). For any category, the difference in the number of deaths was not statistically significant between study arms.

7.1.2 Other Serious Adverse Events

Table 36 summarizes the possibly study-drug related SAEs that were experienced by ≥2% of patients or were statistically significantly different between study arms or were otherwise clinically relevant. Overall, there were no significant differences in the number of patients experiencing possibly study-drug related SAEs between the 2 treatment arms.

The possibly study-drug related SAEs reported as acute renal failure, acute prerenal failure, and renal failure have been considered together as renal failure SAEs. They are known events associated with the AC combination and are therefore presented in **Table 36** as clinically relevant. Twelve patients on the AC arm and 6 patients on the GC arm had a possibly study-drug related renal-failure SAE. In 11 of the 12 renal failure cases on the AC arm, patients had evidence of gastrointestinal toxicity (toxicities included nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding) and/or dehydration prior to developing renal failure.

Table 36: SAE's

System Organ Class Preferred Terma	Number (%) of Patients AC (N=839)	 GC (N=830)	 p-Valueb
Patients with at least 1 event	**139 (16.6)**	**136 (16.4)**	**0.947**
Vomiting	34 (4.1)	23 (2.8)	0.178
Anemia	22 (2.6)	28 (3.4)	0.392
Nausea	30 (3.6)	19 (2.3)	0.147
Thrombocytopenia	16 (1.9)	28 (3.4)	0.067
Febrile neutropenia	9 (1.1)	25 (3.0)	0.005
Anorexia	11 (1.3)	1 (0.1)	0.006
Pyrexia	1 (0.1)	10 (1.2)	0.006
Renal failure acute	6 (0.7)	0	0.031
Renal failure	5 (0.6)	6 (0.7)	0.773
Acute prerenal failure	1 (0.1)	0	1.000

7.1.3 Dropouts and Other Significant Adverse Events

A total of 134 patients discontinued study treatment due to nonserious, clinically significant adverse events; 65 patients (7.7%) on the AC arm and 69 patients (8.3%) on the GC arm. Of these patients who discontinued, 57 patients (6.8%) on the AC arm and 60 patients (7.2%) on the GC arm discontinued due to adverse events that were considered to be possibly related to study drug. On the AC arm, the most common reasons for discontinuation that were possibly related to study drug were blood creatinine increased, creatinine renal clearance decreased, nausea, and fatigue. On the GC arm, the most common reasons for discontinuation possibly related to study drug were creatinine renal clearance decreased, anemia, neutropenia, nausea, and fatigue.

Among the discontinuations possibly related to study drug, increased blood creatinine caused significantly more discontinuations on the AC arm than in the GC arm (p=0.004). Hematologic toxicity (anemia, thrombocytopenia, and neutropenia) caused more discontinuations in the GC arm than in the AC arm; the only significant difference was for neutropenia (p=0.015). Gastrointestinal toxicities such as nausea and vomiting accounted for multiple discontinuations, with similar frequencies in both study arms. Hearing-related toxicities (hypoacusis, deafness, and tinnitus) led to more discontinuations on the GC arm; however, no significant differences were seen between arms for individual hearing-related toxicities. Of note, hearing impairment was more common on AC arm (0.1%) than on the GC arm (0%).

Hospitalizations

Table 37 provides a summary of patients hospitalized for all reasons and for study-drug-related reasons, by treatment group. There were no statistically significant differences between study arms in the number of patients admitted, the mean number of days admitted, or the mean number of admissions per patient.

Table 37: Hospitalizations

Patients with ≥1 hospitalization [n(%)]	271 (32.3%)	289 (34.8%)	0.277
Due to Drug Related Adverse Events	116 (13.8%)	120 (14.5%)	0.726
Due to Non-Drug Related Adverse Events	186 (22.2%)	192 (23.1%)	0.640
Hospitalization(days)[Mean(SD)]			
Average Days per Patient Due to Drug Related Adverse Events	11.3(10.4)	11.1(10.0)	0.893
Average Days per Patient Due to Non-Drug Related Adverse Events	8.9(8.9)	8.3(7.8)	0.521
Average Days per Patient	10.8(10.1)	11.6(10.2)	0.449
Hospitalization(admissions) [Mean(SD)]			
Average Admissions per Patient Due to Drug Related Adverse Events	1.4(0.8)	1.3(0.5)	0.077
Average Admissions per Patient Due to Non-Drug Related Adverse Events	1.3(0.5)	1.1(0.4)	0.063
Average Admissions per Patient	1.2(0.7)	1.2(0.5)	0.774

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

See Table 34.

7.1.6 Laboratory Findings

Overall, patients on the GC arm experienced statistically significantly more Grade 3 and

4 laboratory toxicities than patients on the AC arm (39.9% versus 22.6%, p<0.001). In both treatment arms, the most frequently reported Grade 3/4 toxicity was neutropenia, which was reported in statistically significantly more patients in the GC arm than in the AC arm (26.7% versus 15.1%, p<0.001). Other Grade 3/4 toxicities experienced by significantly more patients on the GC arm than in the AC arm were also hematologic and included anemia (9.9% versus 5.6%, p<0.001), leukopenia (7.6% versus 4.8%, p<0.001), and thrombocytopenia (12.7% versus 4.1%, p<0.001). On both treatment arms, the incidence of nonhematologic laboratory toxicity was low. Grade 3 and 4 renal and hepatic laboratory toxicities occurred in fewer than 1% of patients and with similar frequency across study arms. No Grade 3 and 4 laboratory toxicities occurred significantly more often on the AC arm. Although the incidence of Grade 3 and 4 elevated creatinine was not statistically significantly different between study arms, it has previously been identified as a clinically relevant toxicity for the AC combination and is referenced on the current product label. When CTC Grades 1 through 4 are considered, the incidence of elevated creatinine is statistically significantly higher on the AC arm than on the GC arm (10.1% versus 6.9%, p=0.018).

7.1.7 Vital Signs

All patients were regularly assessed for vital signs and physical findings, including diastolic and systolic blood pressure, heart rate, and temperature. Any clinically significant changes in these measures were reported as AEs and have been previously discussed

7.1.8 Electrocardiograms (ECGs)

No data was reported. No clinical events such as torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, and flutter, syncope, and seizures were observed.

7.1.9 Immunogenicity

There is no relevant information.

7.1.10 Human Carcinogenicity

Carcinogenicity studies have not been performed. Pemetrexed was clastogenic in the in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple in vitro tests (Ames, CHO cell assay).

7.1.11 Special Safety Studies

There is no relevant information.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Pemetrexed has no known potential for abuse..

7.1.13 Human Reproduction and Pregnancy Data

Pregnancy Category D

7.1.15 Assessment of Effect on Growth

No data were reported.

7.1.16 Overdose Experience

No data were reported

7.1.17 Postmarketing Experience

Pemetrexed is approved in the U.S. for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy. Pemetrexed in combination with cisplatin is also approved for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery. Postmarketing AE experience continues to be collected.

7.2 Adequacy of Patient Exposure And Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See section 7.1

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

None

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to the drug, including adequate numbers of various demographic subsets and people with pertinent risk factors

- Doses and durations of exposure were adequate to assess safety for the intended use.
- Design of studies was adequate to answer critical questions.
- Potential class effects were adequately evaluated.
- There were no study exclusions that limit the relevance of safety assessments..

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal and/or In-Vitro Testing was adequate.

7.2.5 Adequacy of Routine Clinical Testing

Adequate

7.2.6 Adequacy of Metabolic. Clearance. and Interaction Workup

Adequate

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Evaluation for potential adverse events was adequate.

7.2.8 Assessment of Quality and Completeness of Data

Data quality and completeness were adequate.

7.2.9 Additional Submissions. Including Safety Update

All relevant information were submitted.

7.3 Summary Of Selected Drug-Related Adverse Events. Important Limitations Of Data. And Conclusions

Clinically relevant safety advantages that occurred in the AC group included:
● **Grade 3/4 Laboratory Toxicity:** Significantly lower incidence of any Grade 3/4 laboratory toxicity considered possibly related to study therapy. Significantly lower incidence of possibly study-therapy related Grade 3/4 neutropenia, anemia, thrombocytopenia, and leukopenia. These lower hematologic toxicities occurred despite significantly less hematologic supportive care, such as growth factors and transfusions, on the AC arm.
● **Grade 3/4 Non-laboratory Toxicity:** Significantly lower incidence of possibly study-drug related Grade 3/4 febrile neutropenia, sensory neuropathy, syncope, and any grade of alopecia.
● **Serious Adverse Events (SAEs):** A significantly lower percentage of patients on the AC arm experienced the possibly study-drug related SAEs of febrile neutropenia and pyrexia.
● Significantly fewer patients on the AC arm received any kind of transfusions, red blood cell transfusions, platelet transfusions, erythropoietin/darbepoetin, G-CSF/GM-CSF, or iron preparations.

By contrast, AEs, SAEs, and other indications of toxicity occurring statistically significantly more frequently on the AC arm included:
● **Grade 3/4 Non-laboratory Toxicity:** Significantly higher incidence of possibly study-drug related Grade 3/4 nausea and anorexia.

● **Serious Adverse Events (SAEs):** Significantly higher incidence of the SAE of possibly study-drug related acute renal failure and anorexia.

Safety results that were similar between study arms included:
Patients on both arms received a similar number of cycles of treatment (median 5 cycles); however, patients on the AC arm required fewer dose adjustments (mainly reductions and delays). The dose intensity achieved in the study was close to the planned dose intensity in both study arms, but was slightly higher in the AC arm. The number of patients experiencing any possibly study-drug related treatment-emergent adverse event (TEAE) or SAE was similar between treatment arms. Despite statistically significantly higher Grade 3/4 anorexia and nausea on the AC arm, there was no statistically significant differences between study arms in Grade 3/4 weight loss or dehydration. The rates of hospitalization were not different between study arms in terms of number of patients admitted, mean number of days admitted, or mean number of admissions per patient. Overall, the number of deaths possibly due to study-drug toxicity according to investigator assessment (AC, 9; GC, 6) and further cases identified by Lilly as notable (AC, 1; GC, 4) were balanced between treatment arms. The causes of deaths possibly due to study-drug toxicity in the AC arm of Study JMDB are consistent with the known safety profile of the pemetrexed plus cisplatin combination. In addition, results from safety analyses with respect to subroups (age, sex, origin, and NSCLC histological classification) were consistent with the toxicity profile of AC compared to GC in the overall study population.

In conclusion, AC showed a more favorable safety profile as compared to GC. The more tolerable safety profile for AC was demonstrated by the fewer clinically relevant, study-drug related toxicities, particularly Grade 3/4 febrile neutropenia and Grade 3/4 hematologic toxicities, which is further supported by the reduced need for transfusions and supportive care therapies.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Safety data were not pooled.

7.4.2 Explorations for Predictive Factors

Dose reductions may be required for patients with severe hepatic impairment (bilirubin ≥2 mg/dL; albumin <3.5 g/dL; INR ≥1.7) or moderate to severe renal impairment (calculated creatinine clearance <50 mL/min)

7.4.3 Causality Determination

AE's occurring with pemetrexed/cisplatin treatment likely represent the effect of the drugs in the population of patients with NSCLC.

8.0 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

See section 1.3.4

8.2 Drug-Drug Interactions

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Ibuprofen - Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with pemetrexed in patients with normal renal function (creatinine clearance ≥80 mL/min). Caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min).

Other NSAIDs - Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following ALIMTA administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

Nephrotoxic Drugs - pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of pemetrexed. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of pemetrexed.

8.3 Special Populations

The incidence of possibly study-drug-related Grade 3/4 laboratory toxicities between study arms is consistent for patients under 65 and 65 or older, except that Grade 3/4 anemia, which was statistically significantly different between study arms in the overall population, was significantly different only for the older subgroup. Younger patients experienced statistically significantly more Grade 3/4 fatigue on the AC arm; the difference was not significant in older patients or in the population as a whole. Grade 3/4 anorexia and Grade 3/4 nausea, which occurred in significantly more patients on the AC arm overall, were not statistically significantly different between study arms in the older patients. Grade 3/4 febrile neutropenia and syncope occurred in significantly more patients on the GC arm overall; the between-arm difference for febrile neutropenia was statistically significant only

in the younger group and for syncope, in the older group. Also, statistically significantly more of the older patients in the GC arm had any possibly related Grade 3/4 nonlaboratory toxicity than older patients in the AC arm; the difference was not significant in younger patients or in the population as a whole.

Pemetrexed is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Renal function monitoring is recommended with administration of pemetrexed. No dose reductions other than those recommended for all patients are necessary for patients 65 years of age or older.

Grade 3/4 toxicities possibly related to study drug where the statistical significance between study arms was different between male and female patients were: hemoglobin and febrile neutropenia (men had significantly more in the GC arm; the difference between arms for women was not significant), leukocytes (women had significantly more in the GC arm; the difference between arms for men was not significant), fatigue and nausea (women had significantly more in the AC arm; the difference between arms for men was not significant).

Patients of Caucasian origin constituted a large majority of patients in this study (78.4%) while the remaining subgroups (East/Southeast Asian and Other) were much smaller in size; therefore, any observations of differences between origin subgroups must be interpreted with caution. No statistically significant differences between arms were observed in Grade 3/4 leukopenia, anorexia, sensory neuropathy, or syncope in any origin subgroup.

8.4 Pediatrics

The safety and effectiveness of pemetrexed in pediatric patients have not been established.

8.5 DSI inspection

Partly because of a shortage in inspection resources and in keeping with a risk based approach to assigning inspections, DSI prefers not to assign inspections for this supplement as the product has been on the market for several years, the product has been recommended for and administered in combination with cisplatin, the supplement is for the same histologic type of cancer for which it is now approved, and if the supplement fails, the product would still be on the market.

8.6 Advisory Committee Meeting

No ODAC meeting is planned. Three consultants Drs. David Johnson, David Harrington and Tom Fleming evaluated aspects of this study answering the following questions:

1. Do you believe that every 3 week schedule of gemcitabine plus cisplatin, rather than the every 4 week approved schedule is an acceptable comparator regimen?

2. Do you believe that the combination of Alimta plus cisplatin has demonstrated to be non-inferior to the combination of gemcitabine and cisplatin?

3. Given the results of study JMDB and the results from JMEI and JMEN studies, do you believe that Alimta has demonstrated efficacy in adenocarcinoma and large cell lung cancer?

Drs. Johnson and Harrington agreed that Alimta was demonstrated to be efficacious for non-squamous NSCLC patients. Dr. Fleming stated that "Based on the JMDB, JMEI and JMEN trials, it appears that the large cell patients provide the only setting where substantial evidence for efficacy could emerge when complete data are available from all three trials…"

8.7 Literature Review

A literature review of relevant manuscripts was performed.

8.8 Postmarketing Risk Management Plan

Continue AE surveillance.

8.9 Other Relevant Materials

No new information is available.

9.0 0VERALL ASSESSMENT

9.1 Conclusions

Study JMDB, a multicenter, randomized Phase 3 study, was conducted at 177 sites in 26 countries. The primary objective of this non-inferiority study was to compare the efficacy of pemetrexed and cisplatin (AC) with gemcitabine plus cisplatin (GC) in terms of the overall survival of patients with previously untreated Stage IIIB (not amenable to curative treatment) and Stage IV NSCLC.

A total of 862 patients on the AC arm and 863 patients on the GC arm were included in the OS analysis. Overall survival time was 10.28 months for both treatment arms. Using the Cox regression adjusted model as the primary analysis, the non-inferiority test was statistically significant (one-sided $p<0.001$), with the primary cofactor-adjusted survival hazard ratio (HR) estimated to be 0.94 (95% CI: 0.84 to 1.05), with the entire confidence interval well below the 1.17645 non-inferiority margin. The confidence interval for the survival HR implies that the risk of death on the AC arm was 16% lower than that on the GC arm in the best-case scenario and 5% higher in the worst-case scenario.

A supporting analysis, which used the Rothmann methodology, showed that AC retained 120% of GC's survival benefit over single-agent cisplatin, with a 95% confidence interval of 83% to 190%. This means that at least 83% of the benefit of GC over C was retained by AC. Therefore, the non-inferiority criteria were met using the Rothmann

method for testing whether AC retained at least 50% of GC's survival benefit over single-agent cisplatin (one-sided, p=0.005).

For all randomized patients, the results of another time-to-event endpoint, PFS, was also similar between the treatment arms. For PFS, the median PFS was 4.83 months on the AC arm and 5.06 months on the GC arm, with a Cox adjusted HR of 1.04 (95% CI: 0.94 to 1.15; non-inferiority p=0.008). Results from an independent review of PFS on a subset of randomly selected patients (n=333) were consistent with the investigator-assessed PFS results of the entire study population.

Objective tumor response rates were higher for the AC arm compared to the GC arm (30.6% versus 28.2%), although this difference was not statistically significant for superiority (p=0.312). Duration of response was longer for the GC arm compared to the AC arm (5.09 months versus 4.50 months); this comparison was not statistically significant for noninferiority (p=0.362) or superiority (p=0.268).

There appeared to be compelling evidence that there was a differential effect on survival according to NSCLC histology for pemetrexed and gemcitabine treatment. There was a favorable survival effect for adenocarcinoma and large cell anaplastic carcinoma patients who received AC treatment and favorable survival results of squamous carcinoma patients who received GC treatment. Two additional studies, JMEI, and NS01, also show a consistent pattern of better efficacy for pemetrexed in non-squamous histology than for squamous histology. Preliminary results from a fourth study, JMEN, (maintenance pemetrexed plus best supportive care (BSC) versus BSC immediately following induction chemotherapy for NSCLC again indicate that non-squamous histology is a predictive factor for better efficacy with Alimta. Prespecified tests for treatment-by-histology interactions resulted in statistically significant interactions for PFS (interaction HR = 0.65, p=0.036) and for preliminary OS (interaction HR = 0.52, p=0.011).

Regarding safety, a median of 5 cycles of therapy was administered to patients in both the arms. Dose adjustments (delays, reductions, and omissions) were less frequent in patients treated with AC compared to patients treated with GC. Most pemetrexed dose reductions were attributed to neutropenia, while gemcitabine and cisplatin dose reductions were mainly attributed to neutropenia, thrombocytopenia, febrile neutropenia, and leukopenia. The dose intensity for pemetrexed and cisplatin was 94.8% and 95.0%, compared with 85.8% and 93.5% for gemcitabine and cisplatin, respectively. Overall, the number of deaths reported by investigators to be possibly due to study-drug toxicity was low on both arms; 9 deaths (1.1%) in the AC arm and 6 deaths (0.7%) in the GC arm. The number of patients experiencing any possibly study-drug related treatment emergent adverse event (TEAE) or serious adverse event (SAE) was similar between treatment arms. Among the possibly study-drug related SAEs, patients on the AC arm experienced statistically significantly lower incidences of febrile neutropenia than patients on the GC arm (9 cases [1.1%] versus 25 cases [3.0%], p=0.005), but statistically higher incidences of renal failure (6 cases [0.7%] versus 0 cases, p=0.031). There were no significant differences in the numbers of patients

who discontinued study treatment due to possibly study-drug related SAEs between treatment arms. Statistically significantly more patients in the GC arm than in the AC arm experienced possibly study-drug related Grade 3 and 4 laboratory toxicity (39.9% versus 22.6%, p<0.001). The individual toxicities experienced by significantly more patients on the GC arm than in the AC arm were hematologic and included anemia (9.9% versus 5.6%, p<0.001), leukopenia (7.6% versus 4.8%, p<0.001), neutropenia (26.7% versus 15.1%, p<0.001), and thrombocytopenia (12.7% versus 4.1%, p<0.001). Grade 3 and 4 renal and hepatic laboratory toxicities occurred in less than 1% of patients and with similar frequency across study arms. No Grade 3 and 4 laboratory toxicities occurred significantly more often on the AC arm. Overall, there was no significant difference in the total number of patients experiencing any possibly study-drug related nonlaboratory toxicity between treatment arms.

However, patients in the AC arm experienced significantly more possibly study-drug related Grade 3/4 anorexia (2.4% versus 0.7%, p=0.009) and Grade 3/4 nausea (7.2% versus 3.9%, p=0.004) than patients on the GC arm, although the incidences of Grade 3/4 vomiting (6.1% versus 6.1%, p=1.000), Grade 3/4 weight loss (0 versus 0.1%, p=0.497), and Grade 3/4 dehydration (1.2% versus 0.7%, p=0.452) were similar between arms. Possibly study-drug related Grade 3/4 febrile neutropenia occurred in significantly more patients on the GC arm than on the AC arm (3.7% versus 1.3%, p=0.002), as did Grade 3/4 sensory neuropathy (0.6% versus 0%, p=0.030), Grade 3/4 syncope (0.6% versus 0%, p=0.030), and any grade of alopecia (21.4% versus 11.9%, p<0.001). Other Grade 3 and 4 toxicities occurred with similar frequency on both study arms.

There was no significant difference in the number of hospitalizations observed between treatment arms. There were significantly fewer patients with red blood cell and platelet transfusions administered to patients on the AC arm as compared to the GC arm.

9.2 ODAC

See section 8.6.

9.3 Recommendation on Regulatory Action

The reviewing medical officer recommends that Alimta® in combination with cisplatin be approved for the initial treatment of patients with locally advanced or metastatic non-squamous NSCLC (adenocarcinoma and large cell anaplastic carcinoma).

9.4 Recommendation On Postmarketing Actions

None at this time.

9.4.1 Risk Management Activity

None at this time.

9.4.2 Required Phase 4 Commitments

None at this time.

9.4.3 Other Phase 4 Requests

To be determined.

9.5 Labeling Review

Labeling review is underway

9.6 Comments To Applicant

None.

10.0 APPENDICES

10.1 Summary of Important Protocol Elements

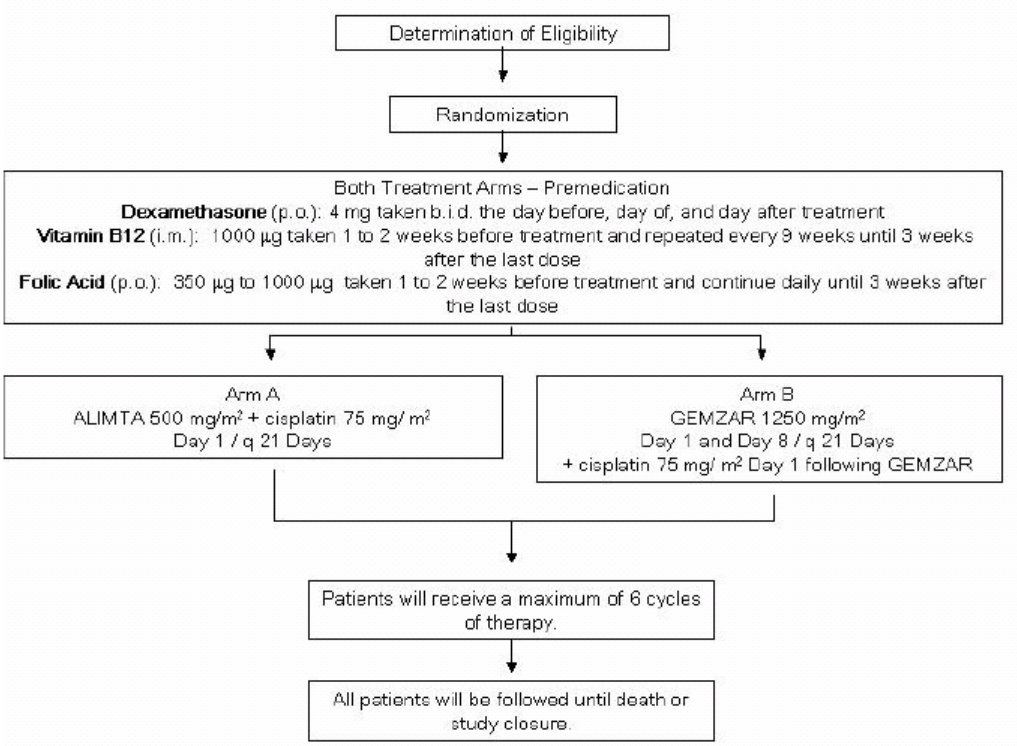
Eligibility Criteria

Inclusion criteria: Patients are eligible to be included in the study only if they meet *all* of the following criteria:
[1] histologic or cytologic diagnosis of NSCLC Stage IIIB (not amenable to curative treatment) or IV.
[2] no prior systemic chemotherapy for lung cancer.
[3] at least one unidimensionally measurable lesion meeting Response Evaluation Criteria in Solid Tumors (RECIST), at least 10 mm in longest diameter with spiral computed tomography (CT) scan, or at least 20 mm with conventional techniques. Positron emission tomography (PET) scans and ultrasounds should not be used for lesion measurements.
[4] ECOG performance status of 0 or 1
[5] at least 18 years of age.
[6] adequate organ function, including the following:
• Adequate bone marrow reserve: absolute neutrophil (segmented and bands) count (ANC) ≥1.5 × 109/L, platelets ≥100 × 109/L, and hemoglobin ≥9 g/dL.
• Hepatic: bilirubin ≤1.5 times the upper limit of normal (× ULN), alkaline phosphatase (AP), aspartate transaminase (AST), and alanine transaminase (ALT) ≤3.0 × ULN (AP, AST, and ALT ≤5 × ULN is acceptable if the liver has tumor involvement).
• Renal: calculated creatinine clearance (CrCl) ≥45 mL/minute based on the standard Cockcroft and Gault formula.
[7] prior radiation therapy allowed to <25% of the bone marrow. Prior radiation to the whole pelvis is not allowed. Prior radiotherapy must be completed at least 4 weeks before study

enrollment. Patients must have recovered from the acute toxic effects of the treatment prior to study enrollment.
[8] signed informed consent document on file.
[9] male and female patients with reproductive potential must use an approved contraceptive method, if appropriate (for example, intrauterine device [IUD], birth control pills, or barrier device) during and for 3 months after the study. Female patients with childbearing potential must have a negative serum pregnancy test within 7 days prior to enrollment.
[10] estimated life expectancy of ≥12 weeks.
[11] patient compliance and geographic proximity that allow adequate follow up.

Exclusion criteria: Patients will be excluded from the study if they meet any of the following criteria:
[12] received treatment within the last 30 days with any experimental drug.
[13] peripheral neuropathy of ≥CTC Grade 1.
[14] inability to comply with protocol or study procedures.
[15] a serious concomitant systemic disorder that, in the opinion of the investigator, would compromise the patient's ability to complete the study.
[16] a serious cardiac condition, such as myocardial infarction within 6 months, angina, or heart disease, as defined by the New York Heart Association Class III or IV.
[17] second primary malignancy that is clinically detectable at the time of consideration for study enrollment.
[18] documented brain metastases unless the patient has completed successful local therapy for central nervous system metastases and has been off of corticosteroids for at least 4 weeks before enrollment. Brain imaging is required in symptomatic patients to rule out brain metastases, but is not required in asymptomatic patients.
[19] presence of clinically detectable (by physical exam) third-space fluid collections, for example, ascites or pleural effusions that cannot be controlled by drainage or other procedures prior to study entry.
[20] significant weight loss (that is, ≥10%) over the previous 6 weeks before study entry.
[21] concurrent administration of any other antitumor therapy.
[22] inability to interrupt aspirin or other nonsteroidal anti-inflammatory agents for a 5-day period (8-day period for long-acting agents, such as piroxicam).
[23] inability or unwillingness to take folic acid or vitamin B12 supplementation.
[24] inability to take corticosteroids.
[25] pregnant or breast-feeding.

Study Design



Method of Assignment to Treatment

The central randomization system will assign patients to treatment arms according to a two-step process. First, there will be an overall stratification based on whether the investigative center is participating in the companion pharmacogenomic study (yes versus no). Second, within each of the two overall strata, randomization will occur independently, according to the method of Pocock and Simon. In each stratum, a given patient will be assigned with probability 0.75 to the treatment arm that minimizes imbalances among the following equally weighted prognostic factors:

- disease stage (IIIB versus IV)
- ECOG performance status (0 versus 1)
- history of brain metastases (yes versus no)
- sex (male versus female)
- basis for initial pathological diagnosis (histopathological versus cytological)
- investigative center

Treatments

Treatment Arm A (21-Day Cycle)		
Drug	**Dose**	**Time for Administration**
Pemetrexed	500 mg/m2 iv	Approximately 10 minutes on Day 1.
Cisplatin	75 mg/m2 iv	Administered per local practice on Day 1, approximately 30 minutes after ALIMTA infusion.

Treatment Arm B (21-Day Cycle)		
Gemzar	1250 mg/m2 iv	Approximately 30 to 60 minutes on Day 1 and Day 8.
Cisplatin	75 mg/m2 iv	Administered per local practice on Day 1, approximately 30 minutes after Gemzar infusion.
Pretreatment–Both Treatment Arms A and B		
Folic acid	350 µg to 1000 µg	Oral dose daily beginning approximately 1 to 2 weeks before the first dose of study therapy, and continuing daily until 3 weeks after the last dose of study therapy.
Vitamin B12	1000 µg intra-muscular injection	Approximately 1 to 2 weeks before the first dose of study therapy, and approximately every 9 weeks until 3 weeks after the last dose of study therapy.
Dexamethasone	4 mg, orally twice per day (or equivalent)	Should be taken on the day before, the day of, and the day after each dose of study therapy. Higher or additional doses are permitted for reasons other than routine rash prophylaxis (for example, antiemetic prophylaxis). Dexamethasone treatment is not required for Day 8 Gemzar

10.2 Line-By-Line Labeling Review

In progress.

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/s/

Martin Cohen
9/15/2008 12:39:51 PM
MEDICAL OFFICER

Robert Justice
9/15/2008 02:42:37 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

CHEMISTRY REVIEW(S)

OFFICE ON NEW DRUG QUALITY ASSESSMENT
DIVISION OF POST-MARKETING EVALUATION, BRANCH VIII
Review of Chemistry, Manufacturing, and Controls
for the Division of Oncology Products, HFD-150

NDA #:	21-462	**CHEM.REVIEW #:**	1	**REVIEW DATE:**	18-JUN-2008

SUBMISSION/TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED DATE**
NDA 21-462/SE1-015	27-AUG-2007	28-AUG-2007	14-SEP-2007

NAME & ADDRESS OF APPLICANT: Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

Colleen Mockbee, R. Ph., RAC
Assoc. Director, U.S. Regulatory Affairs
(317) 277-0199

DRUG PRODUCT NAME

Proprietary:	ALIMTA®
Nonproprietary/USAN:	Pemetrexed disodium
Code Names/#'s:	LY231514
Chemical Type/	1, New Chemical Entity
Therapeutic Class:	P, Priority Review Drug

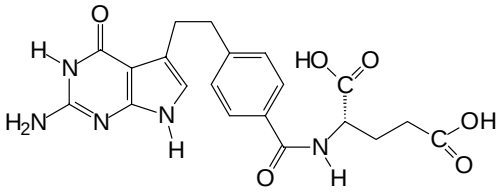
ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Mesothelioma: ALIMTA® in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery. Non-Small Cell Lung Cancer: ALIMTA® as a single-agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

DOSAGE FORM:	Injection
STRENGTHS:	500mg/vial, 100mg/vial
ROUTE OF ADMINISTRATION:	Intravenous injection
DISPENSED:	_X_ **Rx** ___ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate.



Molecular Formula: $C_{20}H_{19}N_5Na_2O_6 \cdot 7H_2O$
Molecular Weight: 597.49
CAS No.: [150399-23-8]

SUPPORTING DOCUMENTS: None

REMARKS/COMMENTS:

This Efficacy Supplement was submitted to provide for a new primary indication. Annotated draft labeling and a claim for categorical exclusion from the requirement for an Environmental Assessment were provided for CMC review.

CONCLUSIONS & RECOMMENDATIONS: **APPROVAL**

The information and data provided in the supplement are adequate to support the proposed changes. Approval is recommended.

(see attached electronic signature page)

Joel S. Hathaway, Ph.D.
Reviewing Chemist

cc: Orig. NDA 21-462
OND/DODP/Division File
ONDQA/DPE/Chem/JSHathaway
ONDQA/DPE/ChemPAL/LZhou
ONDQA/DPE/ChemBranchChf/HPatel
ONDQA/DPE/ProjMgr/RMcKnight

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Approval

CHEMISTRY REVIEW NOTES AND ASSESSMENTS

II. Review of Common Technical Document-Quality (CTD-Q) Module 1

A. Label

The proposed labeling does not contain any changes to the CMC sections of the label.

B. Environmental Assessment or Claim of Categorical Exclusion

Eli Lilly and Company has filed this supplement for a new indication to the NDA for pemetrexed disodium and claims a Categorical Exclusion from the requirement for an environmental assessment. While the new indication will increase the amount of pemetrexed disodium sold in the United States, peak sales are still expected to be less than the (b) (4) that was estimated in the claim for a Categorical Exclusion filed with original NDA 21-462. The daily discharge of water to sewage treatment facilities in the United States is about $1.3x10^{11}$ L (Environmental Protection Agency, 2000 Needs Survey, Report to Congress). The predicted concentration of pemetrexed disodium that may be discharged into the aquatic environment would thus be less than (b) (4) µg/L. This predicted concentration assumes that all human metabolites are active and that the compound is not removed in the sewage treatment plant via biodegradative or sorptive processes.

The Applicant has collected pilot data to assess the environmental fate and effects of pemetrexed disodium. Pemetrexed disodium is highly soluble in water and the log K_{ow} (octanol/water partition coefficient) is <1 at pH 7. When incubated with activated sewage sludge, pemetrexed disodium is extensively degraded in 24 hours (>99% with sludge solids levels of 1.5g/L) and adsorbs poorly to the solids. Therefore, it is unlikely that pemetrexed disodium would be discharged from a wastewater treatment facility because of its high biodegradability.

Based on this information, the Applicant's claim of a categorical exclusion from the requirement for an environmental assessment for pemetrexed disodium is acceptable.

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/s/

Steve Hathaway
6/18/2008 09:15:43 AM
CHEMIST
Efficacy supplt for new indication - EA only
For your concurrence

Hasmukh Patel
6/18/2008 10:11:29 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-462**
SERIAL NUMBER:	**015**
DATE RECEIVED BY CENTER:	**27 August 2007**
PRODUCT:	**Alimta®**
INTENDED CLINICAL POPULATION:	**Locally advanced or metastatic NSCLC**
SPONSOR:	**Eli Lilly and Company**
DOCUMENTS REVIEWED:	**Electronic M4**
REVIEW DIVISION:	**Division of Drug Oncology Products**
PHARM/TOX REVIEWER:	**Kimberly A. Benson, Ph.D.**
	Doo Y. Lee Ham, Ph.D.
PHARM/TOX SUPERVISOR:	**S. Leigh Verbois, Ph.D.**
DIVISION DIRECTOR:	**Robert Justice, M.D.**
PROJECT MANAGER:	**Kim Robertson**

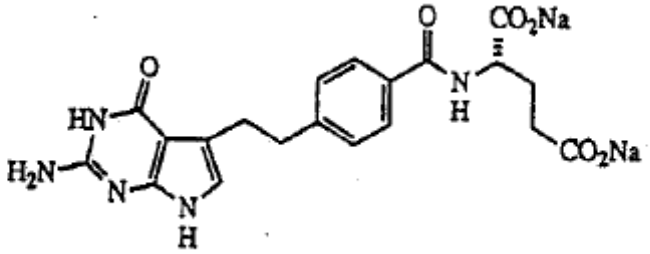
Date of review submission to Division File System (DFS):

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA:	**21-462**
Review number:	2
Sequence number/date/type of submission:	000/10/25/02/NDA
Information to sponsor:	Yes(), No(X)
Sponsor:	Eli Lilly and Company Indianapolis, IN 46285
Manufacturer for drug product:	Eli Lilly and Company Indianapolis, IN 46285
Reviewer name:	Kimberly Benson, Ph. D.
Division name:	Division Drug Oncology Products
Review completion date:	28 August 2008

Drug:

Trade name:	ALIMTA (Pemetrexed for Injection)
Generic name:	Pemetrexed disodium (MTA, LY231514)
Code name:	LY231514
CAS number:	137281-23-3
Chemical name:	N-[4-[2-(2-Amino-4,7-dihydro-4-oxo-1H-pyrrolo [2,3-d] pyrimidin-5-yl) ethyl] benzoyl]-L-glutamic acid disodium salt
Molecular formula:	C20H19N5O6· 2Na
Molecular weight:	579. 49
Structure:	

Relevant IND:	IND 40,061 (LY231514)
Drug Class:	Thymidylate synthase inhibitor
Indication:	Malignant pleural mesothelioma
Clinical Formulation:	Alimta (Pemetrexed Disodium for Injection) 500 mg/vial is supplied as a freeze-dried powder for reconstitution for intravenous infusion.
Route of Administration:	Intravenous Infusion

- **Proposed use:** ALIMTA (Premetrexed Disodium) is a folate antagonist that was previously approved for the treatment of malignant pleural mesothelioma in combination with cisplatin. The current supplemental NDA seeks approval for

ALIMTA in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic non-small cell lung cancer and as a single-agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy. The recommended dose of ALIMTA is 500 mg/m^2 i.v. on Day 1 of each 21-day cycle in combination with cisplatin 75 mg/m^2 i.v. beginning 30 minutes after ALIMTA administration. As a single-agent used in Non-Small Cell Lung Cancer the recommended dose of ALIMTA is 500 mg/m^2 i.v. on Day 1 of each 21-day cycle.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
Approvable. The non-clinical studies submitted with this supplemental NDA do not impact the approvability of Alimta for this indication

B. Recommendation for non-clinical studies
No recommendations for any additional non-clinical studies

C. Recommendations on labeling
The submitted studies do not impact the current labeling of Alimta

II. Summary of nonclinical findings

A. Nonclinical safety issues relevant to clinical use

No new non-clinical safety issues were identified in this supplemental NDA submission. The hERG assay did not show significant channel blockage by LY231514. Therefore there is no indication that Alimta administration may lead to QT prolongation. Chronic dosing of LY231514 in the mouse and the dog did not identify any additional toxicities of the drug than those that had been seen in previous studies.

APPEARS THIS WAY ON ORIGINAL

Studies reviewed within this submission:

PHARMACOLOGY

Safety Pharmacology

Effects of LY231514 disodium (Compound 289739) on cloned hERG channels expressed in mammalian cells.

TOXICOLOGY

Repeat-dose Toxicity

Mouse

A repeat-dose study in cd-1 mice given LY231514 disodium (compound 289739) weekly by intraperitoneal injection for 6 months.

Dog

A repeat dose toxicity study in the beagle dog given LY231514 disodium (compound 289739) by intravenous slow bolus injection every 3 weeks for 9 months (14 doses).

APPEARS THIS WAY ON ORIGINAL

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

The submission contained one pharmacology study that examined the effects of LY231514 on the hERG channel. No inhibition of the channel was seen at the three concentrations of LY231514 tested. This indicates that it is unlikely that Alimta administration will cause QT prolongation.

2.6.2.2 Primary pharmacodynamics

None included

2.6.2.3 Secondary pharmacodynamics

None included

2.6.2.4 Safety pharmacology

Neurological effects:
None included

Cardiovascular effects:
Effects of LY231514 disodium (Compound 289739) on cloned hERG channels expressed in mammalian cells.

A study was conducted to examine the *in vitro* ability of LY231514 to lead to cardiac action potential prolongation via inhibition of the cardiac potassium channel, hERG.

Three concentrations of LY231514 disodium were used in this study; 30, 100 and 300 μM as well as a vehicle control. The test article was applied to three cells expressing the hERG channel. The cells stably expressing hERG were held at -80 mV. Onset and steady-block of hERG current due to the test article treatment were measured.

hERG current blockage by the three concentrations of LY231514 was -0.5 ± 0.2 % at 30 μM, 0.7 ± 0.1 % at 100 μM, and -0.6 ± 0.2 % at 300 μM, with the vehicle control showing a block of 0.3 ± 0.7 % and the positive control (E-4031) showing a block of 89.0 ± 1.1 %. Given the lack of hERG blockage by LY231514, no IC_{50} was determined. This study indicates that LY231514 is unlikely to lead to QT prolongation.

The figure below shows the effects of the vehicle, the highest LY231514 concentration, and the positive control of E-4301 on the hERG current.

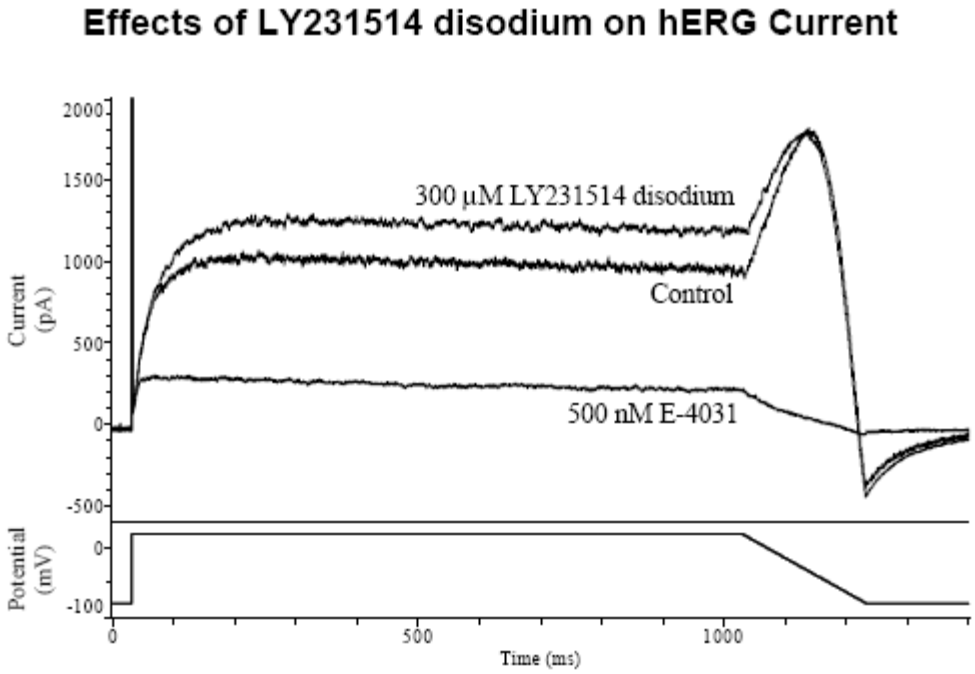


Figure 1: **Sample hERG current traces before and during 300 µM LY231514 disodium application.**

Superimposed records in control, after application of test article, and after application of the reference substance. Lower panel shows voltage stimulus: prepulse +20 mV, repolarizing test ramp (+20 mV to –80 mV at –0.5 V/sec), repeated at 5 s intervals from a holding potential of –80 mV.

[Excerpted from Sponsor]

Pulmonary effects:
None included

Renal effects:
None included

Gastrointestinal effects:
None included

Abuse liability:
None included

Other:
None

2.6.2.5 Pharmacodynamic drug interactions
None included

2.6.3 PHARMACOLOGY TABULATED SUMMARY

2.6.4.1 Brief summary
NA

2.6.4.2 Methods of Analysis
[see under individual study reviews]

2.6.4.3 Absorption
None included

2.6.4.4 Distribution
None included

2.6.4.5 Metabolism
None included

2.6.4.6 Excretion
None included

2.6.4.7 Pharmacokinetic drug interactions
None included

2.6.4.8 Other Pharmacokinetic Studies
None included

2.6.4.9 Discussion and Conclusions
NA

2.6.4.10 Tables and figures to include comparative TK summary
NA

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

No Pharmacokinetics information included in this supplemental NDA.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

The submission contained two chronic toxicity studies, in the mouse and the dog. The mice were dosed intraperitoneally weekly for 6 months and the dogs were dosed intravenously every 3 weeks for 9 months.

2.6.6.2 Single-dose toxicity
None included

2.6.6.3 Repeat-dose toxicity

Study title: A Repeat-Dose Study in CD-1 mice given LY231514 Disodium (Compound 289739) Weekly by Intraperitoneal injection for 6 Months (Reviewed by Doo Y. Lee Ham, Ph.D.)

Key findings:

- No treatment-related deaths were observed. Prior to the scheduled sacrifice, nine animals (6 males and 3 females) were found dead/euthanized across all treatment groups including controls and the cause of deaths could not be determined.
- Hematology changes were limited to an increase in circulating neutrophils in the HD group.
- Decreased testicular weights in males at all dose levels and slightly increased splenic extramedullary hematopiesis were noted in the HD group.
- Microscopically, testicular changes included minimal to severe degeneration of testicular seminiferous tubules with minimal hyperplasia of interstitial cells and epididymal changes.
- The NOEL for weekly IP injection of LY231514 to mice for 26 consecutive weeks was 700 mg/kg/dose (2100 mg/m2/dose).

Study no:	Study no: WL-353055
Volume/Pages:	Module 4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	15-Mar-2004
GLP Compliance:	Yes
QA report:	Yes
Drug, lot #, radiolabel, and % purity:	LY231514 disodium (Compound 289739) lot #RW03437, 99.9% purity
Formulation/vehicle:	Sterile water for injection, USP
Dosing:	Once weekly for 6 months (26 Weeks)
Species/strains:	Crl:CD-1®(ICR) BR mice
#/group or time point (main study):	15/sex/toxicology group (Groups 1-4)
Satellite groups used for TK study:	35/sex/TK group (Groups 1A-4A)
Age:	Approximately 7 weeks old
Weight:	M: 26.0 to 33.9 g; F: 21.3 to 26.9 g

Doses were administered as the following table:

Group #	Dose of LY231514 mg/kg (mg/m2)	Dose Volume (mL/kg)	# of Animals Male	Female
1	0[a] (0)	20	15	15
2	70 (210)	20	15	15
3	300 (900)	20	15	15
4	700 (2100)	20	15	15
1A	0[a] (0)	20	35	35
2A	70 (210)	20	35	35
3A	300 (900)	20	35	35
4A	700 (2100)	20	35	35

[a] = Vehicle control

Toxicokinetics:

Times and Results:

Mortality and clinical sign: Twice daily

No treatment-related mortality was observed. A total of 9 animals were found dead/euthanized prior to the scheduled necropsy. These nine deaths (6 males and 3 females) were not attributed to the test article since they were distributed randomly across all groups and cause of deaths could not be established.

Mortality (day of death)

Group	Dose (mg/kg/day)	Mortality
1	0	1/15 male (74) and 1/15 female (180)
2	70	2/15 males (179, 172) and 1/15 female (131)
3	300	3/15 males (104, 138, 97)
4	700	1/15 female (110)

Clinical signs of mice sacrificed/died (see table above)

Group	Dose (mg/kg/day)	Clinical signs
1	0	Hypoactivity, thin, yellow material at urogenital area
2	70	Labored respiration, hypoactivity, thinness, body and/or extremities pale, absence of feces
3	300	Swollen abdominal, prolapsed penis, yellow material at urogenital area

4	700	Unkempt appearance, impaired use of left forelimb, cool to touch, absence of feces

Clinical signs of surviving mice: Not remarkable

Body weight and food consumption: Weekly for 14 weeks

Not remarkable

Clinical Pathology: Week 26

No treatment-related effects on hematology or clinical parameters were observed. A few male mice in the 700 mg/kg/dose group had slightly increased number of circulating neutrophils (1.44x) when compared to control groups. Mean globulin levels were slightly increased in the HD females when compared to control group, and mean A/G ratios were slightly decreased.

Group	0	70	300	700
Neutrophil	1.24	1.21	1.21	1.78**
Globulin	1.9	2.0	2.0	2.2**
A/G ratio	1.78	1.68	1.72	1.50**

** Significantly different from the control group

Gross Pathology: Week 26

Gross and microscopic findings of nine mice that died/euthanized indicated that individual causes of death included generalized sepsis, penile inflammation (urologic syndrome) and neoplasia.

In scheduled necropsies, small testes were observed in 6/15, 9/15 and 12/15 males for the 70, 300 and 700 mg/kg/dose groups, respectively. Acute, chronic or chronic-active inflammation observed in the abdominal cavities of several HD males and females was considered secondary to the method of drug administration.

Organ weights: Week 26

Relative and Absolute Organ weights at week 26 necropsy in Mice

Organ	Control	70 mg/kg	300 mg/kg	700 mg/kg
Testis	Abs. 0.252	0.080 [a]	0.062 [a]	0.070 [a]
	Rel. 0.615	0.200 [a]	0.161 [a]	0.181 [a]
Spleen	Abs. 0.104	0.105	0.127	0.184 [a]
	Rel. 0.254	0.262	0.331	0.505 [a]

[a] Significantly different from the control group; Abs.=Absolute weight; Rel.=Relative weight

Histopathology: Week 26

Dose, mg/kg/day	0		70		300		700	
No Animals Examined	14	14	13	0	12	0	15	14
Sex of Animals	M	F	M	F	M	F	M	F
Terminal Sacrifice (Week 26)								
Testes								
-Degeneration: Seminiferous tubules	1		13		12		15	
minimal			2				1	
mild			5		3		1	
moderate			6		9		14	
severe	2		2		4		1	
-Vacuolation	2		1		2		1	
minimal			1		2			
mild			13		12		11	
-Hyperplasia, Interstitial cell			1					
minimal			7		8		9	
mild			5		4		2	
moderate								
Epididymides			13		12		15	
-Hypospermia present								
Spleen							3	1
-Extramedullary hematopiesis							3	1
mild								
Abdominal cavity							1	4
-Chronic inflammation								2
minimal							1	2
mild								

Toxicokinetics: Days 0 and 182

For toxicokinetics, CD-1 mice (n=35/sex/group) were administered weekly IP doses of 0, 70, 300 or 700 mg/kg (corresponding to 0, 210, 900 or 2100 mg/m2) for 26 weeks. Blood samples were taken at 0 (pre-dose), 5 and 20 minutes, 1, 2, 4, 8, 10, 12, 24 and 36 hrs post-dose on days 0 and 182. On study Day 0, blood was collected from two mice/sex/group at each time point, and on study Day 182, blood was collected from one mouse/sex/group at each time point. Concentrations of LY231514 were determined by LC/ESI/MS/MS method. Toxicokinetic parameters are shown in the following table.

Systemic Toxicokinetic Parameters of LY231514 in CD-1 Mice Following Weekly IP Administration of 70, 300 or 700 mg/kg as Disodium Salt on Days 0 and 182

	Administered Dose (mg/kg/dose)					
Parameter[a]	70		300		700	
Sex	M	F	M	F	M	F
Day 0						
C_{max} (ng/mL)	72240	50850	184600	191900	699000	520400
$AUC_{0\text{-}36\ hr}$ (ng•hr/mL)	66740	42810	230500	208700	1004000	975600
Day 182						
C_{max} (ng/mL)	66430	71120	315700	243500	506100	809300
$AUC_{0\text{-}36\ hr}$ (ng•hr/mL)	61530	73380	238800	254700	890500	1312000

Abbreviations: M = male, F = female, C_{max} = maximum plasma concentration, $AUC_{0\text{-}36\ hr}$ = area under the plasma concentration versus time curve from time zero to 36 hr.

[a]Values derived from N = 2 mice per sex (pooled sample) and N = 1 mouse per sex in each treatment group for the study day 0 and 182 evaluations, respectively.

On Days 1 and 182, systemic exposure [Cmax and $AUC_{(0\text{-}\infty)}$] increased dose proportionally at low- and mid dose levels, and more than proportional in the high dose group. Tmax ranged from 0.083 to 0.33 hrs for both study days, and t½ values ranged from 1.88 to 8.74 hrs. TK parameters were consistent across gender and on both Days 0 and 182.

Study title: A repeat dose toxicity study in the beagle dog given LY231514 disodium (compound 289739) by intravenous slow bolus injection every 3 weeks for 9 months (14 doses).

Key study findings:

- No mortality was seen with the repeated doses of LY231514 in dogs
- Decreased food consumption and body weight gains were attributed to LY231514
- Decreases in white blood cell parameters were noted

- Increased liver enzymes were seen primarily in female HD dogs, no correlated histopathological or organ weight changes seen
- Histopathological changes in the bone marrow, testes, and kidneys (no clinical chemistry or organ weight changes in kidney parameters)

Study no.: CTBR 500415
Volume #, and page #: Module 4
Conducting laboratory and location: (b) (4)

Date of study initiation: 19 January 2004
GLP compliance: Letter included and signed
QA reports: yes (X) no ( )
Drug, lot #, and % purity: LY231514 disodium, Lot # RW03437, 99.9%

Methods

Doses:	5, 10, and 25 mg/kg
Species/strain:	Dog/ Beagle
Number/sex/group or time point (main study):	4/sex/dose in main study
Route, formulation, volume, and infusion rate:	IV/0.75 mL/kg/slow bolus
Satellite groups used for toxicokinetics or recovery:	TK from main study dogs
Age:	≈ 7-8 months
Weight:	7.0 – 9.1 kg ♂ 6.1 -8.7 kg ♀
Sampling times:	Day 1 and 274 (last Tx day) taken at predose, 0.083, 0.33, 1, 2, 4, 8, 10, 12, 24 and 36 hrs post-dose

Times and Results:

Mortality: Twice daily

No mortality

Clinical signs:
Weekly detailed exams in addition to each dosing day and the 4 days following dosing

A few dogs in all LY231514 dose groups exhibited emesis or evidence of emesis during or after dosing with the experimental compound. One dog, who had continued decreased food consumption also, exhibited emesis, dehydration, decreased locomotor activity, weakness, decreased fecal output and reduced body temperature.

Body weights: Weekly

The sponsor's graphs below show that the administration of LY231514 adversely affected the body weight gains in both the male and female dogs at the HD level. The HD female dogs started out with a higher body weight, making the results more difficult to note in the female dogs. Looking at the body weight gains gives a clearer picture. Over the course of the study, the vehicle dogs body weights increased by 15.15% and 16.50% in the female and male dogs, respectively. In the HD dogs, the body weights increased by only 5.26% and 11.36% in the females and males, respectively.

Figure 1: Group Mean Body Weights - Males

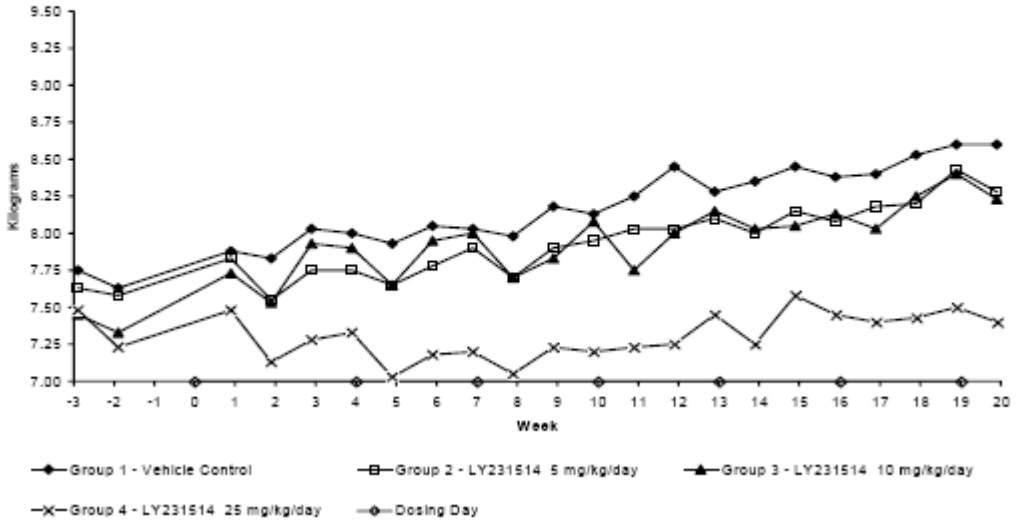


Figure 1: Group Mean Body Weights - Males

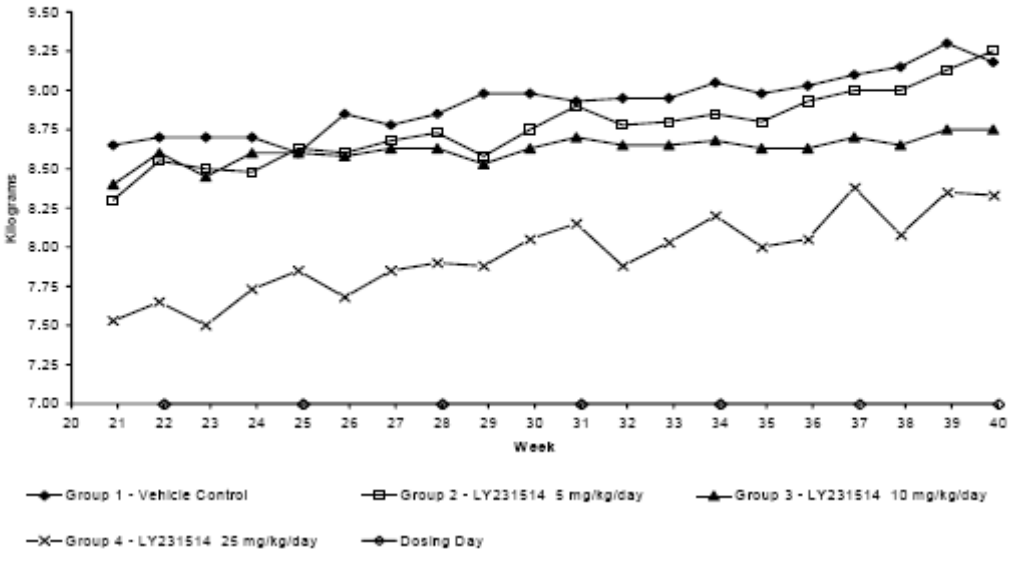


Figure 2: Group Mean Body Weights - Females

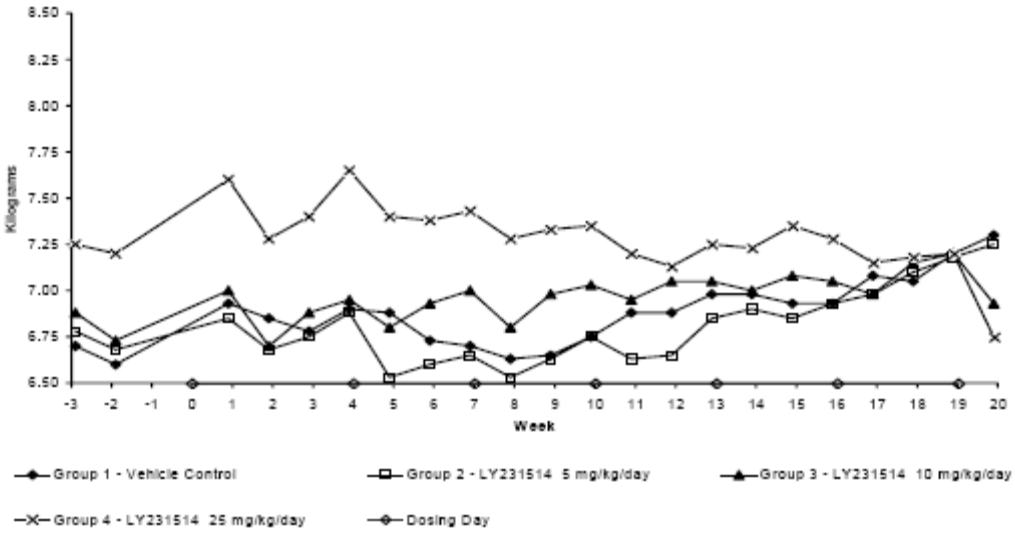
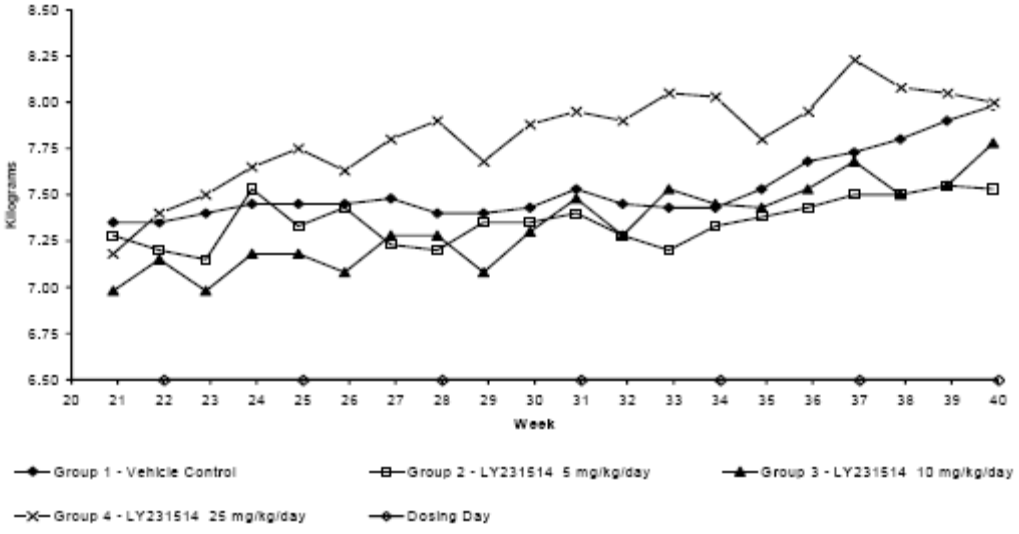


Figure 2: Group Mean Body Weights - Females



[Body weight graphs all excerpted from the Sponsor]

Food consumption: Daily

LY231514 routinely led to decreased food consumption in the dogs in all dose groups. Extended periods of food leftover in the bowls of the LY231514 animals led to

supplementation with moist dog food. One dog (HD female) required additional supplementation with several different types of food to attempt to stimulate the animal's eating.

Ophthalmoscopy: Prior to treatment and then after dose 14

Two dogs showed evidence of discharge; both dogs were in the LD group. It is not likely that this finding is treatment-related. No other ocular findings were noted in the study.

EKG: Prior to treatment period and then just prior to and at 0.5 hrs after doses 2, 6 and 13

No evidence of a treatment related effect on the electrocardiogram was seen.

Hematology: Twice prior to treatment, and 3 days following doses 3, 7 and 14 and within two days prior to doses 2 through 14

The table below shows the relevant changes in hematology parameters seen over the course of the study. Similar results were seen after earlier treatments but only the final blood analysis is presented in the table. Primarily, LY231514 decreased white blood cells. Platelets were also decreased in all groups of LY231514-treated dogs. The decreased platelets are also likely related to the histopathological finding of hemorrhagic foci noted in two of the HD dogs. RBC parameters were slightly and sometimes significantly decreased but the primary effects of LY231514 were seen on white blood cell parameters.

Hematology Parameters
Week 40 of LY231514 Administration in Dogs
Percent Changes from Control

	Males			**Females**		
Dose Mg/kg/day	LD 5	MD 10	HD 25	LD 5	MD 10	HD 25
RBCs	-10 %	-9 %	-16%	+.5%	-5%	-19%
Hemoglobin	-1%	-9%	-16%	-1%	-4%	-17%
Hematocrit	-2%	-9%	-16%	-1%	-6%	-17%
Platelets	-54%	-66%	-63%	-39%	-44%	-47%
WBC	-19%	-35%	-49%	-30%	-43%	-38%
Lymphocytes - Absolute	-16%	-8%	-30%	-34%	-37%	-32%
Monocytes - Absolute	-31%	-61%	-71%	-10%	-49%	-53%
Eosinophils - Absolute	-55%	-68%	-79%	-58%	-42%	-31%
Basophils - Absolute	+100%	-82%	-90%	-61%	-73%	-81%
Neutrophils - Absolute	-16%	-41%	-52%	+11%	-44%	-40%

Clinical chemistry: Twice prior to treatment, and 3 days following doses 3, 7 and 14

The table below shows the relevant changes in clinical chemistry parameters seen over the course of the study. The only changes that were not within normal biological variation were increases in AST, ALT and bilirubin, seen mostly in the female dogs. Despite histopathological changes in the kidney, there were not concurrent clinical chemistry changes in kidney parameters. The increases in liver enzymes were not correlated to any histopathological changes in the liver.

Clinical Chemistry Parameters
Week 40 of LY231514 Administration in Dogs
Percent Changes from Control

	Males			**Females**		
Dose Mg/kg/day	LD 5	MD 10	HD 25	LD 5	MD 10	HD 25
AST	-2 %	+18 %	+68%	+12%	+35%	+58%
ALT	-5%	-13%	-6%	+26%	+36%	+284%
Bilirubin	+13%	-15%	-11%	+15%	+15%	+49%

Urinalysis: Twice prior to treatment, and 3 days following doses 3, 7 and 14

No treatment-related effects were seen on urinalysis parameters

Gross pathology:

The only notable macroscopic findings were seen in one male and one female HD dog. The male dog had dark foci in the lungs and the female dog had dark area/foci in several organs, including the lungs. The histopathology showed these areas to be hemorrhagic.

Organ weights:

No significant or relevant changes in organ weights were noted. Any changes seen were within biological variation or could be attributed to the reduced body weights.

Histopathology: Adequate Battery: yes (X), no ( )
Peer review: yes (X), no ( )

Microscopic Findings Following 14 Doses of LY231514 in Dogs								
	Control		LD 5 mg/kg		MD 10 mg/kg		HD 25 mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
Bone marrow								
Hematopoietic hypocellularity								
Minimal	-	-	-	-	2/4	1/4	1/4	-
Slight	-	-	-	-	-	-	1/4	1/4
Total	-	-	-	-	2/4	1/4	2/4	1/4
Kidney								
Tubular karyomegaly								
Minimal	-	-	2/4	-	2/4	-	1/4	-
Slight	-	-	1.4	-	2/4	-	3/4	-
Total	-	-	3/4	-	4/4	-	4/4	-
Testis								
Degeneration/necrosis, seminiferous epithelium								
Minimal	-		3/4		1/4		3/4	
Slight	-		1/4		3/4		1/4	
Total	-		4/4		4/4		4/4	

Toxicokinetics:

The Sponsor's table below shows the pharmacokinetic data for LY231514 after the first and the last dose was administered to dogs. Not shown in the table is that mean half-life ranged from 3.31 to 5.44 hrs. LY231514 showed no significant gender differences in pharmacokinetics, no accumulation over time and dose-proportionality up to the highest dose tested in this stud.

	Administered LY231514 disodium Dose (mg/kg/dose = 4 dogs/sex/group/time point)					
Parameter	5		10		25	
Sex	M	F	M	F	M	F
Day 1						
C_0 (ng/mL)	23791	24631	43507	45525	122967	121616
SD of C_0	3362	3911	4460	2675	22941	12303
$AUC_{0\text{-}inf}$ (ng•hr/mL)	21227	21427	38123	36734	104898	105877
SD of AUC	2324	3058	4726	1724	6551	21289
Day 274						
C_0 (ng/mL)	25910	29010	60876	52016	167460	139844
SD of C_0	1704	2474	11114	9863	11648	18405
$AUC_{0\text{-}inf}$ (ng•hr/mL)	22214	20212	41400	40080	109585	117586
SD of AUC	3006	3629	4808	2940	6589	19598

Abbreviations: M = male; F = female; C_0 = predicted 0 hour concentration; SD = Standard Deviation of the Mean; $AUC_{0\text{-}inf}$ = area under the plasma concentration versus time curve.

[Excerpted from Sponsor]

Histopathology inventory:

Study	6-month	9-month
Species	Mouse	Dog
Adrenals	X*	X*
Aorta	X	X
Bone Marrow smear	X	X
Bone (femur)	X	X
Brain	X*	X*
Cecum	X	X
Cervix	X*	
Colon	X	X
Duodenum	X	X
Epididymis	X*	X
Esophagus	X	X
Eye	X	X
Fallopian tube		
Gall bladder	X*	X
Gross lesions		
Harderian gland	X	
Heart	X*	X*
Ileum	X	X
Injection site		X
Jejunum	X	X
Kidneys	X*	X*
Lachrymal gland		
Larynx	X	
Liver	X*	X*
Lungs	X*	X
Lymph nodes, cervical		
Lymph node, mandibular	X	X
Lymph node, mesenteric	X	X
Mammary Gland	X	X
Nasal cavity	X	
Optic nerves	X	X
Ovaries	X*	X*
Pancreas	X	X
Parathyroid	X*	X*
Peripheral nerve		
Pharynx		
Pituitary	X*	X*
Prostate	X*	X
Rectum	X	
Salivary gland	X	X
Sciatic nerve	X	X
Seminal vesicles	X	
Skeletal muscle	X	X
Skin	X	X
Spinal cord	X	X
Spleen	X*	X

Sternum		X
Stomach	X	X
Testes	X*	X*
Thymus	X*	X
Thyroid	X*	X*
Tongue	X	X
Trachea	X	X
Urinary bladder	X	X
Uterus	X*	
Vagina	X	X
Zymbal gland		

X, histopathology performed
*, organ weight obtained

2.6.6.4 Genetic toxicology
None included

2.6.6.5 Carcinogenicity
None included

2.6.6.6 Reproductive and developmental toxicology
None included

2.6.6.7 Local tolerance
None included

2.6.6.8 Special toxicology studies
None included

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures
See text of review for pertinent tables and figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

NA

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The non-clinical portion of this supplemental NDA for Alimta included two general toxicity studies and one safety pharmacology study.

In a 6-month toxicity study in mice, CD-1 mice (n=15/sex/group) received weekly IP doses of 0 (0), 70 (210), 300 (900) or 700 mg/kg (2100 mg/m2) for 26 weeks. Prior to scheduled sacrifice, nine animals (6 males and 3 females) were either found dead or euthanized in moribund condition. The deaths were not attributed to LY231514 since they occurred randomly across all groups including controls and cause of death could not be determined. No treatment-related effects on hematology or clinical chemistry parameters were observed. A few male mice in the 700 mg/kg/dose group had slightly increased number of circulating neutrophils, increased globulin levels with decreased A/G ratio when compared to control group. Macroscopically, small testes were observed in males at all dose levels, and acute and chronic inflammations were noted in the abdominal cavities of several HD males and females. Drug-induced lesions were mainly in male reproductive organs and spleen. Microscopically, testicular and epididymal changes were present in all treated males. TK data demonstrated linear pharmacokinetics at the low- and mid dose levels, with greater exposure at the high dose level and male and female mice were similarly exposed to LY231514 following weekly IP injection for 6 months.

In a 9-month toxicity study in dogs, beagles (n=4/sex/group) received IV administration of LY231514 at doses of 0 (0), 5 (100), 10 (200) or 25 mg/kg (500 mg/m^2) given every third week (the clinical schedule) for a total of 14 doses. No mortality was seen in this study. Clinical signs included decreased appetite and emesis or signs of emesis. This correlated with decreases seen in body weight gains, primarily in the HD dogs. No treatment-related effects were seen on the electrocardiograms of the ophthalmologic parameters. Hematology changes were primarily noted in decreased white blood cell parameters. Clinical chemistry parameter changes observed included HD female dogs with elevated liver enzymes and bilirubin. The only macroscopic effects noted were two dogs with dark foci in the lungs and other organs, which microscopically were due to hemorrhagic sites, likely due to the thrombocytopenia seen in these dogs. Histopathology changes seen were hypocellularity in the bone marrow, tubular karyomegaly in the kidneys and degeneration/necrosis of the testes. Linear pharmacokinetics were seen and no accumulation or sex differences were seen when the blood was analyzed on the first and last days of dosing.

Unresolved toxicology issues (if any): None

Recommendations: The submitted studies do not lead to any additional recommendations for Alimta based on non-clinical information.

Suggested labeling:
The reviewed data do not impact the labeling of Alimta.

APPENDIX/ATTACHMENTS

None

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/s/

Kimberly Benson
9/5/2008 03:31:09 PM
PHARMACOLOGIST

Leigh Verbois
9/8/2008 08:55:50 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

STATISTICAL REVIEW(S)

ADDENDUM MEMO

NDA /Serial Number: 21-462 /S-015
Drug Name: Pemetrexed (Alimta)
Applicant: Eli Lilly
Indication(s): NSCLC

This memo documents correction to the Statistical Review and Evaluation by Dr. Fanhui Kong regarding overall survival subgroup analysis by gender in Study JMDB the Alimta + cisplatin treatment was compared to gemcitabine + cisplatin. The position for males and females were reversed in Table 4.1 in the review by Dr. Kong. This also corrects the Addendum Memo submitted on September 26, 2008 at 8:55 am in which only the hazard ratio and confidence intervals were corrected. The revised Table 4.1 is as follows:

Table 4.1 Summary of Overall Survival Subgroup Analyses Based on Patient and Disease Characteristics--All Randomized Patients

Subgroup	AC	GC	HR and CI
Age < 65	N=541	N=578	
Median OS	10.32	10.28	0.96 (0.84, 1.10)
Age ≥ 65	N=321	N=285	
Median OS	10.12	10.15	0.89 (0.74, 1.07)
Male	N=605	N=605	
Median OS	9.63	9.86	0.97 (0.85, 1.10)
Female	N=257	N=258	
Median OS	13.31	11.40	0.86 (0.70, 1.06)
Caucasian	N=669	N=680	
Median OS	10.02	10.09	0.93 (0.82, 1.05)
East/Southeast Asian	N=116	N=104	
Median OS	13.80	11.89	0.86 (0.61, 1.21)
Other	N=77	N=79	
Median OS	9.92	11.47	1.24 (0.84, 1.84)

*: Adjusted HR and superiority and NI p-values from Cox model with treatment only.

Source: FDA analysis.

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/s/

Fanhui Kong
9/26/2008 04:27:27 PM
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Rajeshwari Sridhara
9/26/2008 06:58:20 PM
BIOMETRICS

Aloka Chakravarty
9/29/2008 08:34:31 AM
BIOMETRICS

ADDENDUM MEMO

NDA /Serial Number: 21-462 /S-015

Drug Name: Pemetrexed (Alimta)

Applicant: Eli Lilly

Indication(s): NSCLC

This memo documents correction to the Statistical Review and Evaluation by Dr. Fanhui Kong regarding overall survival analysis by gender in Study JMDB the Alimta + cisplatin treatment was compared to gemcitabine + cisplatin. In the review by Dr. Kong the HRs for males and females were reversed. The corrected results are as follows:

For males the HR for overall survival was 0.97 (95% CI: 0.85, 1.10) and for females the HR was 0.86 (95% CI: 0.70, 1.06).

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/s/

Rajeshwari Sridhara
9/25/2008 09:38:40 PM
BIOMETRICS

Aloka Chakravarty
9/26/2008 08:54:44 AM
BIOMETRICS

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 – TEAM LEADER'S MEMO

NDA/Serial Number:	21-462/S015
Drug Name:	Alimta (Pemetrexed)
Indication(s):	Non-Small Cell Lung Cancer
Applicant:	Eli Lilly & Co.
Date(s):	Submission date: August 27, 2007
	Major Amendment: June 24, 2008
	PDUFA due date: September 28, 2008
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Primary Statistical Reviewer:	Shenghui Tang, Ph.D.
Secondary Reviewer:	Rajeshwari Sridhara, Ph.D., Team Leader/Deputy Division Director
Concurring Reviewer:	Aloka Chakravarty, Ph.D., Division Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Martin Cohen, M.D.
	John Johnson, M.D., Patricia Cortazar, M.D., Robert Justice, M.D.
Project Manager:	Mr. Carl Huntley

Keywords: Non-inferiority, overall survival, treatment interaction

Background

Pemetrexed (as a single agent) received an accelerated approval for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy on August 19, 2004 based on the randomized study JMEI comparing pemetrexed monotherapy with docetaxel in 571 patients (please refer to the statistical review by Dr. Wang, August 11, 2004). As a condition of this approval and Subpart H requirement, further studies (JMDB and JMEN (ongoing)) were required to confirm and describe the clinical benefit of pemetrexed.

In this submission, the sponsor submitted data and results of the Study JMDB. This is a multicenter, randomized, Phase III trial comparing the efficacy and safety of Alimta + cisplatin (AC) with that of gemcitabine + cisplatin (GC) in 1,725 patients with a diagnosis of locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer. First patient was enrolled on July 6, 2004 and the database was locked on January 25, 2007. For further details regarding design and analyses, please refer to the statistical review by Dr. Kong (June 11, 2008).

Study JMEN is an ongoing Phase III trial with 663 enrolled patients comparing the efficacy and safety of pemetrexed + best supportive care versus best supportive care as a maintenance treatment for advanced NSCLC. The results of this study have been submitted as a summary report without data to verify in this sNDA. For further details regarding design and the reported results of this study, please refer to the statistical review by Dr. Tang (September 23, 2008).

This Team Leader concurs with the recommendations and conclusions of both the statistical reviewers (Drs Kong and Tang) of this supplemental application. This memo summarizes the results from each of the studies, the advice received from external consultants (Dr. Harrington (current Oncologic Drugs Advisory Committee (ODAC) member, and Dr. Fleming (Special Government Employee), and this reviewer's recommendation.

Results

Study JMDB: Alimta + cisplatin vs. gemcitabine + cisplatin as first-line treatment in patients with metastatic NSCLC:

The following tables present the analyses of the primary endpoint, overall survival based on data collected in Study JMDB:

Overall survival of squamous vs. non-squamous histology in JMDB study :

	Median OS (mo)				Adjusted** HR (95% CI)	Un-adjusted HR (95% CI)
	AC		GC			
ITT population	10.3	N=862	10.3	N=863	0.94 (0.84 – 1.05)	0.93 (0.84, 1.04)
By Histology:						
Nonsquamous (adeno + large)*	11.8	N=512	10.4	N=488	0.81 (0.70 – 0.94)	0.85 (0.74, 0.96)
Squamous*	9.4	N=244	10.8	N=229	1.23 (1.00 – 1.51)	1.22 (0.99, 1.50)

**Treatment by histology interaction test, p = 0.0011*

***Adjusted co-variates: ECOG PS, Gender, Disease stage & Type of pathological diagnosis*

Overall Survival by Histology in JMDB study:

	Median OS (month)	Adjusted HR[a] (95% CI)	Un-adjusted HR (95% CI)
Adenocarcinoma (N=847)			
AC (n=436)	12.55	0.84 (0.71, 0.99)	0.84 (0.71, 0.98)
GC (n=411)	10.94		
Large Cell (N=153)			
AC (n=436)	10.38	0.67 (0.48, 0.96)	0.68 (0.48, 0.97)
GC (n=411)	6.67		
Unknown or Other Histology (n=252)[b]			
AC (n=436)	8.57	1.08 (0.81, 1.45)	1.12 (0.84, 1.50)
GC (n=411)	9.17		
Squamous Cell (n=473)			
AC (n=436)	9.36	1.23 (1.00, 1.51)	1.22 (0.99, 1.50)
GC (n=411)	10.84		

a. Adjusted HR and superiority from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).
b. The subcategory of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

Study JMEI: Alimta vs. Docetaxel as second-line treatment in patients with metastatic NSCLC:

The following tables present the analyses of the primary endpoint, overall survival based on data collected in Study JMEI:

JMEI Overall survival analysis by histology:

	Median OS (mo)				**Adjusted** HR (95% CI)**	**Un-adjusted HR (95% CI)**
	Alimta		**Docetaxel**			
ITT population	8.3	N=283	7.9	N=288	0.99 (0.82 – 1.20)	0.99 (0.82, 1.20)
By Histology:						
Nonsquamous (adeno + large)*	9.2	N=176	8.2	N=173	0.78 (0.60 – 1.02)	0.91 (0.71, 1.14)
Squamous*	6.2	N=78	7.4	N=94	1.56 (1.08 – 2.26)	1.31 (0.93, 1.86)

**Treatment by histology interaction test, p = 0.001*

*** Adjusted co-variates: ECOG PS, Gender, Disease stage, time since prior chemotherapy (not all randomization stratification factors- factors not pre-specified)*

Following are the sponsor reported results by each histology type. These results could not be verified as there is difference in the classification of patients by histology type between the original submission of JMEI data and the current report.

Overall Survival by Histology in JMEI study:

	Median OS (month)	Adjusted HR[a] (95% CI)	Un-adjusted HR (95% CI)
Adenocarcinoma (N=301)			
A (n=158)	9.0	0.92 (0.69, 1.22)	1.09 (0.83, 1.44)
D (n=143)	9.2		
Large Cell (N=47)			
A (n=18)	12.8	0.27 (0.11, 0.63	0.38 (0.18, 0.78)
D (n=29)	4.5		
Unknown or Other Histology (n=51)[b]			
A (n=29)	9.4	0.57 (0.27, 1.20)	0.62 (0.32, 1.23)
D (n=22)	7.9		
Squamous Cell (n=172)			
A (n=78)	6.2	1.56 (1.08, 2.26)	1.32 (0.93, 1.86)
D (n=94)	7.4		

[a] HRs adjusted for ECOG PS, time since prior chemotherapy, disease stage, and gender. A HR that is less than 1.0 indicates that survival is better in the ALIMTA arm than in the docetaxel arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the docetaxel arm than in the ALIMTA arm.
[b] The subcategory of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

The sponsor has also reported the following imbalances between treatment groups by histology subtypes in the JMEI study:

Demographics by Histology

Characteristic	**Pemetrexed N=283**				**Docetaxel N=288**			
	Adeno	Large	Other*	Squam	Adeno	Large	Other*	Squam
	n=158	n=18	n=29	n=78	n=144	n=29	n=21	n=94
Median Age (yrs)	57.4	60.3	59.3	61.3	56.7	55.6	62.2	60.2
Female/Male (%)	39/61	33/67	45/55	10/90	34/66	28/72	14/86	12/88
Stage III/IV (%)	18/82	22/78	17/83	42/58	20/80	24/76	24/76	34/66
ECOG PS 0/1/2 (%)	23/62/15	13/81/6	14/82/4	17/75/8	19/70/11	18/75/7	10/80/10	16/66/17
Caucasian/E Asian (%)	72/18	78/6	59/24	74/10	66/24	79/4	76/10	70/13

Study JMEN: Alimta vs. Placebo as maintanance treatment in patients with metastatic NSCLC after receiving platinum based doublet chemotherapy:

The following tables present the interim analysis results as reported by the sponsor with respect to overall survival based on Study JMEN. These results have not been verified by FDA reviewers:

JMEN Interim Overall Survival Results by Histology (un-adjusted for co-variates)

	Median Overall Survival (months)		HR (95% CI)
	Alimta	Placebo	
ITT Population	13.0 (n = 441)	10.2 (n = 222)	0.80 (0.63, 1.01)
Nonsquamous* n=482	14.4	9.4	0.66 (0.49, 0.88)
Adeno n=329	16.4	11.7	0.73 (0.51, 1.06)
Large Cell n=20	9.1	5.5	0.42 (0.13, 1.38)
Other n=133	11.3	7.0	0.47 (0.28, 0.80)
Squamous* n=181	9.6	11.8	1.28 (0.85, 1.93)

**Treatment by histology interaction test, p = 0.011*

Comments from Consultants:

Given these results and concerns, Dr. Harrington (Current ODAC member), and Dr. Fleming (SGE) were asked the following questions:

1. Do you believe that every 3 week schedule of gemcitabine plus cisplatin, rather than the every 4 week approved schedule is an acceptable comparator regimen?

2. Do you believe that the combination of Alimta plus cisplatin has demonstrated to be non-inferior to the combination of gemcitabine and cisplatin?

3. Given the results of study JMDB and the results from JMEI and JMEN studies, do you believe that Alimta has demonstrated efficacy in adenocarcinoma and large cell lung cancer?

Dr. Harrington's response to the above questions were: Response to question 1: yes; Response to question 2: no; Response to question 3: yes. Details of Dr. Harrington's advice are attached in Appendix 1.

Dr. Fleming's response to the above questions were: Response to question 1: no; Response to question 2: no; Response to question 3: no. Details of Dr. Fleming's advice are attached in Appendix 2.

Conclusion:

One well-controlled Phase IV commitment study JMDB was submitted to compare the efficacy and safety of AC with that of GC in patients with locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer. In this study, the primary efficacy measure was the overall survival. The study was designed as a non-inferiority study using fixed margin approach. Even though the choice of the control does not lend to NI analysis, control treatment as administered was in itself not of concern.

Although the confidence interval for HR is below the protocol specified fixed non-inferiority margin, (a) highly significant treatment by histology interaction effect, (b) almost 50% of patients receiving post-discontinuation therapy, and (c) the lack of historical study(ies) to estimate effect size of GC, make the interpretation of the study results problematic. The treatment by histology interaction observed in Study JMEI in which Alimta was administered as monotherapy for the treatment of second-line NSCLC can not be considered confirmatory due to the retrospective post-hoc analyses and observed imbalances between treatment groups within each histology subgroup. Interim results of Study JMEN in which Alimta was administered as a maintenance therapy, appear to suggest similar results which needs further follow-up data with the final overall survival analysis.

Recommendation:

This application is seeking approval of Alimta in combination with cisplatin for the first-line treatment of patients with non-squamous NSCLC based on the results of Study JMDB. Because of treatment cross-over in nearly 50% of patients and a highly statistically significant qualitative treatment-histology interaction, the primary hypothesis of non-inferiority with respect overall survival can not be concluded based on this study. The results of JMDB generates the hypotheses that (1) patients with non-squamous NSCLC benefit with the treatment of Alimta in combination with cisplatin, and (2) Alimta plus cisplatin harms the patients with squamous cell NSCLC when compared to gemcitabine plus cisplatin.

Retrospective analyses of Study JMEI where Alimta was administered as monotherapy in the second-line treatment of NSCLC, confirms that Alimta compared to docetaxel harms the patients with squamous cell NSCLC. In this study, majority of the patients with non-squamous histology were those with adeno carcinoma. The advantage of Alimta over docetaxel is not obvious in the

adeno carcinoma group and therefore, benefit of Alimta over docetaxel as treatment for patients with non-squamous NSCLC can not be concluded. Furthermore, post-hoc subgroup analyses with observed imbalances in patient characteristics between treatment arms make the inference of these analyses problematic.

Interim analyses of Study JMEN where Alimta was compared to placebo as maintenance therapy after patients had received platinum containing doublet chemotherapy, confirms that Alimta should not be used in patients with squamous cell NSCLC as the survival in the Alimta treated group is worse than placebo in this subgroup of patients. Although the interim results suggest that Alimta may be beneficial in patients with non-squamous NSCLC, the null hypothesis of no difference between Alimta and placebo in the ITT population could not be rejected based on the pre-specified type I error rate allocation. These results need be confirmed with the verification of the data and final overall survival analyses.

For the above reasons, the data submitted in this application does not provide adequate support to the sponsor's claim that Alimta in combination with cisplatin has demonstrated benefit in the first-line treatment of patients with non-squamous NSCLC. The data presented provides the evidence that Alimta should not be used in patients with squamous cell NSCLC.

Appendix 1
Summary of sNDA 21-462 Review
David Harrington
June 24, 2008

Based on my review of the material provided by FDA statisticians and medical officers, I have the following answers to the questions posed in the briefing document.

1. Do you believe that every 3 week schedule of gemcitabine plus cisplatin, rather than the every 4 week approved schedule is an acceptable comparator regimen?
Yes, it is my opinion that the 4 week schedule used in the Sandler GC vs C trial can be used to establish the GC effect over platinum alone. There is sufficient data to support the claim that a 3 week schedule of GC would have equivalent or better efficacy than a 4 week schedule, when compared to platinum alone. The three week regimen also seems to be more tolerable.

2. Do you believe that the combination of Alimta plus cisplatin has demonstrated to be non-inferior to the combination of gemcitabine and cisplatin?
No, not across all histologies. The primary analysis of AC vs GC seems to support a claim of non-inferiority, whether one uses the fixed non-inferiority margin of 15% or a `percent retention margin' of 50%, but the strong evidence of a qualitative interaction in squamous vs non-squamous histology makes the overall analysis of non-inferiority difficult to interpret. Specifically, the AC regimen seems to be superior in the nonsquamous histologies and inferior in squamous cell histology. Several aspects of the interaction make it credible: statistical tests for interactions typically have low power, and the test in the JMDB study is highly significant; the retrospective analysis of JMEI found the same interaction, confirming the result in JMDB; although the analysis of JMEN is preliminary, there is also a trend toward the same interaction. Because of the significant interaction, I would support a more limited labeling for use in adeno and large cell NSCLC, rather than the broad labeling of NI presented in the briefing document.

The analysis presented in the briefing document does have some aspects that may weaken the evidence for the interaction, but in my opinion these are not serious enough to invalidate the analysis. The adjusted analysis presented for the JMEI study uses a variable (sex) that was not a stratification factor in the randomization, but sex has been shown to significantly associated with outcome in this disease in other studies. The JMEI study shows superiority in large cell but not adeno carcinoma, while the JMDB shows superiority in both subsets.

3. Given the results of study JMDB and the results from JMEI and JMEN studies, do you believe that Alimta has demonstrated efficacy in adenocarcinoma and large cell lung cancer?
Yes, I do believe Alimta has demonstrated efficacy in these subsets; it has certainly demonstrated NI in these subsets. As noted in the briefing document, a large subset of patients received additional therapy after finishing AC or GC treatment. Even though these additional treatments may obscure the `pure effect` of Alimta on survival, I believe they reflect the practice of treating end-stage NSCLC patients, the large majority of whom fail several therapies. As was noted in the briefing document, cross-over therapy after receiving treatment in a randomized trial may dilute treatment differences.

If the indication for AC is limited to non-squamous histology, however, the estimated treatment effect is positive for patients with these histologies, so the cross-overs may be masking an even larger treatment effect in this subgroup.

General comments

The briefing document reports a number of unplanned subgroup analyses done by the sponsor, largely in response to the unexpected and statistically significant interaction between treatment and histology. Because the interaction is a qualitative one (treatment effects in opposite directions in two subsets defined by histology), is highly significant, and appears confirmed in two of three studies, I believe the subgroup analyses are warranted.

AC seems no less tolerable than GC, so there does not seem to be a reason to deny the indication based on side-effects.
It is not clear whether the labeling should include the claim that AC is superior to GC as initial therapy in non-squamous, NSCLC histology, or the more conservative claim that AC is at least as effective as GC in this setting. Had the JMDB trial been designed as an NI trial in this subset of NSCLC, the outcome of the trial may well have supported a claim of superiority because of the confidence interval estimate of the AC vs GC effect. The interaction of treatment by histology appears to have been unexpected, however, and appears not to be present in the adeno-carcinoma subset in JMEI. I would favor the more conservative labeling of `at least as effective' in the non-squamous histology.

Appendix 2

SCHOOL OF PUBLIC HEALTH AND COMMUNITY MEDICINE
DEPARTMENT OF BIOSTATISTICS

August 1, 2008

Carl Huntley, R.Ph., MBA
Senior Regulatory Project Manager
FDAlCDERIOND/OODP/DDOP

Dear Dr. Huntley:

I have reviewed the protocol, addenda and amendments as well as the Statistical Analysis Plan (SAP) for the H3E-MC-JMDB clinical trial evaluating pemetrexed in previously untreated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). I also have reviewed FDA's Pemetrexed Briefing Document for sNDS 21-462.

Several significant issues should be considered:
1. The JMDB protocol does not provide adequately rigorous justification for the noninferiority (NI) design, including choice of margin. While some context is provided in the SAP, several issues of concern arise with arguments presented
2. Irregularities in quality of trial conduct compromise the interpretation of results from the NI trial, JMDB
3. Evidence from JMDB is weakened by lack of internal consistency due to apparent differences in effect of pemetrexed by histologic subgroups
4. The JMEI and JMEN clinical trials do not provide true independent validation of the apparent effect modification of pemetrexed by histologic subgroups

In the remainder of this report, each of these significant issues will be considered in greater detail. A brief concluding assessment also is provided.

1. Lack of adequate justification of the NI design, including choice of margin, in JMDB
1.1 Lack of substantial evidence regarding the effect of the active comparator

It is of substantial concern that the JMDB protocol does not provide justification for the choice of the NI margin. While the SAP does provide some consideration for its choice, it does not provide substantial evidence regarding the magnitude of the survival effect of the active comparator, gemcitabine, when it is used in the context of 1st line co-administration with cisplatin and subsequent supportive care, in patients with locally advanced or metastatic NSCLC. Reference is simply made to the relative risks from the clinical trials by Sandler et.al. (2000), and Wozniak et.al.(1998).

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1.2 Lack of adjustment for uncertainty about the validity of the constancy assumption

The Rothmann method is a gold standard design for a NI trial only in the rare setting where rigorous justification is provided to establish that the effect of the active comparator agent (i.e., gemcitabine in JMDB) in historical controlled trials is the same as its effect in the NI trial (i.e., in JMDB). This "constancy assumption" certainly cannot be assumed to hold in general, given that the NI trial may differ from historical trials in many factors that can modify the effect of the active comparator, such as the patient population, the nature of supportive care, the level of adherence, the choice of the primary and secondary endpoints, and irregularities such as informative missingness in the evaluation of the study endpoints.

The sponsor's justification for the NI margin of 1.17647 for the pemetrexed to gemcitabine relative risk, provided in the SAP on pp. 3277-3278 and pp. 3283-3285, completely ignores the need for adjustments based on uncertainty about the validity of the constancy assumption. (The only specific aspect to the formulation of the NI margin to be used in JMDB is its unnecessary specification to six significant digits.)

1.3 Improper arguments about "enormous and impractical sample sizes"

Congress did not specify that FDA need not require having substantial evidence of efficacy when approving agents in major indications such as 1sl line NSCLC, in circumstances where obtaining such evidence would be difficult. Hence, of what relevance is the sponsor's statement that using a smaller margin than they propose would require "enormous and impractical sample sizes"? (See the SAP, page 3278). The statement also is untrue. If an agent is only slightly more efficacious than the active comparator, one can rule out rigorous margins without needing enormous and impractical sample sizes.

1.4 Imprecise statement regarding what is established by a NI trial

The sponsor's statement, (see the SAP, page 3278), that a NI "trial is designed to demonstrate statistically that a practical and sufficient degree of similarity of survival benefit exists between the two treatments"' is imprecise if not misleading. The objective of a NI trial is not to provide some statistical evidence that the experimental and active comparator agents have a practical and sufficient degree of similarity of efficacy. (That interpretation could be provided for some trials having only a few patients per arm). Rather, the goal is to rule out that the efficacy of the experimental agent is unacceptably worse than that of the active comparator. This reveals that the NI margin needs to be sufficiently small that any difference in efficacy that would be clinically meaningful is excluded. In the JMDB trial, one needs to justify that a 5%, 10% or 15% increase in death rate would not be clinically meaningful to 1sl line NSCLC patients. Such justification usually should be based on clinically meaningful improvements in toxicity or tolerability that the experimental agent will provide relative to the active comparator, possibly further justified by improvements in convenience of administration or cost effectiveness. The sponsor did not provide such justification. (In their attempts to justify a post-hoc revision of the NI margin in

the JMEI trial, the sponsor provided a misleading argument by selectively reporting that pemetrexed improved toxicity/tolerability through a reduction in febrile neutropenic related hospitalizations, without drawing comparable attention to the fact that hospitalizations for other causes were increased in the pemetrexed arm, leaving no difference in the overall hospitalization rate.)

2. Irregularities in quality of trial conduct compromise the interpretation of results from the NI trial, JMDB

2.1 There are important uncertainties about whether the quality of conduct of the JMDB trial met high standards required to ensure the integrity of a NI trial

True differences in efficacy between the experimental and active control regimens can be meaningfully diluted by irregularities in quality of trial conduct, such as nonadherence to the active comparator regimen, withdrawal from therapy, lack of retention, enrollment of non-target patients less response to the active comparator, and some other types of protocol deviations. The data in the FDA's Pemetrexed Briefing Document does not provide required assurances that adequately intensive procedures were in place to ensure high quality of trial conduct and evidence that such procedures were successful.

2.2 The rate of cross-ins to Gemcitabine in the Pemetrexid regimen is problematic

If a substantial fraction of patients on the experimental arm are provided the active comparator and if delayed access to that agent provides substantial benefit, then a conclusion of non-inferiority could be reached even when the experimental agent is meaningfully less effective. Based on Table JMDB.11.32 from the sponsor's JMDB Study Report, at least 144 patients on the experimental arm crossed-in to receive gemcitabine. Furthermore, nearly one-half the patients in the experimental arm received anti-cancer chemotherapy after they discontinued pemetrexed. Unlike a superiority trial, such a degree of rescue therapy greatly compromises the ability to assess efficacy of the experimental regimen.

3. Evidence from JMDB is weakened by lack of internal consistency due to apparent differences in effect of pemetrexed by histologic subgroups

When regulatory considerations are based on a single trial, to have substantial evidence of efficacy and safety, the trial should provide results that are robust and compelling, with internal consistency. One important measure of such internal consistency is evidence that the effect of the experimental regimen is consistent across important subgroups of patients. Section 9.7.1.15 of the SAP defines histology to be among the factors to be considered when conducting subgroup analyses. The evidence about heterogeneity of effect by histology is contradictory to a claim of internal consistency. The suggestion of harm in the squamous cell subgroup strongly motivates the need for independent prospective evidence about the efficacy of pemetrexed in this setting.

4. The JMEI and JMEN clinical trials do not provide true independent validation of the apparent effect modification of pemetrexed by histologic subgroups suggested in JMDB
4.1 Exploratory analyses should be viewed to be hypothesis generating, needing validation from independent prospective trials

While exploratory analyses can be useful in expanding the understanding about benefit to risk beyond what is learned from the primary analysis of the primary endpoint, such analyses should be viewed as hypothesis generating. P-values from exploratory analyses are difficult to interpret due to the complex sampling context in which they are derived, and estimates of treatment effect corresponding to analyses showing particularly positive or negative results suffer from a regression-to-the-mean type bias. Independent validation, ideally from prospective adequate and well controlled trials is necessary. The suggestion of effect modification for pemetrexed by histology needs independent confirmation.

4.2 How can the JMDB or JMEI trial be considered confirmatory for the other trial?

The sponsor proposes to use JMEI as a confirmatory trial regarding the interaction by histology seen in JMDB. However, this is logically inconsistent with the acknowledgment in Section 9.7.1.15 (page 3292) of the JMDB SAP that subgroups by histology will be considered in JMDB "based on retrospective analyses of the Alimta second-line lung study, JMEI. .. ". If the post-hoc subgroup analysis by histology in JMEI served as the basis for considering such subgroup analyses in JMDB, then one cannot circle back and consider JMEI confirmatory for JMDB. Regarding the other direction, JMDB cannot be considered to be confirmatory for JMEI since the results in histologic subgroups from the JMEI trial were not sufficiently persuasive to have such analyses even mentioned in the JMDB protocol or elevated in the JMDB SAP as being any more important than subgroup analyses planned by smoking status, age, origin and stratification factors, including disease stage, ECOG performance status, history of brain metastases, sex, basis for initial pathological diagnosis and investigative center, (see Section 9.7.1.15 of the SAP). Finally, it is noteworthy that JMEI was conducted in patients who had received prior chemotherapy and included patients with Stage IlIA disease.

4.3 If interaction of treatment by histology is real in JMDB and JMEI, is it due to pemetrexed or to the active comparators, (i.e., gemcitabine in JMDB and docetaxel on JMEI)?

Understanding interaction in an active comparator trial is particularly challenging, since it could be due to the active comparator rather than to the experimental regimen. In using an NI trial to evaluate pemetrexed in 1st line NSCLC, it is important to understand whether gemcitabine's effect in 1st line NSCLC and docetaxel's effect in 2nd line NSCLC vary by histology. If it is plausible that pemetrexed's effect differs by cell type, why is it not plausible that this could be true

for the active comparator regimens? If it is true, then it follows that the NI margin in the JMDB and JMEI trials should be determined separately for each histologic subgroup.

4.4 The JMEN trial does not provide independent validation of the JMDB subgroup analyses by histology

JMEN has the strength of being a placebo controlled superiority trial, but was conducted in a restricted population having important differences from that enrolled in JMDB. Furthermore, the data from the JMEN trial do not appear to represent the final analysis of a locked database. The FDA's Pemetrexed Briefing Document also indicates that "The sponsor has not submitted data from this study to the Agency for the FDA reviewer to confirm these results from Study JMEN".

4.5 The large cell and adenocarcinoma subgroups should not be pooled

Computing p-values and confidence intervals for pooled data from the large cell and adenocarcinoma subgroups are inappropriate post-hoc analyses. Effectively, these analyses provide a post-hoc exclusion of those patients (i.e., squamous cell) where unfavorable results were obtained. Such pooling contradicts the JMDB SAP which clearly specifies on p 3293 that the three cell types would be considered separately.

A Brief Concluding Assessment

Based on the JMDB, JMEI and JMEN trials, it appears that the large cell patients provide the only setting where substantial evidence for efficacy could emerge when complete data are available from all three trials. Post-hoc pooling of large cell and adenocarcinoma (i.e., excluding squamous cell patients) would be inappropriate and contradicts the JMDB SAP which clearly specifies on p 3293 that the three cell types would be considered separately. Hence, the evidence for efficacy in adenocarcinoma patients is inconsistent, and is especially problematic in the JMEI trial where the estimate of the pemetrexed to docetaxel hazard ratio is 1.07 and where the justification of any NI margin greater than 1.1 is weak, (e.g., see Fleming, *Statistics in Medicine* 27: 317-332,2008). Finally, the evidence that pemetrexed has a harmful effect on overall survival in squamous cell patients is similarly persuasive to the evidence for benefit in large cell patients. This deserves proper attention in any decisions about approval and labeling.

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA /Serial Number:	21-462/S015
Drug Name:	Alimta
Applicant:	Eli Lilly and Company
Indication(s):	NSCLC
Date(s):	Submission Date: June 24, 2008 PDUFA Date: September 28, 2008 Review Completion Date: September 20, 2008
Review Priority:	No
Biometrics Division:	Division of Biometrics V (HFD-711)
Statistical Reviewer:	Shenghui Tang, Ph.D.
Concurring Reviewer:	Rajeshwari Sridhara, Ph.D., Team Leader Aloka Chakravarty, Ph.D., Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Martin Cohen, M.D., John Johnson, M.D.
Project Manager:	Mr. Carl Huntley
Keywords:	Overall survival, Progression-free survival

Table of Contents

1 Executive Summary

1.1 Conclusions and Recommendations

Pemetrexed (as a single agent, Alimta) received an accelerated approval for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004 based on the randomized study JMEI comparing pemetrexed monotherapy with docetaxel (Please see the statistical review for this study by Dr. Yong-cheng Wang, dated August 11, 2004). As a condition of this approval, as per Subpart H, further studies (JMDB and JMEN) were required to confirm and describe the clinical benefit of pemetrexed.

Study JMDB was a multicenter, randomized, Phase III trial comparing the efficacy and safety of Alimta + cisplatin (AC) with that of gemcitabine + cisplatin (GC) in patients with a diagnosis of locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer. First patient was enrolled on July 6, 2004 and the database was locked on January 25, 2007. In August 2007, the sponsor submitted the study JMDB. Please see the statistical review for this study by Dr. Fanhui Kong, dated June 11, 2008.

When the sponsor submitted Study JMDB, study JMEN was on going. Study JMEN was a Phase III trial comparing the efficacy and safety of pemetrexed + best supportive care versus best supportive care as a maintenance treatment for advanced NSCLC.

On June 23, 2008 FDA requested the final study report for Study JMEN be submitted as an amendment to the pending 1st line application. The sponsor submitted the report on June 24, 2008 without datasets. Therefore, this reviewer will review the submitted analyses without confirming the results.

In February 2007, the primary objective for Study JMEN was changed from overall survival (OS) to progression free survival (PFS). The submitted JMEN study report included the final PFS analysis and an interim analysis for OS. As indicated in the FDA End of Phase 2 (EOP2) meeting minutes and the January 11, 2007 meeting minutes, OS should be the primary efficacy endpoint.

Results from previous randomized, Phase 3 studies in advanced NSCLC (Study JMEI and Study JMDB) indicated that for patients treated with pemetrexed, those with nonsquamous histology (adenocarcinoma, large cell carcinoma, and other or unknown histology) tend to have better overall survival and progression-free survival compared to patients with squamous histology. Patients with squamous-cell NSCLC had worse survival with Alimta compared to control arm. In the JMEN study report, the sponsor also performed analyses for such interactions. Although the analyses of JMEN showed a trend toward the same interaction as

Study JMEI and Study JMDB did, the p-values from interaction and subgroup analyses were not interpretable because no alpha (type-I error) was allocated for the interaction test or any subgroup analyses in the statistical analysis plan for Study JMEN. The OS results should also be interpreted with caution since the submitted OS results were from an interim analysis with a total of 300 deaths,

Nevertheless, the sponsor analyses of JMEN appear to show a trend toward the same interactions for OS and PFS as Study JMEI and Study JMDB did.

1.2 Brief Overview of Clinical Studies

Study JMEN was a global, multicenter, randomized, double-blind, placebo-controlled study. The plan was to enroll approximately 660 patients in this study; eligible patients had a response of CR, PR, or SD following 4 cycles of induction therapy. Eligible patients were randomized to the experimental study arm (pemetrexed plus BSC) or the control arm (placebo plus BSC) following induction therapy. The placebo consisted of normal saline (0.9% sodium chloride), which also served as the diluent for pemetrexed. According to the protocol, patients in both study arms were required to receive folic acid and vitamin B_{12} supplementation and dexamethasone.

Patients were randomized (in a 2:1 ratio) to receive maintenance treatment with pemetrexed plus BSC or placebo plus BSC. A minimization principle was adopted to balance patient assignment between study arms, based on the following factors:

- disease stage prior to administration of induction therapy (IIIB versus IV)
- ECOG performance status just prior to randomization (0 versus 1)
- best tumor response to induction chemotherapy (CR/PR versus SD)
- gender (male versus female)
- previously treated brain metastases (yes versus no)
- nonplatinum component of induction chemotherapy (gemcitabine versus paclitaxel versus docetaxel).

Each patient underwent a treatment period and a follow-up period. The treatment period consisted of treatment cycles, each 21 days long. Patients received treatment (experimental or control) until objective disease progression. The follow-up period began when the patient discontinued study treatment; follow-up included periodic tumor response evaluation until objective disease progression. Investigators followed all patients until death or study closure.

Objective progression-free survival (PFS) was the primary efficacy variable in this study. Objective PFS was measured from the date of randomization (after

completion of induction chemotherapy) to the first date of objective progression of disease or of death from any cause.

1.3 Statistical Issues and Findings

Pemetrexed (as a single agent) received an accelerated approval for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004 based on the randomized study JMEI comparing pemetrexed monotherapy with docetaxel. As a condition of this approval, as per Subpart H, further studies (JMDB and JMEN) were required to confirm and describe the clinical benefit of pemetrexed. In this submission, the sponsor provided a study report for JMEN with datasets.

Statistical Issues:

1. In February 2007, the primary objective for the JMEN study was changed from overall survival (OS) to progression-free survival (PFS). On 12 June 2007, the following comments were conveyed to the sponsor:

   As indicated in the FDA End of Phase 2 (EOP2) meeting minutes and the January 11, 2007 meeting minutes, survival should be the primary efficacy endpoint.

   In general a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision.

2. The database "lock" for the final analysis of PFS (after a minimum of 462 PFS events) occurred on 21 November 2007. Data analyses of this database included the preliminary analysis of OS and the final analyses of all other endpoints. The database lock for the final analysis of OS (after a minimum of 475 OS events) is expected to occur in approximately 1 year.

3. The preliminary analysis of OS presented here included a total of 300 events, so that most patients were censored (56.7% of patients in the pemetrexed arm and 50.9% in the placebo arm). According to the statistical gatekeeping and alpha-spending scheme presented in the protocol, the significance level for this preliminary analysis was a one-sided alpha of 0.00001, leaving a nominal level of 0.02499 to be spent for the final analysis of OS, which will take place when 475 events have occurred.

4. Results from previous randomized, Phase 3 studies in advanced NSCLC (Study JMEI and Study JMDB) indicated that for patients treated with pemetrexed, those with squamous cell histology had inferior survival and

those with nonsquamous histology (adenocarcinoma, large cell carcinoma, and other or unknown histology) tend to have better overall survival and progression-free survival compared to patients with squamous histology. In the JMEN study report, the sponsor also performed analyses for such interactions. Patients with squamous-cell NSCLC had worse survival with Alimta compared to control arm. Although the analyses of JMEN showed a trend toward the same interaction as Study JMEI and Study JMDB did, the p-values from interaction and subgroup analyses were not interpretable because no alpha (type-I error) was allocated for the interaction test or any subgroup analyses in the statistical analysis plan for Study JMEN. The OS results should also be interpreted with caution since the submitted OS results were from an interim analysis with a total of 300 deaths.

Findings:

On June 23, 2008 FDA requested the final study report for Study JMEN be submitted as an amendment to the pending 1st line application. The sponsor submitted the report on June 24, 2008 with datasets. Therefore, this reviewer will review the submitted analyses without confirming the results. FDA had communicated to the sponsor that overall survival would be considered as the primary endpoint to evaluate efficacy.

Objective PFS A total of 504 PFS events had occurred at the time of database lock: 318 events (72.1%) in the pemetrexed arm and 186 events (83.8%) in the placebo arm the PFS analysis. Median PFS was 4.27 months in the pemetrexed arm and 2.60 months in the placebo arm (HR = 0.50; 95% confidence interval [CI]: 0.42 to 0.61; $p < 0.00001$). (Table 3, Figure 1).

Overall survival A total of 300 OS events had occurred at the time of database lock: 191 events (43.3%) in the pemetrexed arm and 109 events (49.1%) in the placebo arm the OS analysis. Median OS was 13.01 months in the pemetrexed arm and 10.18 months in the placebo arm (HR = 0.80; 95% confidence interval [CI]: 0.63 to 1.01; $p = 0.05898$, p-value>0.00001 allocated for the interim analysis). (Table 4, Figure 2).

2 Introduction

2.1 Overview

Pemetrexed (ALIMTA®; LY231514) is an antifolate antimetabolite. Pemetrexed (as a single agent) received an accelerated approval for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004 based on the randomized study JMEI comparing pemetrexed monotherapy with docetaxel in 571 patients (Please see the statistical review for

this study by Dr. Yongcheng Wang, dated August 11, 2004). As a condition of this approval, as per Subpart H, further studies (JMDB and JMEN) were required to confirm and describe the clinical benefit of pemetrexed.

2.1.1 Background

Study JMDB was a multicenter, randomized, Phase III trial comparing the efficacy and safety of Alimta + cisplatin (AC) with that of gemcitabine + cisplatin (GC) in patients with a diagnosis of locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer. First patient was enrolled on July 6, 2004 and the database was locked on January 25, 2007. In August 2007, the sponsor submitted the results from Study JMDB. Please see the statistical review for this study by Dr. Fanhui Kong, dated June 11, 2008.

When the sponsor submitted Study JMDB, study JMEN was on going. Study JMEN was a Phase III trial comparing the efficacy and safety of pemetrexed + best supportive care versus best supportive care as a maintenance treatment for advanced NSCLC.

Results from previous randomized, Phase 3 studies in advanced NSCLC (Study JMEI and Study JMDB) indicated strong evidence of histology-by-treatment interactions for pemetrexed. These interactions indicated that for patients treated with pemetrexed, those with nonsquamous histology (adenocarcinoma, large cell carcinoma, and other or unknown histology) tend to have better survival and PFS compared to patients with squamous histology. Patients with squamous-cell NSCLC had worse survival with Alimta compared to control arm.

On June 23, 2008 FDA requested the final study report for Study JMEN be submitted as an amendment to the pending 1st line application. The sponsor submitted the report on June 24, 2008 without datasets. Therefore, this reviewer will only review the submitted analyses without confirming the results.

2.1.2 Statistical Issues

Pemetrexed (as a single agent) received an accelerated approval for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004 based on the randomized study JMEI comparing pemetrexed monotherapy with docetaxel. As a condition of this approval, as per Subpart H, further studies (JMDB and JMEN) were required to confirm and describe the clinical benefit of pemetrexed. In this submission, the sponsor provided a study report for JMEN with datasets.

Statistical Issues:

1. In February 2007, the primary objective for this study was changed from overall survival (OS) to progression-free survival (PFS). On 12 June 2007, the following comments were conveyed to the sponsor:

   As indicated in the FDA End of Phase 2 (EOP2) meeting minutes and the January 11, 2007 meeting minutes, survival should be the primary efficacy endpoint.

   In general a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision.

2. The database "lock" for the final analysis of PFS (after a minimum of 462 PFS events) occurred on 21 November 2007. Data analyses of this database included the preliminary analysis of OS and the final analyses of all other endpoints. The database lock for the final analysis of OS (after a minimum of 475 OS events) is expected to occur in approximately 1 year.

3. The preliminary analysis of OS presented here included a total of 300 events, so that most patients were censored (56.7% of patients in the pemetrexed arm and 50.9% in the placebo arm). According to the statistical gatekeeping and alpha-spending scheme presented in the protocol, the significance level for this preliminary analysis was a one-sided alpha of 0.00001, leaving a nominal level of 0.02499 to be spent for the final analysis of OS, which will take place when 475 events have occurred.

4. Results from previous randomized, Phase 3 studies in advanced NSCLC (Study JMEI and Study JMDB) indicated that for patients treated with pemetrexed, those with squamous cell histology had inferior survival and those with nonsquamous histology (adenocarcinoma, large cell carcinoma, and other or unknown histology) tend to have better overall survival and progression-free survival compared to patients with squamous histology. In the JMEN study report, the sponsor also performed analyses for such interactions. Patients with squamous-cell NSCLC had worse survival with Alimta compared to control arm. Although the analyses of JMEN showed a trend toward the same interaction as Study JMEI and Study JMDB did, the p-values from interaction and subgroup analyses were not interpretable because no alpha (type-I error) was allocated for the interaction test or any subgroup analyses in the statistical analysis plan for Study JMEN. The OS results should also be interpreted with caution since the submitted OS results were from an interim analysis with a total of 300 deaths.

2.2 Data Sources

No datasets for this study were submitted.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

This study was conducted at 83 study centers in 20 countries. First patient was enrolled on 04 March 2005. Last patient completed the study on 17 August 2007.

3.1.1 Study Design

This was a global, multicenter, randomized, double-blind, placebo-controlled study. The plan was to enroll approximately 660 patients in this study; eligible patients had a response of CR, PR, or SD following 4 cycles of induction therapy. Eligible patients were randomized to the experimental study arm (pemetrexed plus BSC) or the control arm (placebo plus BSC) following induction therapy. The placebo consisted of normal saline (0.9% sodium chloride), which also served as the diluent for pemetrexed. According to the protocol, patients in both study arms were required to receive folic acid and vitamin B_{12} supplementation and dexamethasone.

Patients were randomized (in a 2:1 ratio) to receive maintenance treatment with pemetrexed plus BSC or placebo plus BSC. A minimization principle, introduced by Pocock and Simon (1975), was adopted to balance patient assignment between study arms, based on the following factors:

- disease stage prior to administration of induction therapy (IIIB versus IV)
- ECOG performance status just prior to randomization (0 versus 1)
- best tumor response to induction chemotherapy (CR/PR versus SD)
- gender (male versus female)
- previously treated brain metastases (yes versus no)
- nonplatinum component of induction chemotherapy (gemcitabine versus paclitaxel versus docetaxel).

Each patient underwent a treatment period and a follow-up period. The treatment period consisted of treatment cycles, each 21 days long. Patients received treatment (experimental or control) until objective disease progression. The follow-up period began when the patient discontinued study treatment; follow-up included periodic tumor response evaluation until objective disease progression. Investigators followed all patients until death or study closure.

3.1.2 Study Objectives

The primary objective was to compare maintenance therapy with pemetrexed plus BSC versus placebo plus BSC, in terms of objective progression-free survival time (PFS) in patients with Stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or Stage IV NSCLC who had not progressed during 4 cycles of platinum-based induction chemotherapy.

3.1.3 Efficacy Endpoints

Objective progression-free survival (PFS) was the primary efficacy variable in this study. Objective PFS was measured from the date of randomization (after completion of induction chemotherapy) to the first date of objective progression of disease or of death from any cause. For each patient who was not known to have died or to have had objective progression of disease as of the data-inclusion cutoff date for the analysis, PFS was censored at the date of the patient's last tumor assessment prior to that cutoff date.

The secondary endpoints of the study included: overall survival time (OS), time to objective progressive disease (TPD), time to worsening of symptoms (TWS), objective tumor response rate, adverse events, changes in individual symptom scores and quality of life using the Lung Cancer Symptom Scale (LCSS).

3.1.4 Sample Size Considerations

The study was designed to randomize approximately 660 patients at a 2:1 ratio between 2 maintenance study arms: (a) pemetrexed 500 mg/m2 plus BSC administered until disease progression (approximately 440 patients), or (b) a treatment option utilizing placebo plus BSC until disease progression (approximately 220 patients). The Sponsor originally selected this sample size to provide a final analysis of OS with 80% power using a one-sided alpha level of 0.025, assuming 475 events and an OS HR of 0.767. The implemented protocol Amendment (a) changed the primary endpoint of this trial to PFS while maintaining nearly identical statistical assumptions and error control of the originally planned final analysis of OS.

Assuming the true value of the PFS HR was 0.75, there was an 85% probability of rejecting the null hypothesis H_0. The final PFS would required at least 462 PFS events included in the primary analysis.

At the time of PFS analysis (after a minimum of 462 PFS events). The number of OS events had not yet reached the 475 events required for a final analysis of OS; therefore, the analysis of OS was preliminary. According to the protocol, in order

to maintain an overall one-sided alpha error probability of 0.025 (for the PFS and OS analyses), the study applied the following statistical gatekeeping and alpha-spending scheme:

- First, the primary statistical test of PFS was performed using a nominal one-sided alpha level of 0.025.

- Second, a one-sided alpha level of 0.025 was split between the preliminary and final analyses of OS: a nominal one-sided level of 0.00001 was spent for the preliminary analysis of OS, leaving a nominal level of 0.02499 to be spent for the final analysis of OS.

Reviewer's Comments:

In February 2007, the primary objective for this study was changed from overall survival (OS) to progression-free survival (PFS). On 12 June 2007, the following comments were conveyed to the sponsor:

As indicated in the FDA End of Phase 2 (EOP2) meeting minutes and the January 11, 2007 meeting minutes, survival should be the primary efficacy endpoint.

In general a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision.

The database "lock" for the final analysis of PFS (after a minimum of 462 PFS events) occurred on 21 November 2007. Data analyses of this database included the preliminary analysis of OS and the final analyses of all other endpoints. The database lock for the final analysis of OS (after a minimum of 475 OS events) is expected to occur in approximately 1 year.

3.1.5 Efficacy Analysis Methods

For PFS and OS endpoints, the analyses estimated HRs using Cox proportional hazards models with assigned treatment as the only covariate and compared study arms. If the 95% confidence interval for the PFS HR was found to fall entirely below the margin of 1.00, the null hypothesis would be rejected at a nominal one-sided 0.025 significance level.

In addition, the Kaplan-Meier method was used to estimate medians for each study group. Log-rank test was also used for the comparison between study arms.

3.1.6 Sponsor's Results and Statistical Reviewer's Findings/ Comments

On June 23, 2008 FDA requested the final study report for Study JMEN be submitted as an amendment to the pending 1st line application in order to confirm lack of efficacy in squamous-cell NSCLC and efficacy in the non-squamous NSCLC. The sponsor submitted the report on June 24, 2008 with datasets. Therefore, this reviewer will review the submitted analyses submitted without confirming the results.

The Sponsor locked the final reporting database on 21 November 2007. The reporting database included data from all 741 patients who signed the informed consent document (ICD) and entered the study. Of the 741 consented patients, 663 (89.5%) underwent 2:1 randomization to study arms (pemetrexed arm N = 441; placebo arm N = 222). A total of 653 patients (98.5%) received study treatment consisting of at least 1 dose of pemetrexed or placebo. Summaries and comparative analyses of efficacy data included all 663 randomized patients.

3.1.6.1 Baseline Characteristics

Efficacy analyses were performed on data from the Intent-to-Treat Population. The Intent-to-Treat Population included 441 subjects in the pemetrexed group and 222 subjects in the placebo group (Tables 1, 2).

Table 1. Demographics Characteristics

	Variable	Pemetrexed N = 441	Placebo N = 222	Total N = 663
Gender n (%)	Male	322 (73.0)	161 (72.5)	483 (72.9)
	Female	119 (27.0)	61 (27.5)	180 (27.1)
Age at randomization (years)	Median age (25th-75th percentile)	60.6 (54.3-67.5)	60.4 (53.8-67.0)	60.6 (54.1-67.4)
Age group n (%)	Age < 65 years	294 (66.7)	149 (67.1)	443 (66.8)
	Age ≥ 65 years	147 (33.3)	73 (32.9)	220 (33.2)
Origin n (%)	Aboriginal	0 (0.0)	1 (0.5)	1 (0.2)
	African	6 (1.4)	0 (0.0)	6 (0.9)
	Caucasian	279 (63.3)	149 (67.1)	428 (64.6)
	East Asian	104 (23.6)	50 (22.5)	154 (23.2)
	Hispanic	13 (2.9)	6 (2.7)	19 (2.9)
	West Asian[a]	39 (8.8)	16 (7.2)	55 (8.3)
Smoking status n (%)	Ever smoker	324 (73.5)	158 (71.2)	482 (72.7)
	Never smoker	113 (25.6)	63 (28.4)	176 (26.5)

Abbreviations: N = number of randomized patients; n = number of patients in category.

[a] West Asian refers to patients originating from the Indian subcontinent.

Source: FQBDCA11.

Table JMEN.11.1. in the sponsor's report

Table 2 Histologic Classifications by Study Arm
All Randomized Patients in Study JMEN

Histologic Classifications[a]	Lilly Assigned System Codes	Pemetrexed N = 441	Placebo N = 222	Total N = 663
Nonsquamous Histology[b]		326 (73.9)	156 (70.3)	482 (72.7)
Adenocarcinoma		223 (50.6)	106 (47.7)	329 (49.6)
Bronchioalveolar carcinoma	2140	7 (1.6)	3 (1.4)	10 (1.5)
Adenocarcinoma	1882	216 (49.0)	103 (46.4)	319 (48.1)
Large Cell Carcinoma	920	11 (2.5)	9 (4.1)	20 (3.0)
Other[c] or Indeterminate		92 (20.9)	41 (18.5)	133 (20.1)
NSCLC	1897	65 (14.7)	30 (13.5)	95 (14.3)
Poorly differentiated NSCLC	1432	25 (5.7)	11 (5.0)	36 (5.4)
Mixed cell carcinoma, lung	1883	1 (0.2)	0	1 (0.2)
Other	99	1 (0.2)	0	1 (0.2)
Squamous Cell Carcinoma	1884	115 (26.1)	66 (29.7)	181 (27.3)

Abbreviations: N = number of randomized patients; NSCLC = non-small cell lung cancer.

[a] Grouped by WHO classification of lung tumors (Travis et al. 1999).

[b] Nonsquamous histology includes adenocarcinoma, large cell, and other histologies.

[c] The subcategory of "Other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma. Patient 100-1003 had squamous cell carcinoma of the trachea.

Sources: Histo-freq, JMEN Case Report Form Visit 0, page 3 (Appendix 16.1.2).

Table JMEN.11.3. in the sponsor's report

Reviewer's Comments:

There were no apparent differences between two study arms with regard to demographic and baseline characteristics in the ITT population. Approximately 32% of the patients entered were Asians.

3.1.6.2 Primary Efficacy Analyses

Objective PFS A total of 504 PFS events had occurred at the time of database lock: 318 events (72.1%) in the pemetrexed arm and 186 events (83.8%) in the placebo arm the PFS analysis. Median PFS was 4.27 months in the pemetrexed arm and 2.60 months in the placebo arm (HR = 0.50; 95% confidence interval [CI]: 0.42 to 0.61; $p < 0.00001$). (Table 3, Figure 1).

Table 3. Summary of Objective Progression-Free Survival
All Randomized Patients in Study JMEN

	PFS[a] (N = 663)	
	Pemetrexed N = 441	**Placebo N = 222**
Number (%) of events	318 (72.1)	186 (83.8)
Number (%) censored	123 (27.9)	36 (16.2)
25th percentile (95% CI)	2.10 (1.54 - 2.66)	1.38 (1.35 - 1.41)
Median PFS - months (95% CI)	**4.27** (4.07 - 4.73)	**2.60** (1.68 - 2.83)
75th percentile (95% CI)	8.38 (7.39 - 9.46)	4.21 (3.84 - 4.57)
Rate of patient with PFS of at least:		
3 months (95% CI)	0.62 (0.57 - 0.67)	0.37 (0.30 - 0.44)
6 months (95% CI)	0.38 (0.33 - 0.43)	0.12 (0.07 - 0.17)
9 months (95% CI)	0.22 (0.17 - 0.26)	0.05 (0.02 - 0.09)
12 months (95% CI)	0.15 (0.11 - 0.19)	0.03 (0 - 0.06)
Hazard ratio[b]	0.50	
95% CI for hazard ratio	0.42 - 0.61	
Log rank p-value	< 0.00001	

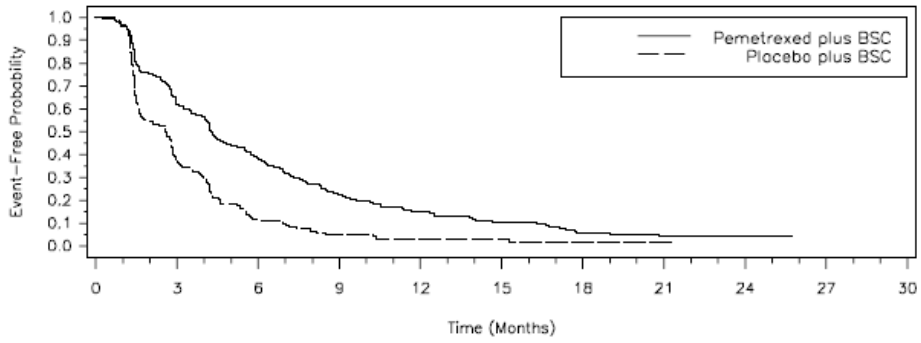
Abbreviations: CI = confidence interval; HR = hazard ratio; N = number of patients; PFS = progression-free survival.

[a] Investigator-assessed data.

[b] Unadjusted HR and p-values from Cox model with treatment as the only cofactor. HR < 1.0 favors pemetrexed study arm, HR > 1.0 favors comparator.

Source: SMPFSA11.

Table JMEN.11.8. in the sponsor's report



Pemetrexed pts at risk:	441	229	122	62	33	20	9	5	1	0	0
Placebo pts at risk:	222	70	19	6	3	2	1	1	0	0	0

Figure 1. Objective PFS in the ITT Population
(Source: Figure JMEN.11.1. Kaplan-Meier graph, Study JMEN)

3.1.6.3 Secondary Efficacy Analyses

Overall survival A total of 300 OS events had occurred at the time of database lock: 191 events (43.3%) in the pemetrexed arm and 109 events (49.1%) in the placebo arm the OS analysis. Median OS was 13.01 months in the pemetrexed arm and 10.18 months in the placebo arm (HR = 0.80; 95% confidence interval [CI]: 0.63 to 1.01; p =0.05898, >0.00001 allocated for the interim analysis). (Table 4, Figure 2).

Table 4. Summary of Preliminary Overall Survival
All Randomized Patients in Study JMEN

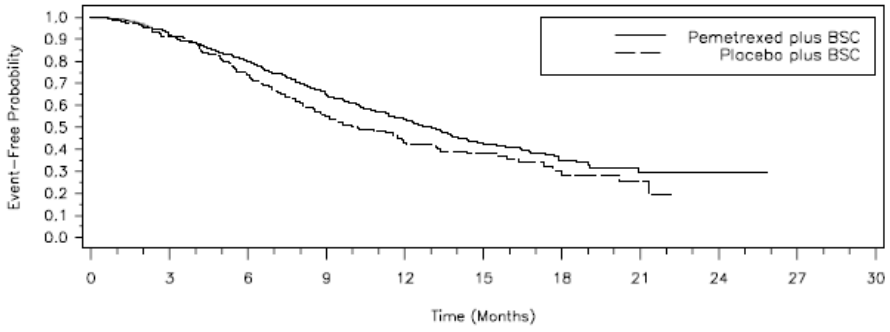
	Pemetrexed N = 441	**Placebo N = 222**
Number (%) of events	191 (43.3)	109 (49.1)
Number (%) censored	250 (56.7)	113 (50.9)
25th percentile (95% CI)	6.90 (6.21 - 8.02)	5.91 (5.03 - 6.87)
Median OS - months (95% CI)	13.01 (11.40 - 14.42)	10.18 (8.57 - 13.17)
75th percentile (95% CI)	-	21.32 (17.28 -)
Rate of patient with survival of at least:		
3 months (95% CI)	0.92 (0.89 - 0.94)	0.92 (0.88 - 0.95)
6 months (95% CI)	0.80 (0.76 - 0.84)	0.74 (0.67 - 0.80)
9 months (95% CI)	0.65 (0.60 - 0.70)	0.55 (0.47 - 0.62)
12 months (95% CI)	0.54 (0.48 - 0.59)	0.43 (0.35 - 0.51)
Hazard ratio[a]	0.80	
95% CI for hazard ratio	(0.63 – 1.01)	
Log rank p-Value	0.05898	

Abbreviations: CI = confidence interval; HR = hazard ratio; N = number of patients; OS = overall survival.

[a] Unadjusted HR and p-values from Cox model with treatment as the only cofactor. HR < 1.0 favors pemetrexed study arm, HR > 1.0 favors comparator.

Source: SMPOSA11.

Table JMEN.11.14 in the sponsor's report



Pemetrexed pts at risk:	441	368	273	190	120	70	38	15	3	0	0
Placebo pts at risk:	222	184	130	78	48	32	15	5	0	0	0

Program Location : CABINETS\SPREE\RMP\Clinical\Oncology\Alimta\NSCLC\H3E-MC-JMEN\CSR\PROGRAMS\KMPOSA1.sas
Output Location : CABINETS\SPREE\RMP\Clinical\Oncology\Alimta\NSCLC\H3E-MC-JMEN\CSR\OUTPUTS\KMPOSA11
Data Set Location : RMP_SAS.H3ES_L_MCJMEN.ADS.INTRM1

Abbreviations: BSC = best supportive care; pts = patients.

Figure 2. Overall Survival in the ITT Population
(Source: Figure JMEN.11.4. Kaplan-Meier graph Study JMEN)

Reviewer's Comments:

The preliminary analysis of OS presented here included a total of 300 events, so that most patients were censored (56.7% of patients in the pemetrexed arm and 50.9% in the placebo arm). According to the statistical gatekeeping and alpha-spending scheme presented in the protocol, the significance level for this preliminary analysis was a one-sided alpha of 0.00001, leaving a nominal level of 0.02499 to be spent for the final analysis of OS, which will take place when 475 events have occurred.

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

This section will focus on PFS analyses by gender, age, and race (Table 5).

Table 5. Summary of Progression-Free Survival by Age, Gender, and Origin All Randomized Patients Study JMEN

	Median PFS (months)		
	Pemetrexed	Placebo	HR (95% CI)
Subgroups	N = 441	N = 222	p-Value
Age			
< 65	**4.21**	**1.68**	0.49 (0.39-0.61)
	n=294	n=149	< 0.00001
≥ 65	**4.99**	**2.83**	0.52 (0.37-0.73)
	n=147	n=73	0.00014
Gender			
Female	**4.44**	**2.79**	0.51 (0.36-0.73)
	n=119	n=61	0.00017
Male	**4.21**	**2.60**	0.49 (0.39-0.61)
	n=322	n=161	< 0.00001
Origin			
Caucasian	**4.30**	**2.63**	0.52 (0.41-0.65)
	n=279	n=149	< 0.00001
East Asian	**4.21**	**1.71**	0.48 (0.33-0.69)
	n=104	n=50	0.00011
Hispanic	**2.37**	**4.60**	1.08 (0.28-4.20)
	n=13	n=6	0.91258
West Asian[a]	**4.44**	**2.10**	0.35 0.17-0.70)
	n=39	n=16	0.00311

Abbreviations: CI = confidence interval; HR = hazard radio; N = number of randomized patients; n = number of patients in category; PFS = progression-free survival.

[a] Indian subcontinent.

Note: Bold text indicates a statistically significant difference between study arms.

Sources: SMPFSA1Q, SMPFSA1R, SMPFSA1S.

Source: Table JMEN.11.13 in the sponsor's report.

4.2 Histologic Subgroups

Results from previous randomized, Phase 3 studies in advanced NSCLC (Study JMEI and Study JMDB) indicated strong evidence of histology-by-treatment interactions for pemetrexed. These interactions indicated that for patients treated with pemetrexed, those with nonsquamous histology (adenocarcinoma, large cell carcinoma, and other or unknown histology) tend to have better survival and PFS compared to patients with squamous histology. Histologic subgroup results for PFS and OS for Study JMEN are presented in Table 6.

For the combined nonsquamous population, median PFS was 4.50 months in the pemetrexed arm and 2.60 months in the placebo arm (HR = 0.44; 95% confidence interval [CI]: 0.36 to 0.55). (Table 4, Figure 1). Median OS was 14.36 months in

the pemetrexed arm and 9.43 months in the placebo arm (HR = 0.66; 95% confidence interval [CI]: 0.49 to 0.88).

For the squamous population, median PFS was 2.79 months in the pemetrexed arm and 2.60 months in the placebo arm (HR = 0.69; 95% confidence interval [CI]: 0.49 to 0.98). (Table 4, Figure 1). Median OS was 9.63 months in the pemetrexed arm and 11.86 months in the placebo arm (HR = 1.28; 95% confidence interval [CI]: 0.85 to 1.93).

The results from the histologic subgroups were consistent with the results from Study JMEI and Study JMDB.

Table 6. Progression-Free Survival and Overall Survival by Histologic Subgroups All Randomized Patients Study JMEN

	Final PFS		Preliminary OS	
	Pemetrexed (N = 441) median mos	Placebo (N = 222) median mos	Pemetrexed (N = 441) median mos	Placebo (N = 222) median mos
Histologic Subgroup	HR (95% CI) p-Value		HR (95% CI) p-Value	
Nonsquamous (n = 482)	4.50	2.60	14.36	9.43
	0.44 (0.36-0.55)		0.66 (0.49-0.88)	
	< 0.00001		0.005	
Adenocarcinoma (n = 329)	4.73	2.60	16.39	11.73
	0.45 (0.35-0.59)		0.73 (0.50-1.05)	
	< 0.00001		0.091	
Large Cell (n = 20)	3.48	2.09	9.13	5.45
	0.40 (0.13-1.22)		0.42 (0.13-1.38)	
	0.109		0.154	
Other/Indeterminate (n = 133)	4.21	2.79	11.27	7.03
	0.43 (0.28-0.670)		0.47 (0.28-0.80)	
	0.0002		0.005	
Squamous (n = 181)	2.79	2.60	9.63	11.86
	0.69 (0.49-0.98)		1.28 (0.85-1.93)	
	0.039		0.231	

Abbreviations: CI = confidence interval; HR = hazard ratio; mos = months; N = number of randomized patients; n = number of patients in category; OS = overall survival; PFS = progression-free survival.
Sources: SMPFSA12, SMPFSA13, SMPFSA14, SMPFSA15, SMPFSA17, SMPOSA12, SMPOSA13, SMPOSA14, SMPOSA15, SMPOSA17.

Source: Table JMEN. 11.20 in the sponsor's report.

Reviewer's Comments:

The subgroup analyses by age, gender, and race showed that the effect of pemetrexed on PFS was consistent cross the subgroups, except for Hispanic patients. However, the HR for Hispanic patients was not robust due to a small sample size.

The sponsor also used Cox models to test histology-by-treatment interaction. The models also included cofactors potentially prognostic for PFS and OS. The tests for interaction were stratified by the nonplatinum component of induction therapy (gemcitabine versus paclitaxel/docetaxel) and included terms for treatment (pemetrexed versus placebo), squamous histology (no versus yes), treatment-bysquamous interaction (nonsquamous pemetrexed versus all other patients), ECOG performances status (0 versus 1), induction response (CR/PR versus SD), East Asian ethnicity (yes versus no), smoking status (never versus ever), gender (female versus male), and age (< 65 versus ≥ 65). The results showed that p-value for interaction for PFS was 0.036 (interaction HR = 0.65) and 0.011 for OS (interaction HR = 0.52).

In February 2007, the primary objective for Study JMEN was changed from OS to PFS. The submitted JMEN study report included the final PFS analysis and an interim analysis for OS. As indicated in the FDA End of Phase 2 (EOP2) meeting minutes and the January 11, 2007 meeting minutes, survival should be the primary efficacy endpoint.

Results from previous randomized, Phase 3 studies in advanced NSCLC (Study JMEI and Study JMDB) indicated that for patients treated with pemetrexed, those with nonsquamous histology (adenocarcinoma, large cell carcinoma, and other or unknown histology) tend to have better overall survival and progression-free survival compared to patients with squamous histology. In the JMEN study report, the sponsor also performed analyses for such interactions. Although the analyses of JMEN showed a trend toward the same interaction as Study JMEI and Study JMDB did, the p-values from interaction and subgroup analyses were not interpretable because no alpha (type-I error) was allocated for the interaction test or any subgroup analyses in the statistical analysis plan for Study JMEN. The OS results should also be interpreted with caution since the submitted OS results were from an interim analysis with a total of 300 deaths.

Nevertheless, the sponsor analyses of JMEN showed a trend toward the same interactions for OS and PFS as Study JMEI and Study JMDB did.

5 Summary and Conclusions

Pemetrexed (as a single agent) received an accelerated approval for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004 based on the randomized study JMEI comparing pemetrexed monotherapy with docetaxel. As a condition of this approval, as per Subpart H, further studies (JMDB and JMEN) were required to confirm and describe the clinical benefit of pemetrexed.

On June 23, 2008 FDA requested the final study report for Study JMEN be submitted as an amendment to the pending 1st line application. The sponsor submitted the report on June 24, 2008 with datasets. Therefore, this reviewer will review the submitted analyses without confirming the results.

5.1 Statistical Issues and Collective Evidence

1. In February 2007, the primary objective for this study was changed from overall survival (OS) to progression-free survival (PFS). On 12 June 2007, the following comments were conveyed to the sponsor:

   As indicated in the FDA End of Phase 2 (EOP2) meeting minutes and the January 11, 2007 meeting minutes, survival should be the primary efficacy endpoint.

   In general a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision.

2. The database "lock" for the final analysis of PFS (after a minimum of 462 PFS events) occurred on 21 November 2007. Data analyses of this database included the preliminary analysis of OS and the final analyses of all other endpoints. The database lock for the final analysis of OS (after a minimum of 475 OS events) is expected to occur in approximately 1 year.

3. The preliminary analysis of OS presented here included a total of 300 events, so that most patients were censored (56.7% of patients in the pemetrexed arm and 50.9% in the placebo arm). According to the statistical gatekeeping and alpha-spending scheme presented in the protocol, the significance level for this preliminary analysis was a one-sided alpha of 0.00001, leaving a nominal level of 0.02499 to be spent for the final analysis of OS, which will take place when 475 events have occurred.

4. Results from previous randomized, Phase 3 studies in advanced NSCLC (Study JMEI and Study JMDB) indicated that for patients treated with pemetrexed, those with squamous cell histology had inferior survival and those with nonsquamous histology (adenocarcinoma, large cell carcinoma, and other or unknown histology) tend to have better overall survival and progression-free survival compared to patients with squamous histology. In the JMEN study report, the sponsor also performed analyses for such interactions. Patients with squamous-cell NSCLC had worse survival with Alimta compared to control arm. Although the analyses of JMEN showed a trend toward the same interaction as Study JMEI and Study JMDB did, the p-values from interaction and subgroup analyses were not interpretable because no alpha (type-I error) was allocated for the interaction test or any subgroup analyses in the statistical analysis plan for Study JMEN. The OS results should also be interpreted with caution since the submitted OS results were from an interim analysis with a total of 300 deaths.

5.2 Conclusions and Recommendations

Pemetrexed (as a single agent) received an accelerated approval for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004 based on the randomized study JMEI comparing pemetrexed monotherapy with docetaxel. As a condition of this approval, as per Subpart H, further studies (JMDB and JMEN) were required to confirm and describe the clinical benefit of pemetrexed.

Study JMDB was a multicenter, randomized, Phase III trial comparing the efficacy and safety of Alimta + cisplatin (AC) with that of gemcitabine + cisplatin (GC) in patients with a diagnosis of locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer. First patient was enrolled on July 6, 2004 and the database was locked on January 25, 2007. In August 2007, the sponsor submitted the study JMDB.

When the sponsor submitted Study JMDB, study JMEN was on going. Study JMEN was a Phase III trial comparing the efficacy and safety of pemetrexed + best supportive care versus best supportive care as a maintenance treatment for advanced NSCLC.

On June 23, 2008 FDA requested the final study report for Study JMEN be submitted as an amendment to the pending 1st line application. The sponsor submitted the report on June 24, 2008 with datasets. Therefore, this reviewer will review the submitted analyses submitted without confirming the results.

In February 2007, the primary objective for Study JMEN was changed from OS to PFS. The submitted JMEN study report included the final PFS analysis and an

interim analysis for OS. As indicated in the FDA End of Phase 2 (EOP2) meeting minutes and the January 11, 2007 meeting minutes, survival should be the primary efficacy endpoint.

Results from previous randomized, Phase 3 studies in advanced NSCLC (Study JMEI and Study JMDB) indicated that for patients treated with pemetrexed, those with squamous cell NSCLC had worse survival compared to control arm and those with nonsquamous histology (adenocarcinoma, large cell carcinoma, and other or unknown histology) tend to have better overall survival and progression-free survival compared to patients with squamous histology. In the JMEN study report, the sponsor also performed analyses for such interactions. Although the analyses of JMEN showed a trend toward the same interaction as Study JMEI and Study JMDB did, the p-values from interaction and subgroup analyses were not interpretable because no alpha (type-I error) was allocated for the interaction test or any subgroup analyses in the statistical analysis plan for Study JMEN. The OS results should also be interpreted with caution since the submitted OS results were from an interim analysis with a total of 300 deaths.

Nevertheless, the sponsor analyses of JMEN appear to show a trend toward the same interactions for OS and PFS as Study JMEI and Study JMDB did.

SIGNATURES/DISTRIBUTION LIST

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-462
Drug Name:	Alimta (Pemetrexed)
Indication(s):	Non-Small Cell Lung Cancer
Applicant:	Lilly Research Laboratory
Date(s):	August 27, 2007
Review Priority:	Regular
Biometrics Division:	Biometrics V (HFD-710)
Statistical Reviewer:	Fanhui Kong
Concurring Reviewers:	Rajeshwari Sridhara
Medical Division:	Division of Oncology Products
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Project Manager:	Carl Huntley

Keywords: Meta-analysis, Non-inferiority analysis, Cox proportional hazard model, Kaplan-Meier estimate, percent retention analysis

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this submission, the sponsor submitted a Phase IV commitment Study JMDB as a part of requirement for the accelerated approval of pemetrexed (Alimta) as a single agent for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004. This is a multicenter, randomized, Phase III trial study to compare the efficacy and safety of pemetrexed in combination with cisplatin (AC) with that of gemcitabine in combination with cisplatin (GC) in patients with locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer. In this study, the primary efficacy measure was the overall survival. The non-inferiority analysis of the treatment efficacy was conducted using Cox proportional hazards model. The survival distribution was displayed using Kaplan-Meier estimator. The percent retention analysis was also conducted to support the efficacy results.

Although the statistical analyses suggested that the AC treatment arm was non-inferior to the GC treatment arm in the reduction of the risk of death in patients with locally advanced or metastatic NSCLC, such a statement seems to be problematic. First, the active control effect size was not well established; second, the non-inferiority margin was not well established; third, there were 50% post-discontinuation therapy and the statistically significant post-discontinuation crossover therapy; finally, there was a statistically significant interaction between treatment arm and patient histology categories. These factors together compromised the statistical findings of this non-inferiority study and greatly reduced the credibility of the findings of the statistical analyses. This also makes the non-inferiority results hard to interpret. From a statistical perspective the data and analyses do not support the sponsor's non-inferiority claim for Alimta in the treatment of patients with locally advanced or metastatic NSCLC who have not received prior chemotherapy.

1.2 Brief Overview of Clinical Studies

Pemetrexed (ALIMTA®; LY231514) is an antifolate antimetabolite. AC is indicated for the treatment of patients with malignant pleural mesothelioma (MPM) whose disease is either unresectable or who are otherwise not candidates for curative surgery. Pemetrexed received regular approval for this indication by the FDA on February 4, 2004. Pemetrexed (as a single agent) received an accelerated approval for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy on August 19, 2004. As a condition of this approval, as per Subpart H, further studies (JMDB and JMEN) were required to confirm and describe the clinical benefit of pemetrexed.

In this submission, the sponsor submitted a pivotal Study JMDB. This is a multicenter, randomized, Phase III trial comparing the efficacy and safety of AC with that of GC in patients with a diagnosis of locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer.

At the same time, the sponsor submitted two supportive studies JMAY and JMBZ. These are Phase II single arm studies assessing the efficacy and safety of AC in patients with a diagnosis of locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy.

According the requirements described in 21 CFR 314.510, the results of Study JMDB are submitted herein as an sNDA in fulfillment of the Phase IV commitment. The sponsor is seeking the following indication:

> *Pemetrexed in combination with cisplatin therapy is indicated for the initial treatment of patients with locally advanced or metastatic non-small cell lung cancer and as a single-agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.*

1.3 Statistical Issues and Findings

The primary noninferiority efficacy in Study JMDB results per sponsor suggest that the risk of death in the AC arm was from 16% lower than that in the GC arm to 5% higher than that in the GC arm, with the entire confidence interval for HR below the pre-specified, fixed 1.17645 noninferiority margin. The sponsor claims that by applying the Rothmann method, AC was estimated to retain 120% of GC's survival benefit over C (95% CI: 83% to 190%). The one-sided statistical test of whether AC retained at least 50% of GC's survival benefit over C was statistically significant (p=0.005).

Furthermore, the sponsor's Cox model analysis on OS with interaction between treatment arm and histology indicates that there was a highly significant treatment-by-histology interaction. The results suggest that AC has better survival compared to GC in patients with adenocarcinoma and large cell lung cancer and it has worse survival compared to GC in patients with squamous cell carcinoma.

The statistical reviewer has the following concerns:

1. In IND and pre-NDA meetings with the sponsor, the agency made it clear that the fixed margin of 15% was not acceptable due to the factor that the determination of the margin was arbitrary and there were no historical studies to support the effect size estimation of the active control for the current study.

2. The efficacy results of GC in the Sandler study with a 28-day regimen cannot be directly used in the non-inferiority Study JMDB with a 21-day GC regimen schedule. The treatment effect of the active control (GC) in the comparison of cisplatin in 21-day GC regimen schedule was not well established. Therefore the retention analysis is questionable and can only be considered as exploratory.

3. Due to the fact that almost 50% of the patients received post-discontinuation therapy and the crossovers of both treatments were statistically significant, the actual efficacy effect of the treatments could have been compromised, which makes the non-inferiority study hard to interpret.

4. There was a statistically significant interaction between treatment arm and patient histology categories. Such an interaction makes it difficult to interpret the noninferiority efficacy results of the treatment. On the other hand, the analysis result suggests a potential treatment benefit only limited to the patients with nonsquamous cell carcinoma, while in squamous cell carcinoma, GC was superior to AC in the treatment of patients with locally advanced or metastatic NSCLC. The benefit of Alimta in adenocarcinoma subgroup was not observed in the retrospective analysis of data from another study (JMEI) of Alimta versus docetaxel in the second-line treatment of advanced NSCLC.

2. INTRODUCTION

2.1 Study Design

Study JMDB was a randomized, multicenter, open-label, Phase 3 study using a noninferiority design to assess the efficacy of AC compared to GC for the initial treatment of patients with locally advanced or metastatic NSCLC. The primary objective was to compare the overall survival (OS) of patients treated with AC to that of patients treated with GC. The secondary objectives include the comparisons of the following time-to-event efficacy variables between treatment arms: progression-free survival (PFS); time-to-progressive disease (TtPD); duration of response (DoR); time-to-treatment failure (TtTF), along with objective tumor response; quantitative and qualitative laboratory and nonlaboratory toxicities and risk/benefit (toxicities relative to survival). Folic acid, vitamin B12, and dexamethasone pretreatment supplementation were included in both treatment arms at the same dose and schedule, see Figure 2.1. The planned enrollment was for approximately 1700 patients.

Patients were randomized with 1:1 ratio between the experimental treatment arm (AC) and the active control arm (GC). Following an initial randomization based on whether the investigative center was participating in the companion biomarker study (yes versus no), randomization was adjusted for baseline factors, including investigative site, disease stage (IIIB versus IV), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), history of brain metastases (yes versus no), sex (male versus female), and basis for initial pathological diagnosis (histological versus cytological).

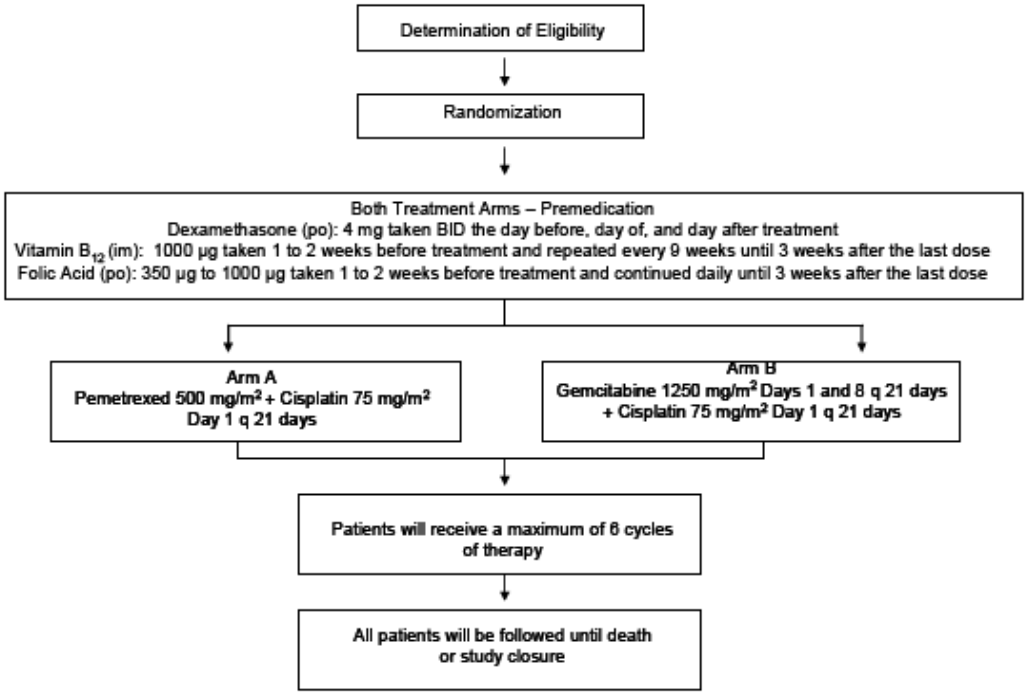
Each patient underwent a treatment period and a follow-up period. The planned treatment period consisted of up to 6 cycles of assigned treatment, and cycles were 21 days in length. The follow-up period included periodic tumor response evaluations until disease progression and follow up for all patients until death or study closure.

The dose of AC was pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on Day 1 every 21 days. The 21-day regimen of GC was the control. The dose of GC was gemcitabine 1250 mg/m^2 on Day 1 and Day 8 plus cisplatin 75 mg/m^2 on Day 1 every 21 days.

In Study JMDB, a total of 1833 patients signed the informed consent document (ICD) and entered the study. Of these 1833 patients, 1725 (AC N=862; GC N=863) were randomized and included in the primary analysis of overall survival (OS) and the secondary time-to-event analyses (PFS, TtPD, and TtTF) in the intent-to-treat (ITT)

population. A total of 1669 patients received study treatment consisting of at least 1 dose of pemetrexed, cisplatin, or gemcitabine (AC N=839; GC N=830).

Figure 2.1: Study Design for Phase III Study JMDB



Abbreviations: BID = twice daily; im = intramuscular; po = oral; q = every.

Source: Figure JMDB.9.1 of sponsor's H3E-MC-JMDB Study Report.

The primary endpoint was the overall survival. The secondary endpoints include: PFS, TtPD, DoR, TtTF, objective tumor response, etc. The planned enrollment was for approximately 1700 patients.

2.1.1 Rationale for Dose Schedule

In Section 5.4 of the protocol, the sponsor explained the reason why they adopted the 21-day regimen of AC and GC treatment arms.

A Phase 1 (JMAP) dose escalation study of AC in patients with solid tumors indicated that the cohort (n=40) of patients receiving both ALIMTA and cisplatin on Day 1 in a 21-day cycle was clinically superior to the cohort (n=11) of patients receiving ALIMTA on Day 1 and cisplatin on Day 2 in a 21-day cycle. This Phase 1 trial suggested a Phase 2 dose schedule of 600 mg/m^2 and cisplatin 75 mg/m^2. However, the toxicities observed in other single-agent Phase 2 studies suggested that the Phase 2/3 dose schedule of 500 mg/m^2 ALIMTA and 75 mg/m^2 cisplatin were more appropriate for this combination. In

addition, the data from a randomized Phase 3 trial (JMCH) of AC in patients with malignant pleural mesothelioma (MPM) showed that this dose and schedule were feasible and well tolerated.

The dose of cisplatin in combination with GEMZAR has varied from 75 mg/m^2 to 100 mg/m^2 every 21 days. Based on the noninferiority study design of this trial, the cisplatin dose has been selected to match the Treatment Arm A cisplatin dose (75 mg/m^2). In addition, the cisplatin dose 75 mg/m^2 in combination with GEMZAR 1250 mg/m^2 has been tested in a large randomized Phase 3 trial (Scagliotti et al. 2003) that produced consistent efficacy and safety data as compared with other GEMZAR/cisplatin studies.

2.1.2 Statistical Analysis Plan

According to the sponsor, the protocol for this study was approved on March 1, 2004 and was amended on May 13, 2004, before the start of study enrollment. The statistical analysis plan (SAP) was approved by the sponsor on December 8, 2005, and was subsequently updated and approved by the sponsor on September 13, 2006 and February 19, 2007. The update of SAP included changes to planned covariate-adjusted analyses, greater detail for some tabulated summaries, and newly prespecified subgroup evaluations. According to the Study Report, the reporting database was validated and subsequently locked for analysis on March 9, 2007.

With the assumption of constant hazard ratio over the period from randomization to death, the primary analysis was conducted on all randomly assigned patients using a Cox proportional hazards model (Cox 1972) with the following baseline covariates: assigned study treatment arm (AC over GC); disease stage (IIIB over IV); ECOG performance status (0 over 1); sex (female over male); basis for initial pathological diagnosis (histological over cytological).

A noninferiority test using fixed margin method was designed as the primary statistical analysis on the OS of the patients. The test was set to demonstrate that AC would not increase the hazard rate of the active control on OS by more than 15%.

Using the Cox model, a two-tailed 95% confidence interval for the HR was used to assess the following statistical hypotheses:

- H_0: $HR \geq 1.17647$ (null hypothesis)
- H_a: $HR < 1.17647$ (alternative, research hypothesis)

The margin of 1.17647 corresponds to GC having a 15% lower survival hazard on death than that of AC. Thus, the alternative hypothesis H_a states that the maximum difference in survival between the treatments is a 15% lower hazard for GC. Assuming HR = 1.0, 1190 deaths needed to achieve 80% power. With an assumption of 30% censoring, a total of 850 patients per arm were needed to be randomized. As suggested by ICH guidelines for analysis of noninferiority studies, the primary OS analysis was performed on all randomized patients who received study treatment.

The statistical analysis plan specified that, if the 95% confidence interval for HR was found to fall entirely below the margin of 1.17647, the null hypothesis H_0 would be

rejected at a one-sided 0.025 significance level and thus support the conclusion that AC is noninferior to GC.

Reviewer's Comments:

1. *In the protocol and statistical analysis plan, the sponsor did not provide the justification for their choice of the non-inferiority margin of 15%.*

2. *In the review of the IND 40061 with SN 918 facsimiled to the sponsor on December 14, 2006, and in the review of the same IND with SN 963, the agency conveyed to the sponsor that the "proposed margin and analysis will not be acceptable for a non-inferiority claim".*

3. *In the pre-NDA meetings on June 6, 2007, the sponsor suggested that the observed survival hazard ratio and percent retention for Study JMDB demonstrate the clinical benefit of AC for the initial treatment of locally advanced or metastatic NSCLC. The sponsor asked if FDA agreed that the results were adequate to submit for review in support of a supplement indication for Alimta as initial treatment of locally advanced or metastatic NSCLC. The agency answered "No" and indicated that the proposed margin for non-inferiority was not adequate for a claim.*

4. *The reason why the fixed margin of 15% was not acceptable is that the determination of the margin was arbitrary and there were no historical studies to support the effect size estimation of the active control to consider a percent retention approach for the current study.*

The primary noninferiority analysis was also repeated using the unadjusted Cox model with assigned treatment as the only cofactor in the model. The secondary endpoints (PFS, TtPD, DoR, and TtTF) were analyzed using the same methods as described for OS, using analogous definitions for H_0 and H_a.

In addition, the Kaplan-Meier method was used to estimate parameters (medians, quartiles, and time-point estimates) for each treatment group for all time-to-event endpoints (OS, PFS, TtPD, DoR, and TtTF). Additional supporting analyses included the log-rank and Wilcoxon statistics to compare unadjusted covariates for all time-to-event endpoints.

According to the final protocol (Section 9.7.1.1), two interim analyses for futility were planned and conducted per protocol, in May and September 2005, respectively. The first interim analysis was planned to occur after approximately 700 patients had been enrolled (after a minimum of 200 patients had progressive disease or had died). Depending on the results of the first interim analysis, a second interim analysis was to occur approximately 2 to 3 months after the first interim analysis (Section 9.7.1.15 of the SAP). The purpose of each interim analysis was to estimate efficacy and safety parameters and consider whether proceeding with full enrollment was scientifically and ethically appropriate.

Section 9.7.1.16 of the protocol indicated that primary and secondary efficacy research hypotheses would not be tested at interim. Instead, interim analyses would test an (alternative) efficacy research hypothesis on progression-free survival. If AC is inferior to GC (with respect to progression-free survival), it would then no longer be scientifically or ethically appropriate to continue the trial, study enrollment would be stopped. If this stopping rule was not met, and the DMC concluded that it was appropriate for the trial to continue as planned, then a second interim analysis would occur only if the point estimate for the progression-free survival hazard ratio was greater than 1.00. The second interim analysis would be a repetition of the first interim analysis (with the same stopping rule), but with an additional 2-3 months of accumulated data (400 to 450 patients experiencing progressive disease or death).

In the trial, after each interim analysis, the decision was made to continue with the study as planned; no changes were made to the study. Since the interim analyses were conducted for futility only, and an (alternative) efficacy research hypothesis was tested for PFS in the opposite direction as supposed to that for the primary endpoint. So there was no impact of the interim analyses on the alpha level of OS at the final analysis.

2.1.3 Percent Retention Analysis

A percent retention analysis was conducted using the Rothmann method as specified in the modified SAP. Percent retention analysis is done using cofactor-adjusted hazard ratios from both the Sandler and JMDB studies. By estimating the "percent retention" directly by combining survival HR estimates (with standard errors) from both historical data and the current trial, Rothmann's method (2003) estimates the percentage of the survival benefit for GC over C that is retained by AC in Study JMDB. The validity of Rothmann's method relies on a "constancy" assumption about the true survival HR for cisplatin over GC (that is, that the survival is constant for all studies included in the analysis). To evaluate the constancy assumption, one needs to evaluate the indirect evidence supporting survival advantage of GC over cisplatin over several studies.

An analysis of 2 earlier trials (Wozniak et al. 1998; Sandler et al. 2000) was conducted to examine the survival advantage of cisplatin-based doublets over cisplatin. The Sandler study estimated the survival HR to be 0.732, indicating an average 27% reduction in the risk of death for the doublet GC over cisplatin. The magnitude of improvement was similar to another cisplatin doublet therapy, with a survival HR in the Wozniak trial estimated to be 0.720, indicating an average 28% reduction in the risk of death for the doublet vinorelbine plus cisplatin over cisplatin.

The approval of GC for first-line NSCLC was based on 2 randomized studies. One study directly compared GC to cisplatin (Sandler et al. 2000) utilizing a 28-day GC regimen (Gemzar 1000 mg/m^2 on Days 1, 8, and 15 with cisplatin 100 mg/m^2 on Day 1) (different from the regimen used in the current study JMDB under review), and a second study (Cardenal et al. 1999) which compared GC to etoposide plus cisplatin on a 21-day GC regimen (GC 1250 mg/m^2 on Days 1 and 8 with cisplatin 75 mg/m^2 on Day 1). There are no other studies that directly compared GC to single agent cisplatin in a randomized setting. The 135-patient study (Cardenal et al. 1999) comparing survival of 21-day GC versus etoposide plus cisplatin was not statistically significant, but did result in an

estimated survival HR that was comparable to the survival HR observed in the Sandler trial.

The sponsor stated that in Phase 3 studies, reported survival results on 21-day regimens (with cisplatin doses typically between 75 mg/m^2 and 80 mg/m^2) has been consistently as good or numerically better than survival results observed with 28-day regimens based on indirect comparisons across several studies. The 3 largest studies of 21-day regimens of GC prior to completion of Study JMDB all show a median survival of over 10 months. In addition, per sponsor, one small randomized Phase 2 study directly comparing 21-day and 28-day regimens showed that the 21-day schedule led to a similar Gemzar and higher cisplatin dose intensity compared with that of the 28-day schedule; per sponsor toxicities of the treatment arms were similar (Soto Parra et al. 2002). Finally, the sponsor claims that the toxicity of the 21-day regimen has been consistently proven to be better than the 28-day regimen. So the sponsor believed that the use of the Sandler study with a 28-day GC schedule was adequate in the percent retention analysis of JMDB study with a 21-day schedule.

Reviewer's Comments:

5. *In the pre-NDA meeting on June 6, 2007, the agency advised the sponsor that a direct comparison of the Sandler study with a 28-day schedule was not acceptable for use in the non-inferiority analysis on a 21-day GC regimen used in Study JMDB. Although the survival effect of GC relative to single-agent cisplatin could be estimated based on data from the Sandler trial, the variation of this effect between trials remains unknown. Therefore, the agency indicated that the sponsor proposed retention analysis could only be considered as exploratory.*

6. *Although the randomized phase 2 study showed a similar Gemzar and higher cisplatin dose intensity and toxicities between 21-day and 28-day regimen, it was a relatively small study with 54 patients in 28-day regimen and 53 patients in 21-day regimen and it's hardly conclusive using such a small size phase 2 study.*

7. *As being pointed out earlier, the validity of Rothmann's method relies on a "constancy" assumption about the true survival for cisplatin over GC in the historical study and the current study for the same treatment regimen. At the same time, to conduct the retention analysis, a treatment effect size of the active control of GC over cisplatin should be able to be estimated using the historical study. However, in the only history study of Sandler, one can only directly estimate the survival effect of GC over cisplatin on 28-day schedule. So the valid use of Rothmann's method for percent retention analysis is questionable.*

8. *Given the above difficulties, publication bias could be another possible factor in the estimation of historical effect of the treatment.*

2.2 Data Sources

The Clinical Study Reports and SAS transport data sets for the studies were provided in electronic form in \\CDSESUB1\EVSPROD\NDA021462\021462.ENX.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Baseline Demographic Characteristics

This was a multicenter study that entered 1833 patients at 177 sites in 26 countries. Of these patients, 1725 (94.1%) were enrolled into the study and randomly assigned (enrolled) to either AC arm or GC arm. Of the enrolled patients, 862 patients were randomized to the AC arm, and 863 patients were randomized to the GC arm. A total of 1669 received study treatment consisting of at least 1 dose of pemetrexed, cisplatin, or gemcitabine (839 in AC group; 830 in GC group).

Table 3.1 shows a summary of baseline demographic characteristics for all patients randomized in the study. The two treatment arms were well balanced with respect to all demographic characteristics. Among all patients randomized, the median age was 61 years, and the majority of patients were Caucasian (78.2%), male (70.1%), and reported ever using tobacco (73.4%).

Table 3.1 Demographic Characteristics for Study JMDB at Baseline

Variable	AC (N=862)	GC (N=863)	ALL (N=1725)	p-Value
Sex n (%)				**1.000***
Number of Patients	862	863	1725	
Male	605 (70.2)	605 (70.1)	1210 (70.1)	
Female	257 (29.8)	258 (29.9)	515 (29.9)	
Origin n (%)				**0.831*****
Number of Patients	862	863	1725	
African Descent	18 (2.1)	18 (2.1)	36 (2.1)	
Caucasian	669 (77.6)	680 (78.8)	1349 (78.2)	
East/Southeast Asian	116 (13.5)	104 (12.1)	220 (12.8)	
Hispanic	27 (3.1)	23 (2.7)	50 (2.9)	
Other	2 (0.2)	1 (0.1)	3 (0.2)	
Western Asian	30 (3.5)	37 (4.3)	67 (3.9)	
Age Group n (%)				**0.078***
Number of Patients	862	863	1725	
Age < 65 Years	541 (62.8)	577 (66.9)	1118 (64.8)	
Age ≥ 65 Years	321 (37.2)	286 (33.1)	607 (35.2)	
Age (years)				**0.473****
Number of Patients	862	863	1725	
Mean	60.52	60.20	60.36	
Median	61.05	60.95	61.00	
Standard Deviation	9.22	9.34	9.28	
Minimum	28.76	26.37	26.37	
Maximum	83.19	79.41	83.19	

* Frequencies were analyzed using Fisher's exact test.
** Means were analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
***Frequencies were analyzed using a chi-square test.
Source: Table JMDB.11.2 of sponsor's H3E-MC-JMDB Study Report.

3.1.2 Baseline Disease Characteristics

In this study, patients were grouped into NSCLC histologic subgroups (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma). Patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as any of the above four categories were grouped into the "other" subcategory.

Table 3.2 summarizes the baseline disease characteristics for all randomized patients. Disease characteristics were well balanced between both treatment arms. In both treatment arms, adenocarcinoma was the predominant histological subtype (50.6% in the AC arm and 47.6% in the GC arm), followed by squamous cell carcinoma (28.3% in the AC arm and 26.5% in the GC arm). Table 3.3 depicts the patient smoking history in the study.

Table 3.2 Patient Baseline Illness Characteristics in Study JMDB

	AC (N=862) n (%)	GC (N=863) n (%)
Diagnosis/Histology		
Adenocarcinoma	436 (50.6)	411 (47.6)
Large cell carcinoma	76 (8.8)	77 (8.9)
Squamous cell carcinoma	244 (28.3)	229 (26.5)
Other*	106 (12.3)	146 (16.9)
Stage of Disease		
Disease Stage IIIB	205 (23.8)	210 (24.3)
Disease Stage IV	657 (76.2)	653 (75.7)

* The subcategory of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

Source: Table JMDB.11.4 of sponsor's Clinical H3E-MC-JMDB Study Report.

Table 3.3 Patient Smoking History in Study JMDB

Variable	AC (N=862)	GC (N=863)	ALL (N=1725)	p-Val
Smoking History n (%)				**0.678**
Number of Patients	862	863	1725	
Yes	629 (73.0)	637 (73.8)	1266 (73.4)	
No	128 (14.8)	122 (14.1)	250 (14.5)	
Unknown****	105 (12.2)	104 (12.1)	209 (12.1)	

****Unknown indicates that data was not recorded for these patients.

Source: Table JMDB.11.2 of sponsor's Clinical H3E-MC-JMDB Study Report.

3.1.3 Drug Delivery

For both treatment arms, systemic steroids were the most commonly reported concomitant medication (note that corticosteroids were required therapy for both treatment arms according to study protocol). Patients in the GC arm received significantly more erythropoietin/darbepoetin than patients in the AC arm (18.1% versus 10.4%; $p<0.001$) and more iron preparations than patients in the AC arm (7.0% versus 4.3%; $p=0.021$). Patients in the GC arm also received significantly more G-CSF/GMCSF than patients in the AC arm (6.1% versus 3.1%; $p=0.004$).

Reviewer's Comments:

9. *Due to the fact that the medications these patients received were different (statistically significantly in nominal sense), it seems that both doctors and patients responded to the treatments differently in the two treatment arms. It's hard to know how much bias this might have introduced to the efficacy outcome.*

On the other hand, since the study was open label, we don't know how much this has affected doctor's judgment on soft endpoints such as PFS, TtPD, DoR, TtTF, etc.

3.1.4 Primary Efficacy Results

3.1.4.1 Primary Efficacy Analysis

This section summarizes the efficacy data for the pivotal study, JMDB, which evaluated the effectiveness of AC versus GC as the initial treatment of locally advanced and metastatic NSCLC in 1725 patients. The primary efficacy analyses on overall survival were based on the intent-to-treat (ITT) population, consisting of all patients who were randomized (regardless of whether they were treated or not), and analyzed according to the therapy they were randomized (regardless of what they received).

A total of 862 patients in the AC arm and 863 patients in the GC arm were included in the OS analysis of randomized patients. The median OS time was 10.28 months for both treatment arms. The 1- and 2-year survival rates were 43.48% and 18.94%, respectively, for the AC arm and 41.94% and 13.98%, respectively, for the GC arm.

Using the Cox regression model adjusted for covariate in the primary analysis, the primary noninferiority test of H_0 versus H_a was statistically significant (one-sided $p<0.001$), with the primary cofactor-adjusted survival HR estimated to be 0.94 (95% CI: 0.84 to 1.05), with the entire confidence interval for HR below the 1.17645 noninferiority margin. The confidence interval for the survival HR implies that the risk of death in the AC arm was from 16% lower than that in the GC arm to 5% higher than that in the GC arm. For sensitivity, an unadjusted estimate of the survival HR (HR = 0.93; 95% CI: 0.83 to 1.04), with a noninferiority p-value of <0.001, was found to be similar to the result for the Cox regression covariate adjusted model.

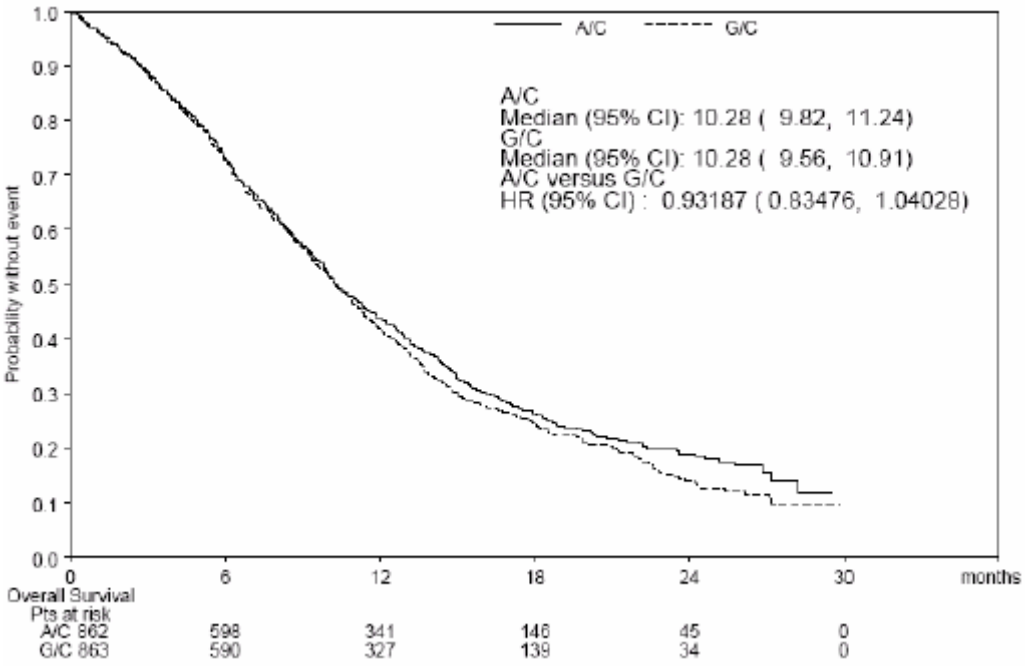
Table 3.4: Treatment Effects on Overall Survival Time (Months)
ITT and PQ Patients

	ITT Patients N=1725		PQ Patients N=1666	
	AC (N=862)	**GC** (N=863)	**AC** (N=838)	**GC** (N=828)
Percent censored	27.73	25.03	27.21	24.28
Minimum	0.03	0.03	0.16	0.07
25th percentile	5.75	5.65	5.85	5.82
Median	**10.28**	**10.28**	**10.38**	**10.45**
95% CI for median	9.82-11.24	9.56-10.91	9.82-11.30	9.72-11.14
75th percentile	18.53	17.84	18.69	17.91
Maximum	29.50	29.83	29.50	29.83
Percent of patients surviving at least:				
6 months	73.05	72.61	73.79	73.72
12 months	43.48	41.94	43.84	42.52
18 months	26.16	24.56	26.52	24.88
24 months	18.94	13.98	19.20	14.20
Unadjusted Hazard Ratio* (95% CI)	0.93 (0.83 – 1.04)		0.93 (0.84-1.04)	
Unadjusted Noninferiority p-value*	<.0001		<.0001	
Adjusted HR** (95% CI)	0.94 (0.84-1.05)		0.94 (0.84-1.05)	
Adjusted Noninferiority p-value**	<0.001		<0.001	

Abbreviations: HR = hazard ratio; PQ = protocol qualified.
*Unadjusted HR and p-value from Cox proportional hazards model with treatment as the only cofactor.
**Adjusted HR and p-values from Cox proportional hazards model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for initial pathological diagnosis (histological/cytological).

Source: Table 2.7.3.8 of the sponsor's Summary of Clinical Efficacy.

Figure 3.2 Kaplan-Meier Graph of Survival Time by Treatment Group for all Randomized Patients



Source: Figure JMDB.11.1 from sponsor's H3E-MC-JMDB Study Report

3.1.4.2 Percent Retention Analysis

The Rothmann method was utilized by the sponsor to evaluate whether AC retained at least 50% of the survival benefit seen with GC over single-agent cisplatin (C). The Rothmann method was applied using both co-factor-adjusted and nonadjusted methods.

Applying the Rothmann method using the cofactor-adjusted log hazard ratios and their standard errors as stated in Table 3.5, AC was estimated to retain 120% of GC's survival benefit over C (95% CI: 83% to 190%). The one-sided statistical test of whether AC retained at least 50% of GC's survival benefit over C was statistically significant (p=0.005). If applying the method using the unadjusted log hazard ratios, AC was estimated to retain 123% of GC's survival benefit over C (95% CI: 86% to 193%). The one-sided statistical test of whether AC retained at least 50% of GC's survival benefit over C was statistically significant (p=0.003).

Table 3.5: Survival Data Used in Percent Retention Analyses (ITT Populations)

Parameter	Hazard Ratio (standard error)
Log HR* for C over GC (standard error)	0.31136 (0.10401)
Log HR* for AC over GC (standard error)	-0.07056 (0.05615)
Adjusted Log HR** for C over GC (standard error)	0.31342 (0.10690)
Adjusted Log HR*** for AC over GC (standard error)	-0.06345 (0.05619)

*Unadjusted log hazard ratio from Cox proportional hazards model with treatment as the only cofactor.

**Adjusted log hazard ratio from Cox proportional hazards model with treatment plus 3 cofactors: ECOG PS, gender, and disease stage.
***Adjusted hazard ratio from Cox proportional hazards model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).

Source: Table JMDB.11.12 from sponsor's H3E-MC-JMDB Study Report.

Reviewer's Comments:

10. *See Reviewer's Comments 5 to 8 in section 2.1.3.*

11. *The p-values reported from these analyses by the sponsor are not interpretable as these are posthoc analyses and not prospectively adjusted for multiplicity.*

3.1.4.3 Crossover Therapy

Table 3.6 provides a summary of the types of post-discontinuation anticancer therapy received among all randomized patients. Approximately 50% of patients received post-discontinuation systemic therapy in each arm. Overall, fewer patients in the AC arm received post-discontinuation systemic anticancer treatment (chemotherapy, targeted therapy, or immunotherapy) than patients in the GC arm (52.6% versus 56.1%), and significantly fewer patients in the AC arm received chemotherapy agents post-discontinuation (41.5% versus 47.3%, p=0.018).

Table 3.7 gives the post-discontinuation for specific chemotherapy drugs. Here the reviewer only listed some post-discontinuation drugs received with higher frequency. A small percentage of patients were reported to receive the same drug (pemetrexed or gemcitabine) post-discontinuation as was received according to randomized study treatment, and some patients crossed over to receive the drug in the other arm in post-discontinuation treatment. The post-discontinuation systemic anticancer agents received were generally balanced between treatment arms, with the exception of post-cisplatinum, post-pemetrexed and post-gemcitabine exposure. The rates of crossover were low but were statistically significant between treatment arms.

Table 3.6 Patients with any Post-Discontinuation Anticancer Therapy --All Randomized Patients[e]

Anticancer Therapy[a]	AC (N=862)	GC (N=863)	p-Value[b]
Radiotherapy	273 (31.7%)	289 (33.5%)	0.441
Surgery	28 (3.2%)	26 (3.0%)	0.784
Any postdiscontinuation systemic treatment:	453 (52.6%)	484 (56.1%)	
Chemotherapy[c]:			
Any line	358 (41.5%)	408 (47.3%)	0.018
1 lines	245 (28.4 %)	285 (33.0%)	0.042
2 lines	77 (8.9%)	98 (11.4 %)	0.111
3 or more lines	36 (4.2 %)	25 (2.9 %)	0.154
Targeted therapy[d]	216 (25.1%)	196 (22.7%)	0.259
Immunotherapy[d]	0	0	
Other	31 (3.6%)	37 (4.3%)	0.536

a. Patients could have received more than 1 type of post-discontinuation anticancer therapy as well as more than 1 type of post-discontinuation systemic treatment.
b. p-value is from Fisher's exact test.
c. Refer to Table 3.7 for a list of the types of chemotherapies administered.
d. Refer to Table JMDB.11.33 from sponsor's H3E-MC-JMDB Study Report for a list of targeted therapies, immunotherapies, and other therapies administered.
e. These p-vlaues are nominal values, not interpretable, not adjusted for multiplicity.

Source: Table JMDB.11.31 from sponsor's H3E-MC-JMDB Study Report.

Table 3.7 Post-Discontinuation Anticancer Chemotherapy Drug Names --All Randomized Patients[b]

Drug Name	A/C (N=862) n (%)	G/C (N=863) n (%)	p-value[a]
Carboplatin	73 (8.5)	84 (9.7)	0.403
Cisplatinum	53 (6.1)	34 (3.9)	0.037
Docetaxel	219 (25.4)	238 (27.6)	0.326
Etoposide	16 (1.9)	12 (1.4)	0.454
Gemcitabine	144 (16.7)	74 (8.6)	<.001
Paclitaxel	42 (4.9)	37 (4.3)	0.567
Pemetrexed	30 (3.5)	116 (13.4)	<.001

a. P-value is from Fisher's Exact Test
b. These p-vlaues are nominal values, not interpretable, not adjusted for multiplicity.

Source: From Table JMDB.11.32 from sponsor's H3E-MC-JMDB Study Report.

Reviewer's Comments:

12. *Note the fact that almost 50% of the patients received post-discontinuation therapy and crossover treatment. Due to this effect, the actual efficacy effect of the treatments has been compromised. In a superiority study, such a compromise*

will make the treatment less significant and will reduce the ability of distinguish between treatment arms, therefore will not be of much concern. However, in a non-inferiority study, such a compromise will contribute to the non-inferiority of the overall treatment effect. Consequently, the seriousness of such compromise in the evaluation and interpretation of the treatment efficacy is of great concern.

3.1.4.4 Overall Survival on Histology

Table 3.8 provides the results of the Cox and Kaplan-Meier analyses of OS by treatment arm for each of 4 histologic groups analyzed. The results show that AC statistically significantly reduced the OS risk of patients treated with GC with adenocarcinoma and large cell carcinoma with a nominal significance level of 0.05 (adenocarcinoma: n=847, OS of 12.6 months versus 10.9 months with adjusted HR 0.84 and superiority p=0.033; large cell carcinoma: n=153, OS of 10.4 months versus 6.7 months with adjusted HR 0.67 and superiority p=0.027). On the other hand, AC increased the OS risk in patients treated with GC with squamous histology with a nominal significance level of 0.05 (n=473, OS of 10.8 months versus 9.4 months with adjusted HR 1.23 and superiority p=0.050). Figures 3.2 to 3.4 show the Kaplan-Meier survival curves, by treatment arm, for the 3 histologic groups of adenocarcinoma, large cell and squamous.

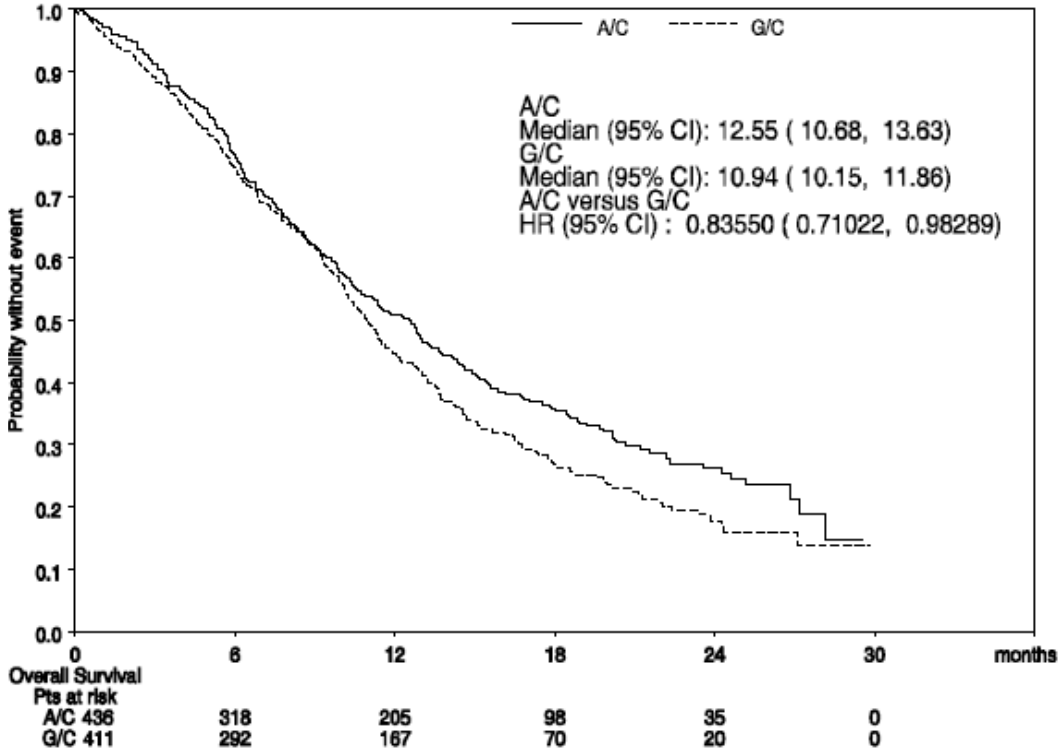
Table 3.8 Analysis of Overall Survival in Histologic Subgroups
All Randomized Patients

	Median OS (month)	Adjusted HR[a] (95% CI)	Un-adjusted HR (95% CI)
Adenocarcinoma (N=847)			
AC (n=436)	12.55	0.84 (0.71, 0.99)	0.84 (0.71, 0.98)
GC (n=411)	10.94		
Large Cell (N=153)			
AC (n=436)	10.38	0.67 (0.48, 0.96)	0.68 (0.48, 0.97)
GC (n=411)	6.67		
Squamous Cell (n=473)			
AC (n=436)	9.36	1.23 (1.00, 1.51)	1.22 (0.99, 1.50)
GC (n=411)	10.84		
Unknown or Other Histology (n=252)[b]			
AC (n=436)	8.57	1.08 (0.81, 1.45)	1.12 (0.84, 1.50)
GC (n=411)	9.17		

a. Adjusted HR and superiority and NI p-values from Cox model with treatment plus 4 cofactors: ECOG PS, gender, disease stage, and basis for pathological diagnosis (histopathological/cytopathological).
b. The subcategory of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

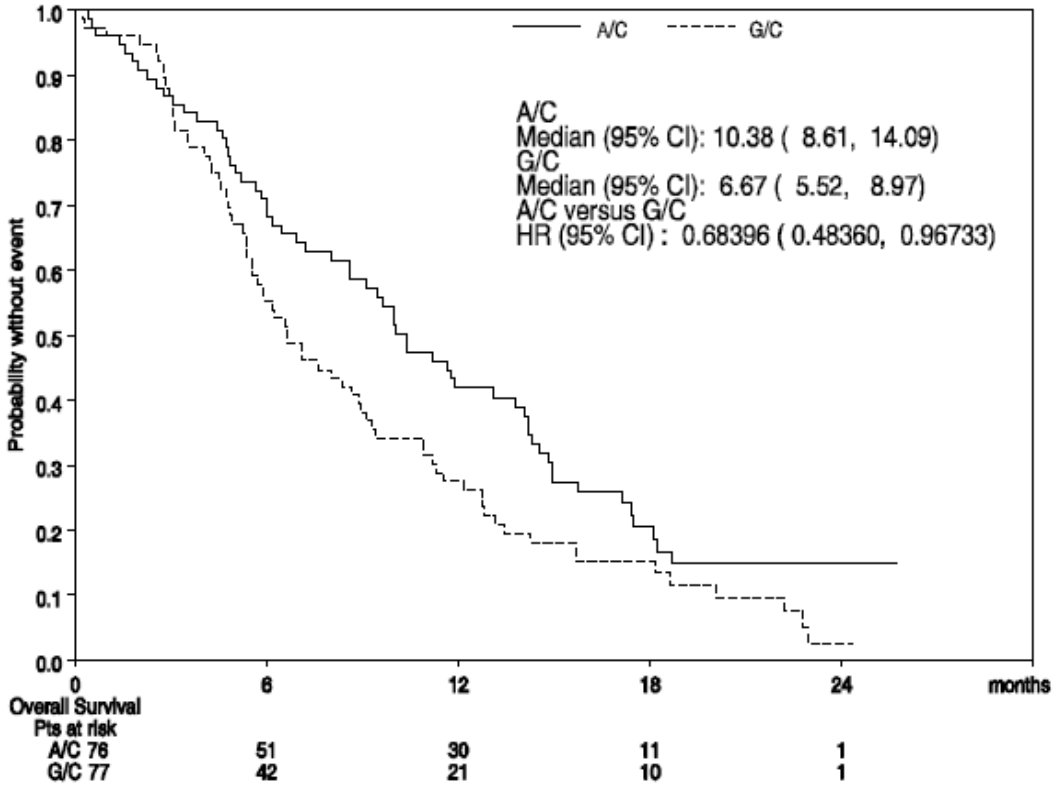
Source: Table JMDB.11.40 from sponsor's H3E-MC-JMDB Study Report.

Figure 3.2 Overall Survival in Adenocarcinoma Subgroup (ITT Population)



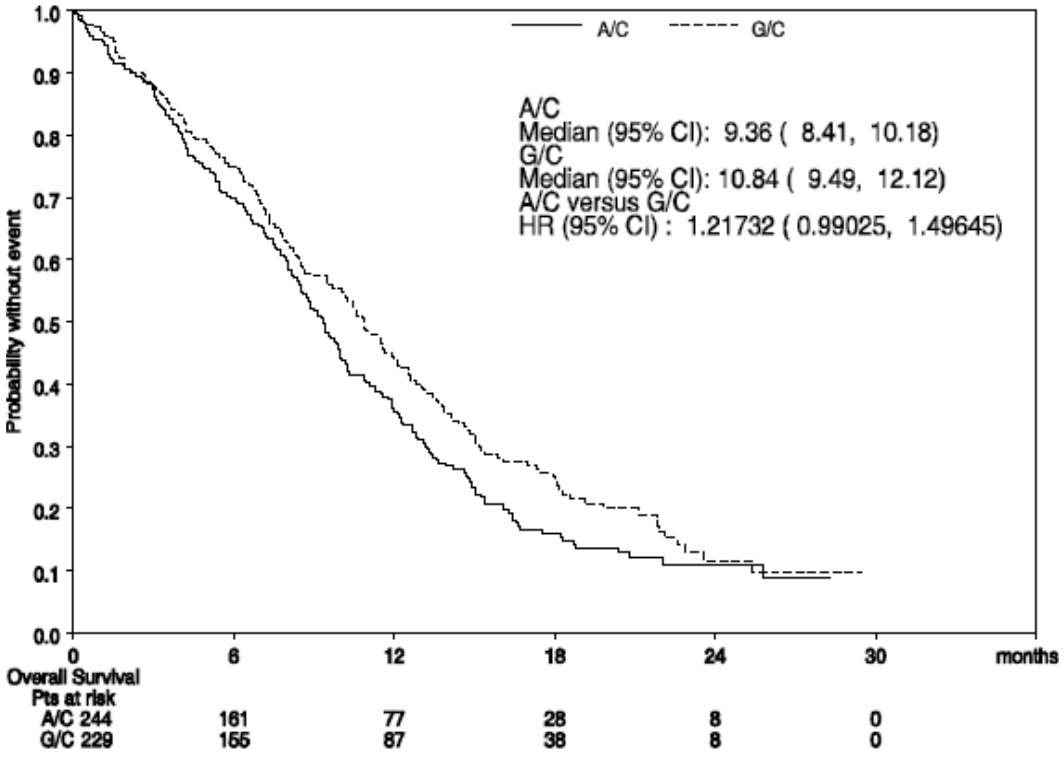
Source: Figure JMDB.11.10 from sponsor's H3E-MC-JMDB Study Report.

Figure 3.3 Overall Survival in Large-Cell Subgroup (ITT Population)



Source: Figure JMDB.11.11 from sponsor's H3E-MC-JMDB Study Report.

Figure 3.4 Overall Survival in Squamous Subgroup (ITT Population)



Source: Figure JMDB.11.12 from sponsor's H3E-MC-JMDB Study Report.

In addition to the differences in the survival hazard ratios for adenocarcinoma, large cell, and squamous cell carcinoma subgroups, a statistical test was performed to assess treatment-by-histology interaction. This test was performed using a Cox model on OS with main effects for assigned treatment arm, histology (adenocarcinoma, large cell carcinoma, squamous cell carcinoma, and other histology as 3 indicator variables), and baseline cofactors of performance status (ECOG PS), disease stage, gender, and basis for pathological diagnosis, plus the treatment-by-histology interaction terms (as a joint test of 3 interaction terms).

The interaction was found to be statistically significant (adjusted p=0.0059 and unadjusted p=0.0054), indicating that there was a significant treatment-by-histology interaction, based on the 4 histology categories. Evaluating this interaction as a two-level histology variable as squamous versus nonsquamous also resulted in a significant interaction (adjusted p=0.0024 and unadjusted p=0.0038). Given the observed subgroup results, it is evident that the statistical interaction is primarily the result of a differential treatment effect for AC, with apparently better survival in patients with adenocarcinoma and large cell lung cancer than in patients with squamous cell carcinoma. As shown in Table 3.8 above, the median OS with GC did not differ greatly between squamous cell and adenocarcinoma groups (10.84 months and 10.94 months, respectively); however, in large cell patients which consists of only 153 patients (about 9% of the patient populations), median survival with GC was estimated to be roughly 4 months lower (6.67 months).

Statistical Comments:

13. *A significant interaction between treatment and histologic was observed. This interaction was consistent with Kaplan-Meier estimate and the Cox proportional hazards model analyses. Analyses of PFS and response rates for histologic subgroups also generated consistent results with that of OS. That is: AC appeared to perform better than GC in nonsquamous cell carcinoma. While in squamous cell carcinoma, GC tended to perform better than AC. This is especially clear in Figures 3.2 to 3.4 where the survival curve for AC treatment arm is above that for GC treatment arm in adenocarcinoma and large-cell carcinoma subgroup while it is below that for GC treatment arm in squamous subgroup. Such a difference seems to be negligible in the first 12 months in adenocarcinoma group. Furthermore, the similar results hold in supporting Studies JMEN and JMEI.*

14. *In a superiority study, such interaction works against the overall significance of the treatment effect so it will not cause interpretation problem if the overall analysis was statistically significant. In that situation, the interaction will help us to identify which subgroup will benefit from the treatment, therefore if prespecified, sponsor could claim the effectiveness of the treatment in the particular subgroup. However, this is not the case in the noninferiority study. First, such an interaction works for the noninferiority of the overall treatment effect, so it's difficult to interpret the noninferiority efficacy results when such an interaction exists. Second, given the noninferiority of the overall treatment effect cannot be claimed, no subgroups effect can be claimed either. Although these data suggest that pemetrexed may be more effective in patients with nonsquamous histology as compared to patients with squamous histology, such subgroup results can only serve as exploratory purpose.*

3.2 Evaluation of Safety

Please see the review by Medical Officer.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

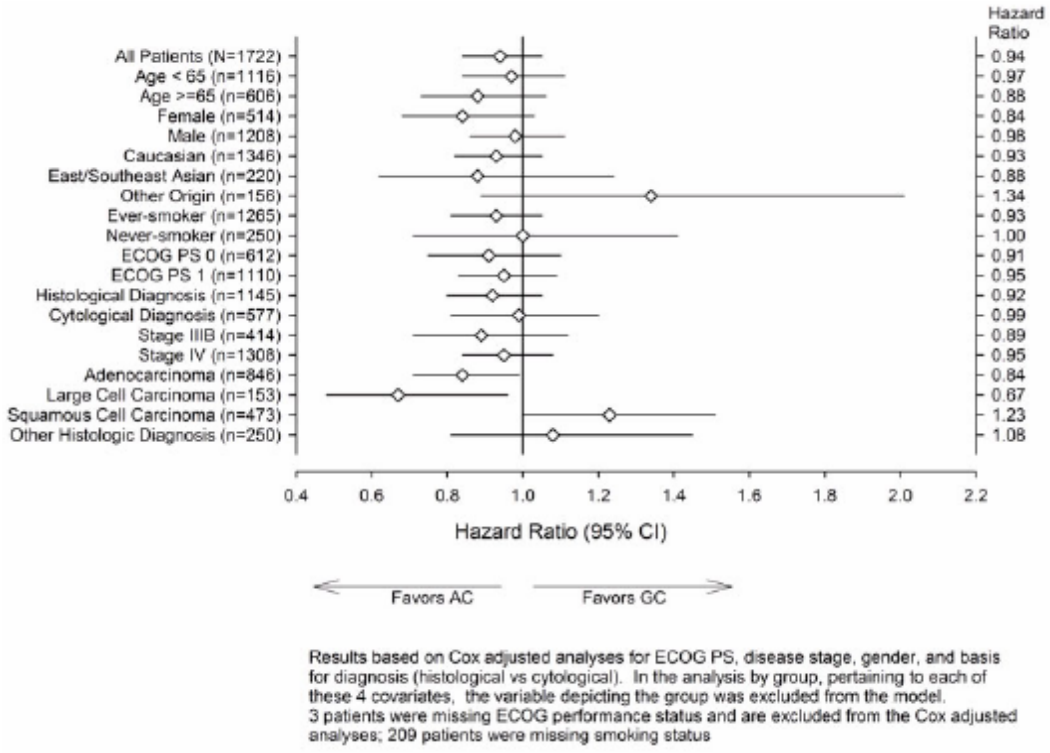
4.1 Gender, Race and Age

As prespecified in the statistical analysis plan (SAP), subgroup analyses were performed to assess whether the survival results within certain key subgroups were consistent with that for the overall study, or whether there is evidence of differential treatment benefit in certain subgroups.

Subgroup analyses of OS were performed using Cox regression model and Kaplan-Meier estimate. Subgroups were analyzed separately as defined by the following factors: disease stage, performance status, sex, basis for initial pathological diagnosis, smoking status, age, ethnic origin, and NSCLC histology. The subgroup analyses for sex, age and origin were required for regulatory requirement. The categories for origin were divided into 3 groups based on a blinded review of Study JMDB baseline data, permitting adequately

sized categories for meaningful comparisons. The results of such analyses are summarized in Figure 4.1.

Figure 4.1 Survival Hazard Ratios (AC over GC) in Subgroups According to Baseline Characteristics.



Source: Figure JMDB.11.9 from sponsor's H3E-MC-JMDB Study Report.

Table 4.1 Summary of Overall Survival Subgroup Analyses Based on Patient and Disease Characteristics--All Randomized Patients

Subgroup	AC	GC	HR and CI
Age < 65	N=541	N=578	
Median OS	10.32	10.28	0.96 (0.84, 1.10)
Age ≥ 65	N=321	N=285	
Median OS	10.12	10.15	0.89 (0.74, 1.07)
Female	N=605	N=605	
Median OS	9.63	9.86	0.97 (0.85, 1.10)
Male	N=257	N=258	
Median OS	13.31	11.40	0.86 (0.70, 1.06)
Caucasian	N=669	N=680	
Median OS	10.02	10.09	0.93 (0.82, 1.05)
East/Southeast Asian	N=116	N=104	
Median OS	13.80	11.89	0.86 (0.61, 1.21)
Other	N=77	N=79	
Median OS	9.92	11.47	1.24 (0.84, 1.84)

*: Adjusted HR and superiority and NI p-values from Cox model with treatment only.

Source: FDA analysis.

Statistical Comments:

15. *The results in the subgroups were similar to the overall population except for histological subgroups,*

4.2 Other Special/Subgroup Populations

Subgroup analyses for smoking status were performed for exploratory purposes. This was because the Tarceva® (erlotinib) data showed that erlotinib was more effective in patients who had never been smokers than in current or former smokers (Shepherd et al. 2005). In addition, smoking status may be associated with histologic cell type and other patient comorbidities, which may impact patient prognosis.

Table 4.2 Summary of Overall Survival Subgroup Analyses Based on Patient's Smoking Status-- All Randomized Patients

Smoking Status	AC	GC	HR and CI
Never Smoker	N=128	N=123	
Median OS	15.90	16.49	1.06 (0.75, 1.48)
Ever Smoker	N=638	N=642	
Median OS	10.05	10.25	0.91 (0.80, 1.03)

*: Adjusted HR and superiority and NI p-values from Cox model with treatment only.

Source: FDA analysis.

Statistical Comments:

16. *The analysis results suggest that the smoking status does not make a difference on the treatment effect of AC versus GC.*

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

One well-controlled Phase IV commitment study JMDB was submitted to compare the efficacy and safety of AC with that of GC in patients with locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer. In this study, the primary efficacy measure was the overall survival. The non-inferiority analysis of the treatment efficacy was conducted using Cox proportional hazards model. The survival distribution was displayed using Kaplan-Meier estimator. The percent retention analysis was also conducted to support the efficacy results.

Using the pre-specified fixed margin analysis, the primary noninferiority results suggest that the risk of death in the AC arm was from 16% lower than that in the GC arm to 5% higher than that in the GC arm, with the entire confidence interval for HR below the 1.17645 noninferiority margin. Applying the Rothmann method, AC was estimated to retain 120% of GC's survival benefit over C (95% CI: 83% to 190%). Per sponsor, the one-sided statistical test of whether AC retained at least 50% of GC's survival benefit over C was statistically significant (p=0.005).

Cox model analysis on OS with interaction between treatment arm and histology indicates that there was a significant treatment-by-histology interaction. The results appear s to suggest that AC has better survival compared to GC in patients with adenocarcinoma and large cell lung cancer and it has worse survival compared to GC in patients with squamous cell carcinoma.

On the other hand, the statistical reviewer has the following concerns:

1. In IND and pre-NDA meetings with the sponsor, the agency made it clear that the fixed margin of 15% was not acceptable due to the factor that the determination of the margin was arbitrary and there were no historical studies to support the effect size estimation of the active control for the current study.

2. The efficacy results of GC in the Sandler study with a 28-day regimen cannot be directly used in the non-inferiority Study JMDB with a 21-day GC regimen schedule. The treatment effect of the active control (GC) in the comparison of cisplatin in 21-day GC regimen schedule was not well established. Therefore the retention analysis is questionable and can only be considered as exploratory.

3. Due to the fact that almost 50% of the patients received post-discontinuation therapy and the crossovers of both treatments were statistically significant, the actual efficacy effect of the treatments could have been compromised, which makes the non-inferiority study hard to interpret.

4. There was a statistically significant interaction between treatment arm and patient histology categories. Such an interaction makes it impossible to interpret the noninferiority efficacy results of the treatment. On the other hand, the analysis result suggests that the treatment benefit was only limited to the patients with nonsquamous cell carcinoma. While in squamous cell carcinoma, AC tended to reduce the benefit of GC in the treatment of patients with locally advanced or metastatic NSCLC.

5.2 Conclusions and Recommendations

One well-controlled Phase IV commitment study JMDB was submitted to compare the efficacy and safety of AC with that of GC in patients with locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer. In this study, the primary efficacy measure was the overall survival. The non-inferiority analysis of the treatment efficacy was conducted using Cox proportional hazards model. The survival

distribution was displayed using Kaplan-Meier estimator. The percent retention analysis was also conducted to support the efficacy results.

Although the pre-specified statistical analysis suggested that the AC treatment arm was non-inferior to the GC treatment arm in the reduction of the risk of death in patients with locally advanced or metastatic NSCLC, such an inference is problematic. First, the active control was not well established; second, the non-inferiority margin was not well established; third, there were 50% post-discontinuation therapy and the statistically significant post-discontinuation crossover therapy; finally, there was a statistically significant interaction between treatment arm and patient histology categories. These factors together compromised the statistical findings of this non-inferiority study and greatly reduced the credibility of the findings of the statistical analyses. Therefore a non-inferiority claim can not be made based on the results of this single trial. The results from non-squamous subgroup of patients can only be considered as exploratory.

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Aloka Chakravarty
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	21-462/SE1-015
BRAND NAME:	ALIMTA
GENERIC NAME:	Pemetrexed
DOSAGE FORM:	500 mg in Single-Dose Vials for Intravenous Injection
INDICATION:	Advanced Non Small Cell Lung Cancer (NSCLC)
SUBMISSION DATES:	27-Aug-2007 and 19-Nov-2007
SUBMISSION TYPE:	NDA-Supplement
APPLICANT:	Eli Lilly
OODP:	Office of Oncology Drug Products
OCPB DIVISION:	Division of Clinical Pharmacology 5
OCPB REVIEWER:	Sophia Abraham, Ph.D.
PHARMACOMETRICS REVIEWER:	Young-Jin Moon, Ph.D.
OCPB TEAM LEADER:	Brian Booth, Ph.D.

TABLE OF CONTENTS:

1. EXECUTIVE SUMMARY

The Applicant submits a Supplemental New Drug Application (NDA 21-462/SE1-015) in accordance with the requirements described in 21 CFR 314.510. In this NDA Supplement, the Applicant submits **Study JMDB** as a fulfillment of a Phase 4 Commitment that will support the conversion of the accelerated approval of ALIMTA (pemetrexed) to regular approval. The proposed indication is for use of pemetrexed in combination with cisplatin for

the initial treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

Study JMDB compared the efficacy and safety of pemetrexed plus cisplatin with that of gemcitabine plus cisplatin in 1725 patients with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC. The results of this study indicate that the median overall survival (OS), primary clinical endpoint, was 10.3 months on both arms. The adjusted survival hazard ratio was 0.94 (95% CI: 0.84 to 1.05), with a non-inferiority p-value of < 0.001.

The Applicant revised the current package insert for ALIMTA only with respect to the results from this Phase 3 study (**Study JMDB**) and submitted the package insert in the PLR format (Physician Labeling Rule) to this NDA Supplement.

The pharmacokinetics of the combination of pemetrexed and cisplatin were previously examined in the original NDA for ALIMTA. A statement already exists in the package insert indicating that the pharmacokinetics of either pemetrexed or cisplatin are not altered when both drugs are given in combination. The Applicant did not make any changes in the Clinical Pharmacology/Pharmacokinetics section of the labeling.

1.1 RECOMMENDATION

The Supplemental NDA 21-462/SE1-015 submitted for the use of ALIMTA in combination with cisplatin for the treatment of patients with non-small cell lung cancer (NSCLC) is acceptable from the clinical pharmacology perspective.

Please forward the above Recommendation, the Comment below, and the Clinical Pharmacology Labeling Recommendations (outlined in Section 3 of this review, pp. 9) to the Applicant.

COMMENT

We recommend that you address the clinical evaluation of the potential of ALIMTA to cause QT/QTc interval prolongation (see ICH E14).

1.2 PHASE 4 COMMITMENTS

[None]

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

ALIMTA (pemetrexed) as a single agent received an accelerated FDA approval for second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) on 19-Aug-2004 (Submission dated 24-Oct-2002). ALIMTA 500 mg/m^2 in combination with cisplatin 75 mg/m^2 received also FDA approval for the treatment of patients with malignant pleural mesothelioma (MPM) on 04-Feb-2004.

In the original NDA submission of 24-Oct-2002, the potential interactions between pemetrexed and cisplatin were evaluated in two studies (**Studies JMAP and JMCH**).

- **Study JMAP** was a Phase 1, single-arm, dose-escalation study in 15 patients with advanced Cancers. Patients were treated with ALIMTA at a starting dose of 500 mg/m^2 administered intravenously (IV) over 10 minutes followed by cisplatin at a fixed dose of 75 mg/m^2 administered IV over 30 minutes. Treatment was repeated once every 21 days (1 cycle).

- **Study JMCH** was a multi-center, randomized, two-arm, Phase 3 study in Western patients with malignant pleural mesothelioma. The PK of pemetrexed and cisplatin were determined using a population (NONMEM) PK analysis of the sparse plasma data collected during the study. The population PK database included patients who were treated with either **Arm A:** pemetrexed (500 mg/ m^2) IV over 10 minutes followed by cisplatin (75 mg/m^2) IV over 2 hours beginning 30 minutes after the completion of pemetrexed infusion on Day 1 of each 21-day cycle (N=63) or **Arm B:** cisplatin **alone** (75 mg/m^2) IV over 2 hours on Day 1 of each 21-day cycle (N=71).

The results from both **Studies JMAP** and **JMCH** indicated that the co-administration of cisplatin did not alter the pharmacokinetics of pemetrexed, or vice versa.

In support of the current NDA Supplement, the Applicant submitted a multi-center, single-arm, Phase 1/2 study (**Study ME01**) conducted in 25 Japanese patients with malignant pleural mesothelioma. In this study, patients were treated with pemetrexed 500 mg/m^2 administered IV over 10 minutes followed by cisplatin 60 mg/m^2 or 75 mg/m^2 administered IV over 2 hours beginning 30 minutes after the completion of pemetrexed infusion on Day 1 of each 21-day cycle. The PK of both pemetrexed and total platinum determined in 25 Japanese patients in this study were compared to those previously determined in Western patients in **Study JMCH** using a population (NONMEM) PK analysis. This analysis affirmed that the combined administration of pemetrexed and cisplatin has no effect on the exposure of either drug which it has already been mentioned in the current labeling for ALIMTA. The Applicant did not make any changes in the Clinical pharmacology/Pharmaco-kinetics section of the current labeling for ALIMITA.

2 QUESTION BASED REVIEW

The following questions were addressed based on the information submitted in the Supplemental NDA 21-462/SE1-015:

- **What are the design features of the clinical studies used to support dosing or claims?**

In support of the efficacy claim for the use of ALIMTA in combination with cisplatin in the initial treatment of locally advanced or metastatic NSCLC, the Applicant conducted a pivotal Phase 3 study (Study JMDB). This was an open-label, multi-center, randomized, non-inferiority, Phase 3 study in 1725 NSCLC patients. Patients were randomized (1:1) to receive pemetrexed plus cisplatin or gemcitabine plus cisplatin combination therapy, as follows:

- **Arm A:** Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on Day 1 every 21 days (N=862).
- **Arm B:** Gemcitabine 1250 mg/m^2 on Day 1 and Day 8 plus cisplatin 75 mg/m^2 on Day 1 every 21 days (N=863).

Patients in both treatment arms received vitamin B12 and folic acid supplementation. Vitamin B12 1000 µg was given intramuscularly 1 to 2 weeks before treatment and repeated every 9 weeks until 3 weeks after the last dose. Folic Acid 350 µg was taken orally 1 to 2 weeks before treatment and continued daily until 3 weeks after the last dose. Drug concentration measurements were not assessed in this study. The primary efficacy variable was overall survival (OS), measured from the date of randomization to the date of death from any cause. According to the Applicant, the median OS time was 10.28 months for both treatment arms. The estimated survival HR (hazard ratio) was 0.94 (95% CI: 0.84 to 1.05), with the entire confidence interval for HR well below the 1.17645 non-inferiority margin.

Safety Results:

TABLE 1. Study-Drug-Related Treatment-Emergent Adverse Events (TEAE) by Treatment Group Occurring in ≥ 10% Patients

Study Arm	**AC**		**GC**		
	(N=839)		**(N=830)**		
	n	**%**	**n**	**%**	**p-Value**
Overall Patients with at least TEAE	**751**	**89.5 %**	**755**	**%91.0%**	**0.324**
Hematological					
Anemia	256	30.5%	356	42.9%	<0.001
Leukopenia	146	17.4%	165	19.9%	0.209
Neutropenia	231	27.5%	299	36.0%	<0.001
Thrombocytopenia	79	9.4%	209	25.2%	<0.001
Non-Hematological					
Constipation	171	20.4%	160	19.3%	0.581
Diarrhoea	105	12.5%	107	12.9%	0.826
Nausea	466	55.5%	433	52.2%	0.170
Stomatitis	66	7.9%)	68	8.2%	0.857
Vomiting	333	39.7%	294	35.4%	0.077

Overall, there was no significant difference in the total number of patients experiencing any study-drug related toxicity between the two treatment arms (p=0.324). However, patients in the GC arm experienced significantly higher incidence of hematological toxicities (p< 0.001) such as anemia (43% versus 30.5%), neutropenia (36% versus 27.5), and thrombocytopenia (25.2% versus 9.4%).

The Applicant revised the current package insert for ALIMTA with respect to the efficacy and safety results from this Phase 3 study.

- **Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?**

The label specifies that ALIMTA (pemetrexed) is to be administered in combination with cisplatin in the treatment of patients with non-small cell lung cancer: initial treatment in combination with cisplatin.

In support of the current NDA Supplement, the Applicant submitted a multi-center, single-arm, Phase 1/2 study (**Study ME01**) conducted in 25 Japanese patients with malignant pleural mesothelioma. The primary objectives of this study were to characterize the pharmacokinetics (PK) of pemetrexed and cisplatin when co-administered in Japanese patients and to compare the PK of pemetrexed and cisplatin determined in Japanese patients with those determined in Western patients in Study JMCH (Original NDA submission).

In **Study ME01**, patients were treated with pemetrexed 500 mg/m^2 administered as an intravenous (IV) infusion over 10 minutes followed by cisplatin 60 mg/m^2 or 75 mg/m^2 administered as a IV infusion over 2 hours beginning 30 minutes after the completion of pemetrexed infusion on Day 1 of each 21-day cycle. Sparse blood samples were collected for both pemetrexed and total platinum during Cycles 1 and 3. A population (NONMEM) PK approach was used to analyze plasma concentration/time data for both pemetrexed and total platinum in **Study ME01**. The population database for **Study ME01** included plasma data collected from 25 Japanese patients for both pemetrexed and total platinum when pemetrexed and cisplatin were given in combination during Cycle 1 (N=25) and Cycle 3 (N=19).

The population PK parameters obtained in this study was compared to those obtained in previous **Study JMCH** (Original NDA). **Study JMCH** was a multi-center, randomized, two-arm, Phase 3 study in Western patients with malignant pleural mesothelioma. Patients who were randomized to receive either **Arm A:** pemetrexed (500 mg/ m^2) IV over 10 minutes followed by cisplatin (75 mg/m^2) IV over 2 hours beginning 30 minutes after the completion of pemetrexed infusion on Day 1 of each 21-day cycle or **Arm B:** cisplatin **alone** (75 mg/m^2) IV over 2 hours on Day 1 of each 21-day cycle.

The population *database for **Study JMCH** included plasma data for both pemetrexed and total platinum collected from 63 Western patients who were treated with the combination and from 71 Western patients who were treated with cisplatin alone (original NDA).

*[For pemetrexed, sparse blood samples were collected during Cycle 1 (N=63) and Cycle 3 (N=37) of **Arm A** of this study. For total platinum, sparse blood samples were collected during Cycle 1 (N=59) and Cycle 3 (N=35) of Arm A and during Cycle 1 (N=71), Cycle 2 (N=1), and Cycle 3 (N=27) of **Arm B** of this study]

The results are summarized in Tables 2 and 3.

TABLE 2. Post-hoc Pharmacokinetic Parameter Estimates for Pemetrexed

	AUC (μg•h/mL)	CL (mL/min)	CL (mL/min/m^2)	V_{ss} (L)	V_{ss} (L/m^2)
Study ME01 (N=44 Japanese Patients) (Cisplatin + Pemetrexed)					
Median Range	162 111 – 211	80.0 65.2 – 115	50.4 39.4 – 75.0	14.4 12.5 – 16.9	8.93 7.42 – 11.1
Study JMCH (N=100 Western Patients) (Arm A: Cisplatin + Pemetrexed)					
Median Range	180 72.9 – 253	87.0 58.8 – 130	46.4 31.3 – 68.5	14.3 12.2 – 30.2	7.43 6.26 – 13.8

TABLE 3. Post-hoc Pharmacokinetic Parameter Estimates for Total Platinum

	AUC (μg•h/mL)	CL (L/h)	CL (mL/min/m^2)	V_{ss} (L)	V_{ss} (L/m^2)
Study ME01 (N=44 Japanese Patients) (Cisplatin + Pemetrexed)					
Median Range	173 134 – 213	0.667 0.495 – 0.828	0.409 0.353 – 0.526	53.7 34.9 – 69.4	31.8 25.9 – 40.4
Study JMCH (N=94 Western Patients) (Arm A: Cisplatin + Pemetrexed)					
Median Range	192 83.2 – 295	0.745 0.550 – 1.08	0.386 0.255 – 0.582	83.5 51.2 – 138	42.7 31.1 – 67.7
Study JMCH (N=99 Western Patients) (Arm B: Cisplatin Alone)					
Median Range	197 95.6 – 262	0.736 0.578 – 1.03	0.372 0.281 – 0.556	86.2 35.3 – 141	42.4 18.4 – 67.3

The pharmacokinetics of pemetrexed when given in combination with cisplatin were similar in Study ME01 and Study JMCH as seen by the comparable distributions of post-hoc parameter estimates from the pemetrexed final model (Tables 2 and 3 above). No changes were made in the the Clinical pharmacology/Pharmacokinetics section of the current labeling for ALIMITA.

Refer to the original NDA 21-462 (Submission Date: 24-Oct-2002) for the following issues:

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

2.1.3 What are the proposed dosage(s) and route(s) of administration?

2.2 General clinical pharmacology

2.2.1 What are the design features of the clinical studies used to support dosing or claims?

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD) and how are they measured in clinical pharmacology and clinical studies?

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

2.2.4.3 Does this drug prolong the QT or QTc interval?

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

2.2.5.3 What are the characteristics of drug absorption?

2.2.5.4 What are the characteristics of drug distribution?

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

2.2.5.6 What are the characteristics of drug metabolism?

2.2.5.7 What are the characteristics of drug excretion?

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

2.2.5.9 How do the PK parameters change with time following chronic dosing?

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

2.5 General Biopharmaceutics (NOT APPLICABLE)

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

2.5.4 When would a fed BE study be appropriate and was one conducted?

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

2.5 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

2.6.2 Which metabolites have been selected for analysis and why?

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

2.6.4 What bioanalytical methods are used to assess concentrations?

3. OCPB Labeling Recommendations

7 DRUG INTERACTIONS

7.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Ibuprofen

Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with ALIMTA in patients with normal renal function (creatinine clearance ≥80 mL/min). *[see Clinical Pharmacology (12.3)]* Caution should be used when administering ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min).

Other NSAIDs

Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of ALIMTA.

In the absence of data regarding potential interaction between ALIMTA and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following ALIMTA administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Preclinical studies have shown that pemetrexed inhibits the in vitro growth of mesothelioma cell lines (MSTO-211H, NCI-H2052). Studies with the MSTO-211H mesothelioma cell line showed synergistic effects when pemetrexed was combined concurrently with cisplatin.

Absolute neutrophil counts (ANC) following single-agent administration of pemetrexed to patients not receiving folic acid and vitamin B_{12} supplementation were characterized using population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the depth of the ANC nadir, correlates with the systemic exposure, or area under the curve (AUC) of pemetrexed. It was also observed that lower ANC nadirs occurred in patients with elevated baseline cystathionine or homocysteine concentrations. The levels of these substances can be reduced by folic acid and vitamin B_{12} supplementation. There is no cumulative effect of pemetrexed exposure on ANC nadir over multiple treatment cycles.

Time to ANC nadir with pemetrexed systemic exposure (AUC), varied between 8 to 9.6 days over a range of exposures from 38.3 to 316.8 mcg•hr/mL. Return to baseline ANC occurred 4.2 to 7.5 days after the nadir over the same range of exposures.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of pemetrexed administered as a single-agent in doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period have been evaluated in 426 cancer patients

with a variety of solid tumors. The total systemic clearance of pemetrexed is 91.8 mL/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min). The clearance decreases, and exposure (AUC) increases, as renal function decreases. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increase proportionally with dose. The pharmacokinetics of pemetrexed do not change over multiple treatment cycles.

Distribution

Pemetrexed has a steady-state volume of distribution of 16.1 liters. In vitro studies indicate that pemetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

Metabolism and Excretion

Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration.

Effect of Age

No effect of age on the pharmacokinetics of pemetrexed was observed over a range of 26 to 80 years.

Effect of Gender

The pharmacokinetics of pemetrexed were not different in male and female patients.

Effect of Race

The pharmacokinetics of pemetrexed were similar in Caucasians and patients of African descent. Insufficient data are available to compare pharmacokinetics for other ethnic groups.

Effect of Hepatic Insufficiency

There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed. However, studies of hepatically impaired patients have not been conducted *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

Effect of Renal Insufficiency

Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed decreases as renal function decreases, with a resultant increase in systemic exposure. Patients with creatinine clearances of 45, 50, and 80 mL/min had 65%, 54%, and 13% increases, respectively in pemetrexed total systemic exposure (AUC) compared to patients with creatinine clearance of 100 mL/min *[see Warnings and Precautions (5.4) and Dosage and Administration (2.4)]*.

Pediatric: Pediatric patients were not included in clinical trials.

Drug Interactions

Ibuprofen — Ibuprofen doses of 400 mg four times a day reduce pemetrexed's clearance by about 20% (and increase AUC by 20%) in patients with normal renal function. The effect of

greater doses of ibuprofen on pemetrexed pharmacokinetics is unknown *[see Drug Interactions (7.1)]*.

Aspirin — Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed. The effect of greater doses of aspirin on pemetrexed pharmacokinetics is unknown.

Chemotherapeutic Agents — Cisplatin does not affect the pharmacokinetics of pemetrexed and the pharmacokinetics of total platinum are unaltered by pemetrexed.

Vitamins — Coadministration of oral folic acid or intramuscular vitamin B_{12} does not affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes — Results from *in vitro* studies with human liver microsomes predict that pemetrexed would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

18 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

4.2 Pharmacometric Review

PHARMACOMETRICS REVIEW

NDA:	21-462/SE1-015
Submission Date	27-Aug-2007
Type of Submission	NDA-Supplement
Generic Name	Pemetrexed
Brand Name	ALIMTA
Dosage Form	500 mg in Single-Dose Vials for Intravenous Injection
Sponsor	Eli Lilly
Primary PM Reviewer	Young-Jin Moon, Ph.D.
Secondary PM Reviewer	Christoffer W. Tornoe, Ph.D.
OCPB Team Leader:	Brian Booth, Ph.D.
PDUFA Date:	28-Jun-2008

Population Pharmacokinetic Evaluation of LY231514 Administered in Combination with Cisplatin in Patients with Malignant Pleural Mesothelioma (MPM)

The sponsor has conducted a population PK analysis for LY231514 and total platinum using combined data from **Study ME01** with data from **Study JMCH**.

The primary objective of this analysis was to characterize the pharmacokinetics (PK) of LY231514 and cisplatin when co-administered in Japanese patients (Study **ME01**) and to compare the pharmacokinetics to that characterized in Western patients (Study H3E-MC-**JMCH**).

Study ME01 is a multicenter, combined Phase 1/2 study in Japanese patients. LY231514 500 mg/m^2 was administered as an intravenous infusion over 10 minutes followed by a 2-hour cisplatin (60 or 75 mg/m^2) infusion beginning approximately 30 minutes after completion of the LY231514 infusion. The study medications were administered on Day 1 of each 21-day cycle. Pharmacokinetics sampling was conducted in Cycles 1 and 3 for characterization of both LY231514 and total platinum pharmacokinetics. A sparse blood sampling strategy was employed with 5 plasma samples obtained from each patient per Cycle.

Study JMCH was a multicenter, randomized, single-blind, Phase 3 study of LY231514 combined with cisplatin compared with cisplatin monotherapy in Western patients with MPM naïve to chemotherapy. Patients were randomized to receive either LY231514 500 mg/m^2 administered as an intravenous infusion over 10 minutes followed by a 2-hour cisplatin (75 mg/m^2) infusion beginning approximately 30 minutes after completion of the LY231514 infusion or normal saline administered as an intravenous infusion over 10 minutes followed by a 2-hour cisplatin (75 mg/m^2) infusion beginning approximately 30 minutes after termination of the saline infusion. The study medications were administered on Day 1 of each 21-day cycle.

Plasma concentrations of LY231514 were determined by validated liquid chromatography /electron spray ionization with tandem mass spectrometry (LC/ESI/MS/MS) methods over the concentration ranges 10.0 to 2000.0 ng/mL and 1000.0 to 200000.0 ng/mL. Platinum was measured by validated atomic absorption with a tube atomizer method. In study JMCH the assay was valid over the concentration range of approximately 50.0 ng Pt/mL to 2000 ng Pt/mL. For study ME01, the assay measured total platinum, but the reported units were ng Cisplatin/mL and the assay was valid over the concentration range of 150 ng Cisplatin/mL to 5000 ng Cisplatin/mL.

1) LY231514

The population pharmacokinetic model was an open three-compartment model parameterized in terms of clearance (CL), central volume of distribution (V1), intercompartmental clearance (Q1 and Q2), and peripheral volume of distribution (V2 and V3). Interpatient variability (η) with respect to CL and V3 and residual variability (σ) were modeled using a proportional error structure. Pharmacokinetic parameters were estimated using the first-order conditional estimation method with interaction (FOCEi). Estimates of the pharmacokinetic parameters and error terms were obtained by fitting the plasma LY231514 concentration-time data by means of the nonlinear mixed-effects modeling program, NONMEM (version V) with PREDPP. The model included Cockroft-Gault creatinine clearance as a covariate with respect to CL. Parameter sensitivity was performed on the final base model to ensure that NONMEM had converged to a global minimum objective function (MOF) and that all pharmacokinetic parameters were well estimated. Leverage analysis was performed to ensure that no patient had an undue influence on parameter estimates.

Previously identified covariates (creatinine clearance, body surface area) were incorporated into the model(s). Since Study ME01 was conducted in Japanese patients and Study JMCH was conducted in Western patients, ethnicity differences on the pharmacokinetics of LY231514 was also assessed as covariate with respect to CL, V1, V2 and V3 individually. Covariate analysis was performed using forward selection (decrease in MOF of at least 6.635 points, $p < 0.01$) and backward elimination (decrease in MOF of at least 10.828 points, $p < 0.001$) procedures.

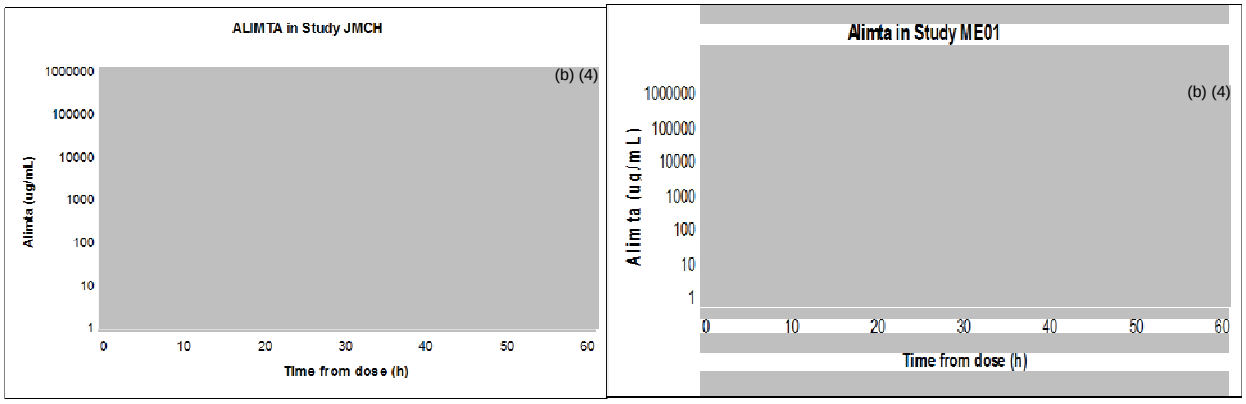
PK data from 25 patients in Study ME01 and 69 patients in Study JMCH were available. Both two- and three-compartment models were investigated for the base structural model. A three compartmental model parameterized in terms of clearance (CL), central volume of distribution (V1), intercompartmental clearances (Q2 and Q3), and peripheral volume of distributions, (V2 and V3) was selected as the base structural model. Three residual error models - additive, proportional, and combined - were tested to describe residual random error, and proportional residual was selected.

The final model fitted the data well, as indicated by the Goodness-of-fit in sponsor's Figure ME01.9.4. PK parameters and variability estimates are shown in sponsor's Table ME01.9.6. Intersubject variability of CL and V3 were estimated to be 13.8% and 42.2%, respectively. The relative standard error (%SEE) of typical and variability parameter estimates were reasonable. The random residual constant coefficient of variation was about 30%. The

addition of creatinine clearance onto the base structure model resulted in a decrease in intersubject variability in CL.

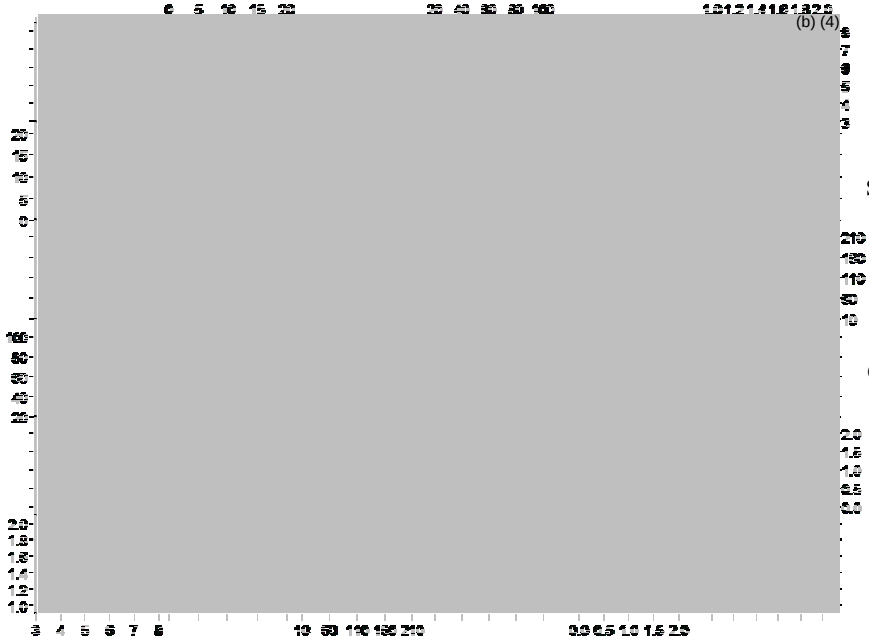
Reviewer's Analysis for LY231514

• The sponsor combined the plasma concentration of LY231514 obtained during therapy Cycle 1 and the data obtained during Cycle 3 (sponsor's Figure ME01.9.2). PK profiles at Cycle 1 and Cycle 3 appear similar, as seen in FDA Figure 1.



FDA Figure 1. Observed plasma Alimta (LY231514) concentrations versus time from start of infusion in Study JMCH and ME01 at Cycle 1 (○) and Cycle 3 (■).

• FDA Figure 2 illustrates the relationships of each of the individual posterior Bayesian estimates of CL and V3 against potential covariates. A significant effect of creatinine clearance (CRCL) on the LY231514 CL was identified (r^2=0.5324), which is consistent with literature. The influence of ethnicity was investigated by using Study code (PRO), but was not found to be a significant covariate for PK parameters for LY231514 (FDA Figure 2).



FDA Figure 2. A matrix plot for covariate search for CL, V3, for creatinine clearance (CRCL), weight (WTVV), body surface area (BSAV) and study code (PRO).

FDA Table 2. Comparison of estimates before and after data were combined.

Parameter Description		Combined		JMCH only		ME01 only	
		Population Estimate (%SEE)	Interpatient Variability (%SEE)	Population Estimate (%SEE)	Interpatient Variability (%SEE)	Population Estimate (%SEE)	Interp Varia (%S
Clearance[a]	TVCL (mL/min)	82.7 (2.13)	13.8% (25.5)	83.4 (3.71)	14.6% (48.6)	84.7 (3.72)	13 (4
	Effect of CRCL on CL (θ1)	0.512 (13.9)		0.462 (18.9)		0.735 (21.9)	
Central Volume of Distribution	TVV1(L)	8.07 (3.04)		8.28 (5.02)		7.55 (4.17)	
Intercompartmental Clearance between V1&V2	TVQ2 (mL/min)	0.899 (13.9)		0.905 (20.7)		0.733 (8.61)	
Peripheral Volume of Distribution	TVV2 (L)	1.36 (11.1)		1.38 (16.3)		2.00 (0.000540)	
Intercompartmental Clearance between V1&V3	TVQ3 (mL/min)	39.4 (15.3)		51.8 (56.2)		30.5 (10.9)	
Peripheral Volume of Distribution	TVV3 (L)	5.03 (8.03)	42.2 % (38.3)	5.91 (24.4)	43.2% (55.1)	4.34 (7.65)	18 (3
Residual Error (proportional)		30.1% (9.77)		31.1% (14.1)		27.0% (12.2)	

• To see if estimates obtained by using combined data were mostly driven by JMCH data due to the larger patient number in JMCH than in ME01, separate population PK analysis was performed using data from each study and the estimates were compared with the estimates obtained from combined data (Table 2). Since the effect of creatinine clearance on CL (θ1) seems higher in ME01 group (0.735) than the one in JMCH (0.462) or combined group (0.512), the influence of study code ME01 on θ1 was evaluated by incorporating study code ME01 as a covariate affecting θ1. However, the addition of study code ME01 did not significantly change MOF based on sponsor's criteria (≥ 6.635 changes in MOF) compared to when it was not added, suggesting that θ1 is not significantly different in ME01 group. Other estimated parameters appeared generally similar in Japanese (ME01) and Western (JMCH) patients.

• In conclusion, PK of LY231514 was similar between Japanese and Western patients administered combination therapy and no dosage adjustments are warranted based on ethnicity. The sponsor's method and interpretation of population PK analyses for LY231514 was found adequate.

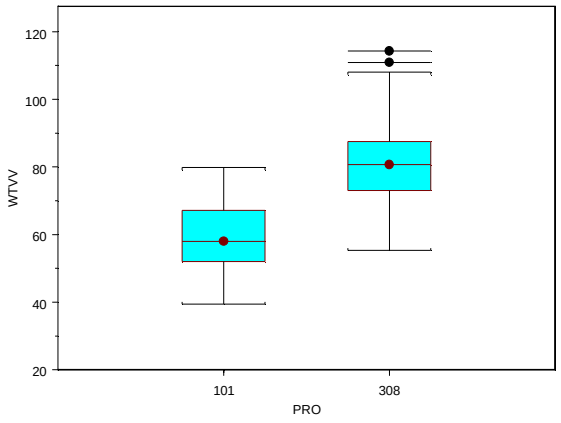
2) Total Platinum

Plasma total platinum concentration-time data were modeled with a two-compartment structure parameterized in terms of CL, V1, V2, and Q. Estimates of the pharmacokinetic parameters and error terms were obtained by fitting the plasma total platinum concentration-time data using NONMEM. Pharmacokinetic parameters were estimated using the FOCEi. Ethnicity differences on the pharmacokinetics of total platinum were assessed as covariate with respect to CL, V1, and V2 individually. Covariate analysis was performed using forward selection (decrease in MOF of at least 6.635 points, $p < 0.01$) and backward elimination (decrease in MOF of at least 10.828 points, $p < 0.001$) procedures. Parameter sensitivity and leverage analyses were performed on the final model.

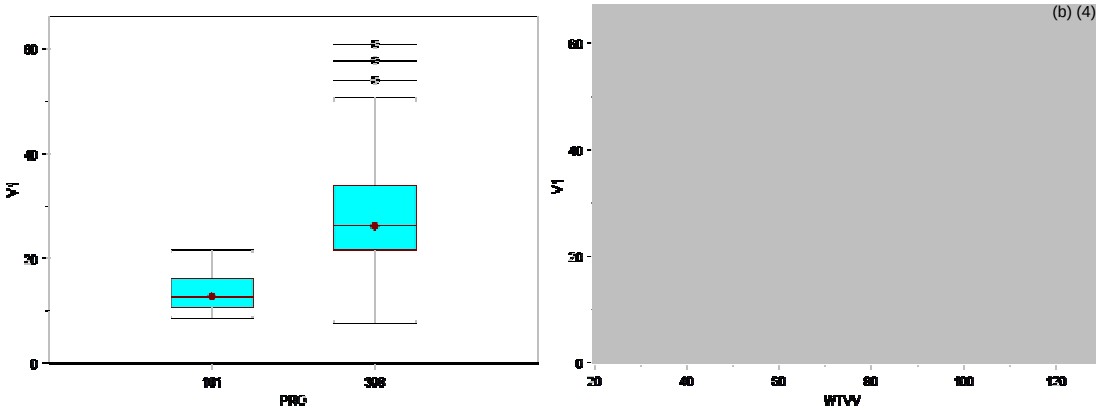
The final model incorporated CRCL on total platinum clearance, study code on total platinum central volume of distribution (V1), and body weight on platinum peripheral volume of distribution (V2). Inclusion of CRCL on CL, study code on V1, and body weight on V2 decreased in interpatient variability.

Reviewer's Analysis for Total Platinum

• The sponsor included study code as covariate with respect to V1. Since there was a significant difference in body weight between Japanese patients (ME01) and Western patients (JMCH) (FDA Figure 3), it was needed to show that V1 isnot simply dependent on body weight, but dependent on ethnicity (FDA Figure 4).

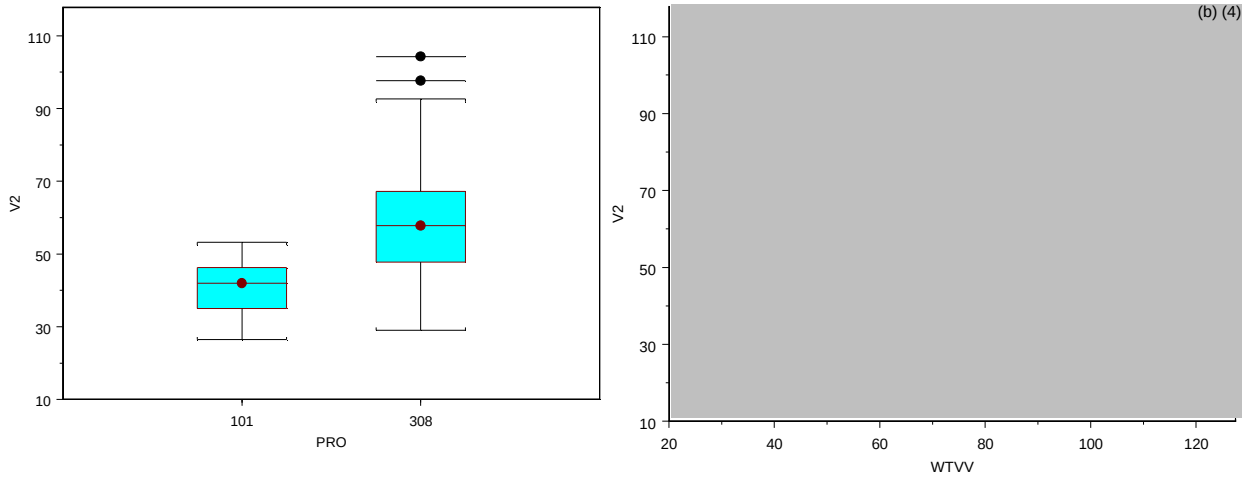


FDA Figure 3. Body weight (WTVV, kg) vs. Study code (PRO, 101:ME01, 308: JMCH).



FDA Figure 4. Central volume of distribution (V1, L) vs Study code (Left), and V1 versus WTVV (kg) (Right). The data trend is visualized with a loess smoothers (S-Plus 7).

From the FDA Figure 4, it is not clear whether there was a correlation between V1 and WTVV. Study code may be confounded covariates by body weight.



FDA Figure 5. Central volume of distribution (V2, L) vs Study code (Left), and V2 versus WTVV (kg) (Right). The data trend is visualized with a loess smoothers (S-Plus 7).

Although there was also significant difference in peripheral volume of distribution (V2) between Study code, the difference appears to come from difference in body weight rather than ethnicity as seen in FDA Figure 5 (Right).

• To see if estimates obtained by using combined data were mostly driven by JMCH data due to the larger patient number in JMCH than in ME01, separate population PK analysis was performed using data from each study and the estimates were compared with the estimates obtained from combined data (Table 3). The estimated parameters appeared generally similar in Japanese (ME01) and Western (JMCH) patients. Since the effect of creatinine clearance on

CL (θ1) seems higher in ME01 group (0.704) than the one in JMCH (0.465) or combined group (0.443), the influence of study code ME01 on θ1 was evaluated by incorporating study code ME01 as a covariate affecting θ1. However, the addition of study code ME01 did not significantly change MOF based on sponsor's criteria (≥ 6.635 changes in MOF) compared to when it was not added, suggesting that θ1 is not significantly different in ME01 group.

FDA Table 3. Comparison of estimates before and after the data were combined.

		Combined		JMCH only		ME01 only	
Parameter Description		Population Estimate (%SE)	Interpatient Variability (%CV)	Population Estimate (%SE)	Interpatient Variability (%CV)	Population Estimate	Interpatient Variability
Clearance[a]	TVCL (L/h)	0.694 (3.24)	8.48% (101)	0.673	11.4%	0.730	8.19%
	Effect of CRCL on CL (θ1)	0.466 (21.2)		0.443		0.704	
Central Volume of Distribution	TVV1(L)						
	Study JMCH TVV1 (L)	28.5 (7.62)		27.1		28.5	
	Study ME01 TVV1 (L)	12.5 (15.6)	48.2% (21.9)	12.5	41.4%	15.8	30.8%
Intercompartmental Clearance	TVQ3 (L/h)	25.8 (7.46)		24.7		22.2	
	TVV3 (L)	55.9 (3.53)	27.3% (26.4)	55.2	28.5%	46.6	11.4%
	Effect of WTV on V2 (θ2)	0.881 (13.0)		0.764		0.870	
Residual Error (proportional)		13.7% (5.73)		14.3%		11.4%	

• The sponsor's method and interpretation of the population PK analyses for total platinum was found adequate.

• Overall, the sponsor's model characterized data properly, and covariate selection procedure was reasonably conducted. Clearances of both LY231514 and total platinum were affected by creatinine clearance, which is consistent with literature.

The sponsor concluded that LY231514 pharmacokinetics following combination therapy with cisplatin behaves similarly in Japanese and Western by showing that ethnicity was not covariate for clearance, which determines systemic total platinum exposure (AUC). For total platinum, even though there was difference in central volume of distribution (V1) between Japanese and Western patients, the sponsor concluded that this difference in V1 does not appear to affect total platinum exposure, because study code (ethnicity) was not covariate for CL. However, it is known that the antitumor activity of cisplatin depends on its total administered dose and cumulative AUC [1], whereas its toxicity appears related to peak plasma cisplatin concentration (C_{max}) rather than AUC [2]. Therefore, whether difference in volume of distribution between Japanese and Caucasian affects dose determination/exposure or not may need further evaluation.

References

[1] Desoize B, Marechal F, Millart H, Cattan A. Correlation of clinical pharmacokinetic parameters of cisplatin with efficacy and toxicity. Biomed Pharmacother 1991;45(4-5):203-7.

[2] Nagai N, Kinoshita M, Ogata H, Tsujino D, Wada Y, Someya K, Ohno T, Masuhara K, Tanaka Y, Kato K, Nagai H, Yokoyama A, Kurita Y. Relationship between pharmacokinetics of unchanged cisplatin and nephrotoxicity after intravenous infusions of cisplatin to cancer patients. Cancer Chemother Pharmacol. 1996;39(1-2):131-7.

4.3 *Filing Memo*

I. Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-462**	**Brand Name**	**Alimta**
OCPB Division (1, 2,3,4,5)	**5**	**Generic Name**	**Pemetrexed**
Medical Division	**DODP**	**Drug Class**	**Antifolate agent**
OCP Reviewer	**Sophia Abraham**	**Indication(s)**	**NSCLC**
OCP Team Leader	**Brian Booth**	**Dosage Form**	**500 mg vial for Injection**
		Dosing Regimen	**500 mg/m^2 Alimta + 75 mg/m^2 cispatin once every 21 days**
Date of Submission	**8/27/07**	**Route of Administration**	**IV**
Estimated Due Date of OCP Review	**4/01/07**	**Sponsor**	**Eli Lilly**
PDUFA Due Date	**6/27/08**	**Priority Classification**	**S**
Division Due Date	**4/27/08**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
II. Patients-				
single dose:	**3**			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	***Comments***
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-426, DDOP (Electronic Entry), DDOP (Garvey), DCP5 (Booth, Rahman), CDR (Biopharm)

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

/s/

Sophia Abraham
5/20/2008 03:00:07 PM
BIOPHARMACEUTICS

Young-Jin Moon
5/20/2008 03:01:12 PM
PHARMACOLOGIST

Brian Booth
5/30/2008 12:44:51 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

OTHER REVIEW(S)

NDA 21-462/S-015

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Drug Oncology Products

Application Numbers: NDA 21-462/S-015

Name of Drug: ALIMTA (pemetrexed disodium) Injection, Powder, Lyophilized, For Solution for Intravenous use. 100 mg and 500 mg vials

Applicant: **Eli Lilly and Company**

Material Reviewed:

Submission Date(s): August 27, 2007; June 24, 2008 (Major Amendment)

Receipt Date(s): August 28, 2007 and June 24, 2008, respectively

Type of Labeling Reviewed: Package Insert-WORD (not in PLR format); this submission was in PLR format. The team reviewed under PLR.

Location: **\\CDSESUB1\EVSPROD\NDA021462\0005**
\\CDSESUB1\EVSPROD\NDA021462\0028

Background and Summary

In the August 27, 2007 submission, the sponsor submitted results of the study JMDB. This is a multicenter, randomized, Phase 3 trial comparing the efficacy and safety of Alimta plus cisplatin (AC) with that of gemcitabine plus cisplatin (GC) inpatients with a diagnosis of locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer.
On June 23, 2008, the Agency requested the final study report for study JMEN as an amendment to the 1st line application. This major amendment was submitted on June 24, 2008.

Review

The approved label dated January 9, 2006 was used to compare the label submitted in the supplement dated August 27, 2007 and the major amendment dated June 24, 2008. The submissions dated August 27, 2007 and June 24, 2008 were in PLR. The team had made

NDA 21-462/S-015
pertinent changes to the label based on content (data) of the submission with respect to PLR. These were conveyed to the sponsor and negotiated accordingly.

Recommendations

The division approves this supplement with the appropriate labeling changes.

Please see the action letter for further information.

Carl Huntley, R.Ph, MBA.
Senior Regulatory Project Manager
DDOP, OODP

Concur/Date:
Frank Cross, Jr.
Chief, Project Management Staff
DDOP, OODP

Drafted: ch/9 25 08
Revised/Initialed: ch/9 25 08
Finalized: ch/9 25 08
Filename: ALIMTA S-015 labeling review 9 25 08

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

/s/

Carl Huntley
9/26/2008 02:13:02 PM
CSO

Frank Cross
9/26/2008 04:43:10 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-462 Supplement # 015 Efficacy Supplement Type SE- 1

Proprietary Name: Alimta
Established Name: pemetrexed disodium
Strengths:

Applicant: Lilly
Agent for Applicant (if applicable):

Date of Application: 8-27-07
Date of Receipt: 8-28-07
Date clock started after UN:
Date of Filing Meeting: 1-23-07
Filing Date: 10-27-07
Action Goal Date (optional): User Fee Goal Date: 6-28-08

Indication(s) requested: NSCLC

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: NDA 21-462 has NCE exclusivity until 8-11-09 and Orphan Drug Exclusivity until 8-11-11

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☒
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☐ NO ☒
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act 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 . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☐ NO ☒

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☐ NO ☒
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒

- PDUFA and Action Goal dates correct in tracking system? YES ☐ NO ☒
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 40,061

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 1-11-07 and 6-6-07 NO ☐
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO ☒

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☒

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☐ NO ☒

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☐ NO ☒

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☐ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☒

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 23, 2007

NDA #: 21-462/S015

DRUG NAMES: Alimta (pemetrexed disodium)

APPLICANT: Lilly

BACKGROUND: Alimta is approved for malignant pleural mesothelioma and locally advanced or metastatic NSCLC (accelerated approval). This supplement is for use with cisplatin for initial therapy of locally advanced or metastatic NSCLC and as single agent for locally advanced or metastatic NSCLC after prior chemotherapy.

Lilly also requests this supplement convert the initial NSCLC approval to regular approval.

ATTENDEES: PGarvey, RJustice, AFarrell, JJohnson, MCohen, RSridhara, BBooth, SAbraham, PGarvey

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Martin Cohen, M.D.
Secondary Medical:	John Johnson, M.D.
Statistical:	Somesh Chattopadhyay, Ph.D./Raji Sridhara, Ph.D.
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	Joel Hathaway, Ph.D./Liang Zhou, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Sophia Abraham, Ph.D./Brian Booth, Ph.D.
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Patty Garvey
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the 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?

N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☐

PHARMACOLOGY/TOX N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? N/A ☐ NO ☐ YES
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☒

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Dotti Pease for Patty Garvey
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

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 ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☒

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☒

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☒

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☒

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☒

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). no listed drug

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

10. 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 less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☒

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? N/A (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☒ Not applicable (e.g., solely based on published literature. See question # 7 supplement

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☒

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☒

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☒

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Dotti Pease
10/30/2007 02:23:55 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-462/S-015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-462 SUPPL # 015 HFD # 150

Trade Name ALIMTA

Generic Name pemetrexate disodium

Applicant Name Eli Lilly and Company

Approval Date, If Known September 26, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-462 ALIMTA (pemetrexed disodium) Injection, Powder, Lyophilized, For Solution for Intravenous use. 100 mg and 500

mg vials

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

JMDB: A multicenter, randomized, phase 3 trial comparing the efficacy and safety of Alimta + cisplatin (AC) with that of gemcitabine + cisplatin (GC) inpatients with a diagnosis of locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

JMDB: A multicenter, randomized, phase 3 trial comparing the efficacy and safety of Alimta + cisplatin (AC) with that of gemcitabine + cisplatin (GC) inpatients with a diagnosis of locally advanced or metastatic NSCLC who have had no prior systemic chemotherapy for lung cancer.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 40,061	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Carl Huntley
Title: Senior Regulatory Project Manager
Date: September 26, 2008

Name of Office/Division Director signing form: Robert L. Justice, M.D.
Title: Division Director

cc:
Archival NDA
HFD-610/Mary Ann Holovac

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

APPEARS THIS WAY ON ORIGINAL

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

/s/

Robert Justice
9/26/2008 06:30:20 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-462 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** 015

Stamp Date: 8-28-07 **PDUFA Goal Date:** 6-28-08

HFD-150 **Trade and generic names/dosage form:** Alimta (pemetrexed sodium) for injection

Applicant: Lilly **Therapeutic Class:** _____

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ■ **Yes. Please proceed to the next question.**
- ❑ **No. PREA does not apply. Skip to signature block.**

**** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.***

Indication(s) *previously approved* (please complete this section for supplements only): 2nd line NSCLC/malignant pleural mesothelioma

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: 1st line NSCLC with cisplatin

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

■ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

❑ **Yes: Please proceed to Section A.**

■ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ■ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Dotti Pease

10/26/2007 01:42:44 PM

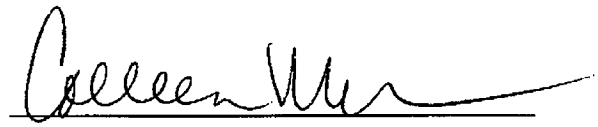
Debarment Certification

NDA Application No.: 21-462

Drug Name: Alimta (pemetrexed)

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Colleen Mockbee, R.Ph., RAC, hereby certifies that it did not knowingly and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: 

Colleen Mockbee R.Ph., RAC

Title: Associate Director, U.S. Regulatory Affairs

Date: August 24, 2007

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 21-462 BLA #	NDA Supplement # 015 BLA STN #	If NDA, Efficacy Supplement Type: SE1
Proprietary Name: ALIMTA Established/Proper Name: pemetrexed Dosage Form: vial		Applicant: Eli Lilly and Company Agent for Applicant (if applicable):
RPM: Carl Huntley		Division: DDOP

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2) (A 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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	9/28/08 9/26/08
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None AZ 6/24/08
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed *(indicate dates of reviews)*	☐ Requested in AP letter ☒ Received and reviewed 9/25/03

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application[2] Characteristics	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 1

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☒ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☒ Submitted in response to a PMC

Comments: Study JMBD

❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• If yes, exception for review granted *(file Center Director's memo in* Administrative/Regulatory Documents *section,with* Administrative Reviews*)*	☐ Yes
• If yes, OC clearance for approval *(file communication in* Administrative/Regulatory Documents *section with* Administrative Reviews*)*	☐ Yes ☐ Not an AP action
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: ☒	Peds Waived
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Burst

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/nonconsent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 9/26/08
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	9/25/08
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	see packet
❖ Original applicant-proposed labeling	see packet
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	see packet
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
❖ Original applicant-proposed labeling	see packet
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 9/25/08 ☐ DMEDP ☐ DRISK ☐ DDMAC ☐ CSS ☒ Other reviews see original NDA
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	see packet
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If approval action, OC clearance for approval	☒ Not on AIP
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☐ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	see action letter
• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	see packet
❖ Internal memoranda, telecons, etc.	see packet
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☒ No mtg
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	see meeting minutes in packet

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	9/15/08
• Clinical review(s) *(indicate date for each review)*	9/15/08
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	in MO review 9/15/08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	in MO review 9/15/08
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ REMS • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • Review(s) and recommendations (including those by OSE and CSS) *(indicate location/date if incorporated into another review)*	☒ None
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clinical Pharmacology Studies	
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None 9/24/08
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 9/24/08
Statistical Review(s) *(indicate date for each review)*	☐ None 6/11/08
Clinical Pharmacology ☒ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None

[5] Filing reviews should be filed with the discipline reviews.

Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None
❖ DSI Clinical Pharmacology Inspection Review Summary	☐ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	☐ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/TeamLeader Review(s) *(indicate date for each review)*	☒ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 9/25/08
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology	9/5/07 ☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date for each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☒ Review & Environmental Impact Statement *(indicate date of each review)*	submitted
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
• BLAs: ➢ TBP-EER	Date completed: ☐ Acceptable ☐ Withhold recommendation
➢ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Requested ☐ Accepted ☐ Hold

❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ODE’s ADRA.

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/s/

Carl Huntley

9/29/2008 03:46:29 PM

MEMORANDUM

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

DATE: September 26, 2008

TO: The NDA file for 21-462

FROM: Carl Huntley, RPM

SUBJECT: **Labeling meetings**
NDA 21-462/S-015, pemetrexed disodium (Alimta) 100 mg and 500 mg vial

The internal labeling meetings were held on the following dates with the various teams, clinical pharmacology, CMC, pharmacology/toxicology, biometrics and clinical. Although the discussion involved primarily clinical and statistics, regarding the submission of the JMDB study, the teams met to discuss the label conversion to PLR.

The meetings took place on the following dates: September 16, 17, 18, 19, 22, 23, and 24, 2008.

Accordingly, subsequent labels were forwarded to the sponsor on September 18, 19, 22, 23 and 24, 2008.

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/s/

Carl Huntley

9/26/2008 03:19:01 PM

CSO

Huntley, Carl

From: Hathaway, Joel S
Sent: Thursday, September 25, 2008 6:06 PM
To: Huntley, Carl
Cc: Zhou, Liang; Patel, Hasmukh B
Subject: RE: ALIMTA sNDA 21-462/S-015

The PI, PPI and AP Letter are acceptable to me.
Steve Hathaway, Ph.D.
Reviewer, (18B)
ONDQA/DPE Branch VIII
White Oak 21
Room 2665
301-796-1677
joel.hathaway@fda.hhs.gov

From: Huntley, Carl
Sent: Thursday, September 25, 2008 5:11 PM
To: Hathaway, Joel S; Zhou, Liang; Verbois, Leigh; Tang, Shenghui; Cohen, Martin H
Subject: ALIMTA sNDA 21-462/S-015
Importance: High

Dear Steve, Liang, Leigh, Shenghui and Marty,
I didn't get a chance to get your signatures today on the approval letter. Instead, would you mind taking a look at the letter via e-mail? I'll also include the label and the PPI, of course.
If you 'approve', please let me know and I'll enter the date by your name on the document information page of the letter that goes to Dr. Justice. I'll need to change the file name to tomorrow's date anyway (Dr. Justice is planning on signing tomorrow).

<< File: ALIMTA label final 9 25 08.doc >> << File: ALIMTA PPI final 9 25 08.doc >> << File: NDA supplment accelerated app ltr 9 25 08.doc >>

If you wish to see the actual jacket with all the reviews, please let me know!

Carl Huntley, R. Ph., MBA
Senior Regulatory Project Manager
FDA/CDER/OND/OODP/DDOP
pH. (301) 796-1372
FAX (301) 796-9845

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/s/

Carl Huntley

9/26/2008 06:32:25 PM

CSO

Huntley, Carl

From: Huntley, Carl
Sent: Wednesday, April 23, 2008 2:35 PM
To: 'Colleen M Mockbee'
Cc: Huntley, Carl
Subject: RE: Alimta NDA 21-462

Hi Colleen,
The reviewer had this question/observation:
Please see below.
-carl

Carl,

Please ask the sponsor to explain why the numbers of patients in the two tables don't add up. For example what groups from table 1 (top) make up the nonsquamous group in table 2. Why are there 93 squamous docetaxel treated patients in table 1 and 94 in table 2?

Table 1. Histologic Diagnosis of JMEI study patients

Diagnosis/Histology (%)	Pemetrexed	Docetaxel
Adenocarcinoma	154 (54.4)	142 (49.3)
Squamous	78 (27.6)	93 (32.3)
Bronchoalveolar	4 (1.4)	1 (0.3)
Other	51 (18.1)	53 (18.5)

Table 2. Analysis of Overall Survival in Study JMEI (ITT Population)

Squamous and Nonsquamous Subgroups

	Nonsquamous Group		**Squamous Group**	
	Pemetrexed	**Docetaxel**	**Pemetrexed**	**Docetaxel**
	(N=205)	**(N=194)**	**(N=78)**	**(N=94)**
Median survival, months	9.3	8.0	6.2	7.4
Survival HR (95% CI)	0.778 (0.607-0.997)		1.563 (1.079-2.264)	
Median PFS, months	3.1	3.0	2.3	2.7
PFS HR (95% CI)	0.823 (0.664-1.020)		1.403 (1.006-1.957)	

Marty

From: Colleen M Mockbee [mailto:MOCKBEE_COLLEEN_M@LILLY.COM]
Sent: Monday, April 21, 2008 12:39 PM
To: Huntley, Carl
Subject: Re: Alimta NDA 21-462

Hello Carl,

Thank you for the message below. I did not know you would be covering this NDA. Based on your message it appears you will take over the S015 supplement for 1st line NSCLC- correct?

I need some clarification on the request below. We do have a treatment by histology effect and this was described in the Summary documents submitted to S015 and in the clinical study report. Here are the locations in the submission where histology is reviewed..
Module 2.5 Clinical Overview- Discussion of histology results for JMDB and retrospective analysis of JMEI (Module 2.5.4.5.4- JMDB Overall Survival Subgroup Analyses)
Module 2.7.3 Summary of Clinical Efficacy- Discussion of histology results for JMDB and retrospective analysis of JMEI, including graphs, tables, etc. (Module 2.7.3.2.1.1.8- Examination of Sugruops)
Module 5- Controlled Study- Study JMDB-
Presentation of data begins in 11.4.6.3- Subgroup Analysis Defined by Baseline Characteristics; JMEI and NSO1 are discussed in 11.4.6.3.1; safety by subgroup in 12.5.2.

We also had a subsequent study that completed after submission of the 1st line S015 application- Study JMEN. This study also confirmed the histology treatment effect observed in Study JMDB, JMEI and NSO1 (discussed in S015 as outlined above). We included a discussion of the data across the Phase 3 studies in the briefing package for the February 27, 2008 meeting (submitted 29-January-2008, SN1060, section 3.6.2) . We also subsequentlysubmitted this data formally to the S015 application (Seq 0019, 29-March-2008). I am attaching the cover letter which includes a description of the submission contents.

Please let me know if this addresses Dr. Cohen's request. If not, I would like to make sure we discuss a bit more to ensure we provide what he is needing.

Kind Regards,

Colleen Mockbee RPh
Associate Director
Eli Lilly and Company
Indianapolis, Indiana
Phone 317-277-0199
Cell: 317-997-4906

"Huntley, Carl" <Carl.Huntley@fda.hhs.gov>

04/21/2008 11:49 AM

To Mockbee_Colleen_M@Lilly.com

cc "Huntley, Carl" <Carl.Huntley@fda.hhs.gov>

Subject Alimta NDA 21-462

Dear Colleen,
Frank Cross may have mentioned to you that I'll be handling the Alimta NDA.
I just received a request from the medical reviewer for some information.
This may have been asked before but I'm not quite sure. The question is if we had heard about the study report described below:

There are apparently 3 Alimta studies demonstrating an effect of histology on treatment outcome of NSCLC patients.

Please ask the sponsor to provide a study report and analysis of these 3 studies and any other studies that support a relationship of histology to treatment outcome..

This analysis will provide support for the beneficial effects of alimta in NSCLC patients with adenocarcinoma and large cell anaplastic carcinoma observed in the currently submitted first-line study.

Let me know if you have any questions or if I may have missed something. Also, I will work soon on the earlier issues you had for Frank.

Thanks
-carl

Carl Huntley, R. Ph., MBA
Senior Regulatory Project Manager
FDA/CDER/OND/OODP/DDOP
pH. (301) 796-1372
FAX (301) 796-9845

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/s/

Carl Huntley

9/29/2008 02:41:38 PM

CSO

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Colleen Mockbee, R.Ph. – Eli Lilly and Company	From:	Patty Garvey, R.Ph.
Fax:	317-276-1652	Fax:	301-796-1356
Phone:	317-277-0199	Phone:	301-796-9845
Pages (including cover):	2	Date:	March 4, 2008
Re:	NDA 21-462/S-015 Alimta		

☐ Urgent x For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Dear Colleen,

Please refer to your NDA 21-462 supplement 015, submission dated August 27, 2007, for the following proposed new indication, ALIMTA in combination with cisplatin therapy is indicated for the initial treatment of patients with locally advanced or metastatic non-small cell lung cancer and as a single- agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

We have completed the review of your proposed PLR labeling. There were no issues regarding the PLR format, however the Division recently updated the references for all cytotoxics products. Please revise your labeling REFERENCES section according to the new references provided.

In addition, we request that you include your CBE labeling changes submitted in supplement 018, submission dated September 27, 2007, in your revised labeling submission. Please re-submit your revised labeling by April 1, 2008.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193.

4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

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/s/

Patricia Garvey
3/13/2008 12:21:00 PM
CSO
Sent to the sponsor on March 4, 2008

From: Pease, Dorothy W
Sent: Wednesday, February 06, 2008 9:54 AM
To: 'Colleen M Mockbee'
Cc: Garvey, Patricia
Subject: Pending Alimta Supplement

We have the following statistical request:

We are not able to reproduce the same subgroups for histology as you using data sets: cxcovsrv.xpt and diagdata.xpt, with variables ICDACODE and ICDACODZ. We request you clarify which data sets and variables you used to classify the subgroups by histology.

Thanks
Dotti

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/s/

Dotti Pease
2/6/2008 10:08:48 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-462/S015 **PRIOR APPROVAL SUPPLEMENT**

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Colleen Mockbee, R. Ph.
Associate Director, U.S. Regulatory Affairs

Dear Ms. Mockbee:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Alimta (pemetrexed disodium)

NDA Number: 21-462

Supplement number: S015

Review Priority Classification: Standard (S)

Date of supplement: August 27, 2007

Date of receipt: August 28, 2007

This supplemental application proposes the following change(s): updating the labeling with the results of Study JMDB and conversion of the accelerated approval in the treatment of patients with NSCLC after prior therapy to regular approval.

We filed the application on October 27, 2007 in accordance with 21 CFR 314.101(a). The user fee goal date will be June 28, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Patty Garvey, Regulatory Project Manager, at (301) 796-1356.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Dotti Pease

12/5/2007 09:14:33 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-462/S015

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Colleen Mockbee, R. Ph.
Associate Director, U.S. Regulatory Affairs

Dear Ms. Mockbee:

Please refer to your August 27, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alimta (pemetrexed disodium).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on October 27, 2007 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 796-1356.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Drug Oncology Products
Center for Drug Evaluation and Research

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/s/

Dotti Pease

12/5/2007 09:11:34 AM

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Friday, November 09, 2007 11:51 AM
To: 'Colleen M Mockbee'
Subject: PK request for Alimta S015

Please submit the detailed study report for Study EM01 and the population PK analysis data files

Thanks

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
301 796-1434 fax 301 796-9845

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

/s/

Dotti Pease
11/9/2007 11:56:14 AM
CSO

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

To:	Colleen Mockbee, R.Ph. – Eli Lilly and Company	From:	Patty Garvey, R.Ph.
Fax:	317-276-1652	Fax:	301-796-1356
Phone:	317-277-0199	Phone:	301-796-9845
Pages (including cover):	1	Date:	September 17, 2007
Re:	NDA 21-462/S-015 Alimta		

☐ Urgent x For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

● Comments:

Dear Dan,

Please refer to your NDA 21-462 supplement 015, submission dated August 27, 2007 for the following proposed new indication, ALIMTA in combination with cisplatin therapy is indicated for the initial treatment of patients with locally advanced or metastatic non-srna11 cell lung caneer and as a single- agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

The medical has the following information request.

> Please provide an electronic listing of participating sites for study JMDB, the prinicipal investigator at each site and patient accrual, by study arm, at each.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Senior Regulatory Project Manager
Division of Drug Oncology Products

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/s/

Patricia Garvey
9/17/2007 06:56:32 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
See attached Listing 1.0 of protocol H3E-MC-JMDB(a) clinical investigators	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Allen Melemed, MD	Medical Director
FIRM / ORGANIZATION: Eli Lilly and Company	
SIGNATURE: A Melemed	DATE: 06 AUG 2007

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Listing 1.0. Investigators and Sub-Investigators in compliance with the requirement for financial clarification and disclosure information (21 CRF, Part 54). Protocol H3E-MC-JMDB(a).

Investigator Name (Last Name first)	Institution Name and City and State, Province, etc.	Site Number	Lilly Affiliate
(b) (6)			

72 Pages have been Withheld as b4 (CCI) immediately following this page

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☒ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Allen Melemed, MD	Medical Director
FIRM / ORGANIZATION: Eli Lilly and Company	
SIGNATURE: A Melemed	DATE: 06-Aug-07

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

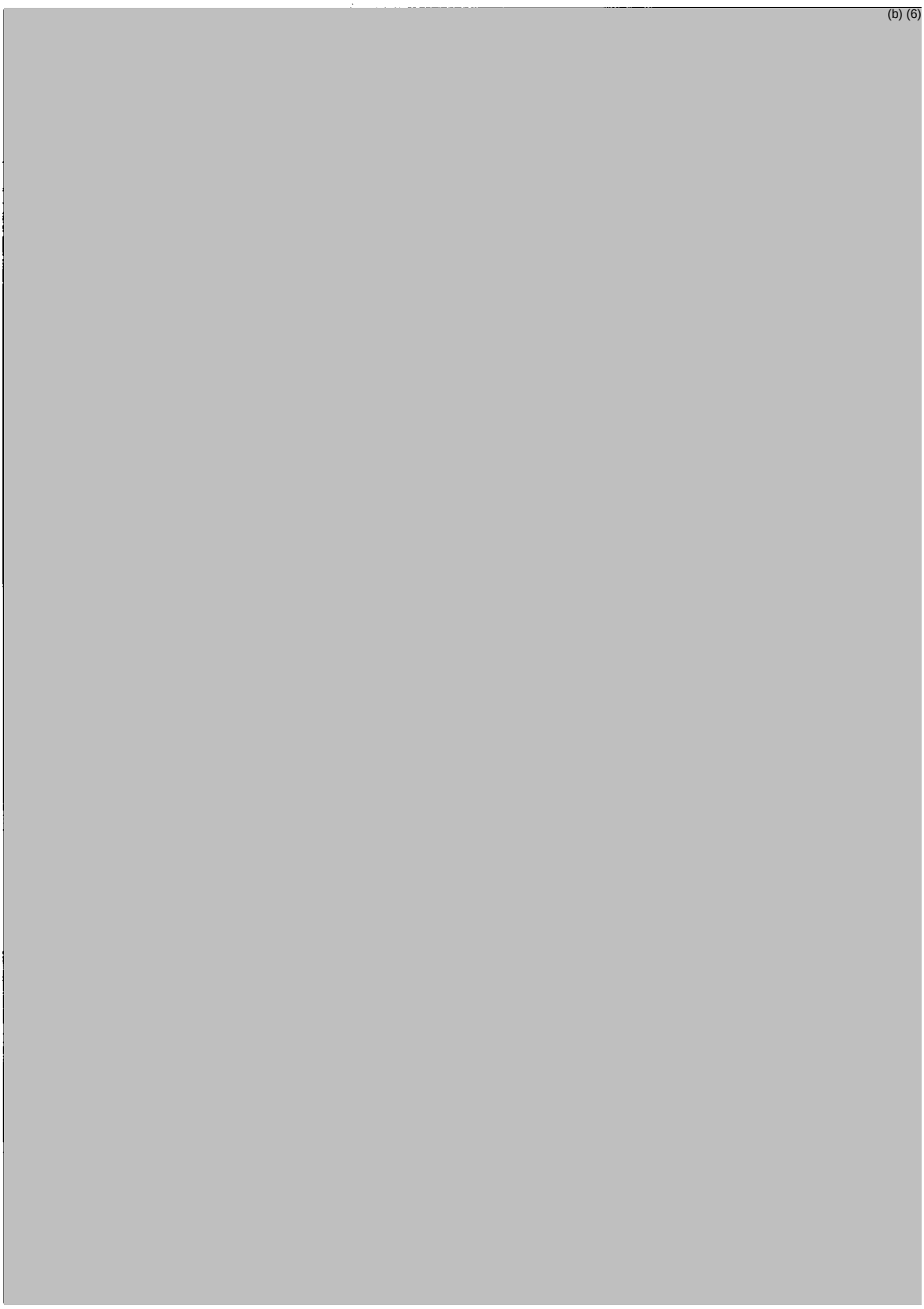
PSC Graphics: (301) 443-1090 EF

Listing 2.0. Investigators and Sub-Investigators in noncompliance with the requirement for financial clarification and disclosure information (21 CFR Part 54). Protocol H3E-MC-JMDB(a).

Description: Listing 2.0 presents a listing of investigators who did not provide financial certification and disclosure information. Due diligence was conducted to obtain this information from each of the investigators listed. These investigators did not respond to either certified mail, electronic mail, or telephone requests. Based on Eli Lilly and Co's records of payments, the following investigators did not have a disclosable financial interest as defined in 21 CFR Part 54.

Investigator Name (Last Name First)	Institution Name and City and State, Province, etc.	Site Number	Lilly Affiliate
(b) (4)			

(b) (6)



(b) (6)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

TO BE COMPLETED BY APPLICANT

The following information concerning Dr. (b) (6) _____, who participated
Name of clinical investigator

as a clinical investigator in the submitted study (b) (6) _____
Name of

_____, is submitted in accordance with 21 CFR part 54. The
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Allen Melemed, MD	Medical Director
FIRM / ORGANIZATION: Eli Lilly and Company	
SIGNATURE: A J Melemed	DATE: 06-Aug-07

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Disclosure of Financial Interest and Arrangement of Clinical Investigators:

The following clinical investigator was identified as having participated in financial arrangements or has had financial interests that are required to be disclosed (Form FDA 3455). The equity interests that the investigator holds did not influence in any way the outcome of this trial.

(b) (6)			
Investigator Name	Institution Name	Lilly Affiliate	Site Number
(b) (6), MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$32,208.00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

TO BE COMPLETED BY APPLICANT

The following information concerning Dr. (b) (6) _____, who participated
Name of clinical investigator

as a clinical investigator in the submitted study (b) (6) _____
Name of

_____, is submitted in accordance with 21 CFR part 54. The
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Allen Melemed, MD	Medical Director
FIRM / ORGANIZATION: Eli Lilly and Company	
SIGNATURE	DATE: 06-AUG-07

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

PSC Graphics: (301) 443-1090 EF

Disclosure of Financial Interest and Arrangement of Clinical Investigators:

The following clinical investigator was identified as having participated in financial arrangements or has had financial interests that are required to be disclosed (Form FDA 3455). The equity interests that the investigator holds did not influence in any way the outcome of this trial.

(b) (6)			
Investigator Name	Institution Name	Lilly Affiliate	Site Number
(b) (6) MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$53,288.09
Professional Services	$37,500.00
Symposia	$ 8,403.26
Speakers Program	$10,823.30

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

TO BE COMPLETED BY APPLICANT

The following information concerning (b) (6) _____, who participated
Name of clinical investigator

as a clinical investigator in the submitted study (b) (6) _____
Name of

_____, is submitted in accordance with 21 CFR part 54. The
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

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☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Allen Melemed, MD	Medical Director
FIRM / ORGANIZATION: Eli Lilly and Company	
SIGNATURE: A Melemed	DATE: 06-Aug-07

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

PSC Graphics: (301) 443-1090 EF

Disclosure of Financial Interest and Arrangement of Clinical Investigators:

The following clinical investigator was identified as having participated in financial arrangements or has had financial interests that are required to be disclosed (Form FDA 3455). The equity interests that the investigator holds did not influence in any way the outcome of this trial.

(b) (6)			
Investigator Name	Institution Name	Lilly Affiliate	Site Number
(b) (6) A/Prof.	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$12,406.94
Speakers Program	$14,584.75
Symposia	$ 6,565.45

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Dr. (b) (6) _____, who participated
Name of clinical investigator

as a clinical investigator in the submitted study (b) (6) _____
Name of

_____, is submitted in accordance with 21 CFR part 54. The
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Allen Melemed, MD	Medical Director
FIRM / ORGANIZATION: Eli Lilly and Company	
SIGNATURE: A Melemed	DATE: 06-Aug-07

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

PSC Graphics: (301) 443-1090 EF

Disclosure of Financial Interest and Arrangement of Clinical Investigators:

The following clinical investigator was identified as having participated in financial arrangements or has had financial interests that are required to be disclosed (Form FDA 3455). The equity interests that the investigator holds did not influence in any way the outcome of this trial.

(b) (6)			
Investigator Name	Institution Name	Lilly Affiliate	Site Number
(b) (6), MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$43,258.36

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

TO BE COMPLETED BY APPLICANT

The following information concerning Prof. (b) (6) _____, who participated
Name of clinical investigator

as a clinical investigator in the submitted study (b) (6) _____
Name of

_____, is submitted in accordance with 21 CFR part 54. The
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named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

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☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Allen Melemed, MD	Medical Director
FIRM / ORGANIZATION: Eli Lilly and Company	
SIGNATURE	DATE: 06-Aug-07

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(b) (6)			
Investigator Name	Institution Name	Lilly Affiliate	Site Number
(b) (6), Prof.	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$46,220.94
Professional Services	$46,875.00
Speakers Program	$46,646.31
Symposia	$19,783.65

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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SIGNATURE	DATE: 06-AUG-07

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FORM FDA 3455 (4/06)

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(b) (6)			
Investigator Name	Institution Name	Lilly Affiliate	Site Number
(b) (6), MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Honoraria	$39,600

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

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FIRM / ORGANIZATION: Eli Lilly and Company	
SIGNATURE	DATE: 06-AUG-07

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(b) (6)			
Sub-Investigator Name	Institution Name	Lilly Affiliate	Site Number
(b) (6), MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$ 5,936.40
Professional Services	$ 2,666.14
Speakers Program	$17,439.33
Symposia	$ 1,269.75

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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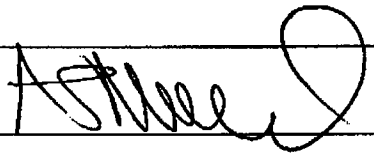
NAME	TITLE
Allen Melemed, MD	Medical Director
FIRM / ORGANIZATION Eli Lilly and Company	
SIGNATURE 	DATE 06-AUG-07

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FORM FDA 3455 (4/06)

PSC Graphics (301) 443-1090 EF

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(b) (6)			
Investigator Name	Institution Name	Lilly Affiliate	Site Number
(b) (6), MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Consulting Fees	$29,702.97

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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Allen Melemed, MD	Medical Director
FIRM / ORGANIZATION: Eli Lilly and Company	
SIGNATURE: A S Melemed	DATE: 06-Aug-07

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(b) (6)			
Investigator Name	Institution Name	Lilly Affiliate	Site Number
(b) (6) Prof.	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$78,757.00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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(b) (6)			
Investigator Name	Institution Name	Lilly Affiliate	Site Number
(b) (6) MD	(b) (6)	(b) (6)	(b) (6)

Disclosure of Financial Information (USD)	
Speaker and Consulting Fees	$22,371.24
Speakers Program	$61,477.75
Symposia	$12,194.91

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

IND 40,061

Eli Lilly and Company
Attention: Colleen Mockbee, R.Ph., RAC
Associate Director, Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Mockbee:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alimta® (pemetrexed).

We also refer to the meeting between you and the FDA on June 6, 2007, the purpose of this meeting was to review the key results of study JMDB.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions me at (301)796-1356.

Sincerely,

{See appended electronic signature page}

Patricia N. Garvey, R.Ph.
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

CHERYL BEAL ANDERSON

JUL - 5 2007

MEETING MINUTES

MEETING DATE: June 6, 2007 **TIME:** 10:00 a.m.

IND 40,061 **Meeting Request Submission Date:** 3-22-07; sn970
Briefing Document Submission: 5-3-07; sn979

DRUG: Alimta® (pemetrexed)

SPONSOR/APPLICANT: Eli Lilly and Company

TYPE OF MEETING:

1. Guidance - Clinical (Type B)

2. **Proposed Indication:**
   a. Alimta as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy. The effectiveness of Alimta in second-line NSCLC was based on the surrogate endpoint, response rate. There are no controlled trials demonstrating a clinical benefit, such as a favorable survival effect or improvement of disease-related symptoms.
   b. Alimta in combination with platinum-based therapy or as a single agent used as maintenance therapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer.

FDA PARTICIPANTS:

Robert Justice, M.D.	--	Director, Division of Drug Oncology Products (DDOP)
John Johnson, M.D.	--	Medical Team Leader, DDOP (Chair)
Martin Cohen, M.D.	--	Medical Reviewer, DDOP
Rajeshwari Sridhara, Ph.D.	--	Statistical Team Leader, Division of Biometrics I (DBI)
Shenghui Tang, Ph.D.	--	Statistical Reviewer, DBI
Patty Garvey, R.Ph.	--	Senior Regulatory Project Manager, DDOP (Facilitator)
Pre-meeting: Ann Farrell, M.D.	--	Acting Deputy Director, DDOP

INDUSTRY PARTICIPANTS:

Richard Gaynor, M.D.	--	Vice President, Cancer Research and Oncology Platform Team
Cheryl Beal Anderson, Pharm.D.	--	Director, U.S. Regulatory Affairs
Allen Melemed, M.D.	--	Medical Director, Oncology
Patrick Peterson	--	Statistician, Oncology
Lorinda Simms	--	Statistician, Oncology
Colleen Mockbee, R.Ph.	--	Associate Director, U.S. Regulatory Affairs

MEETING OBJECTIVES:

1. To seek FDA input on the proposed submission plans for Study JMDB.
2. To discuss plans to submit the proposed sNDA including label formatting in compliance with Physician's Labeling Rule.

BACKGROUND:

On August 19, 2004, Alimta received accelerated approval for Alimta as a single agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy. As a condition of the approval, as per Subpart H, studies JMDB, "A Multicenter, Randomized Phase III Trial of Alimta and Cisplatin Versus Gemzar and Cisplatin in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer" and JMEN were required to confirm and describe the clinical benefit of Alimta. Study JMDB is indicated for 1st line non-small cell lung cancer and will be completed in first quarter 2007. Study JMEN is indicated for maintenance treatment for advanced non-small cell lung cancer.

On January 11, 2007, the sponsor met with the FDA to discuss the sponsor proposed sNDA submission in support of converting the approval status of Alimta from accelerated approval to full approval and completion of the Phase 4 commitments. At this meeting, FDA indicated that the proposed margin for non-inferiority in Study JMDB would not be adequate for a claim. However, FDA agreed to meet and further discuss the submission of Study JMDB once results were available. Therefore, the purpose of this meeting is to review the key results for Study JMDB. The sponsor is seeking a claim for Alimta in 1st line NSCLC and in the maintenance setting.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

I. JMDB Study Results: sNDA in First-line NSCLC

1. Lilly believes that the observed survival hazard ratio and percent retention for Study JMDB demonstrate the clinical benefit of Alimta in combination with cisplatin for the initial treatment of locally advanced or metastatic NSCLC. Does FDA agree that the results are adequate to submit for review in support of a supplemental indication for Alimta as initial treatment of locally advanced or metastatic NSCLC?

   FDA Response:

   No. As indicated, in the facsimile dated December 14, 2006 and January 11, 2007 meeting minutes, the Sandler study with 28 days Gemzar plus cisplatin regimen is not acceptable for use in your non-inferiority analysis of a 3 week Gemzar plus cisplatin regimen. Also, the cisplatin dose in the Sandler trial and Study JMDB were different.

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JUL - 5 2007

The Sandler trial was the only randomized trial directly comparing Gemzar plus cisplatin to single-agent cisplatin. Its 28 day gemzar/cisplatin regimen is different from the regimen used in Study JMDB. Although the survival effect of Gemzar plus cisplatin relative to single-agent cisplatin could be estimated based on data from the Sandler trial, the variation of this effect between trials remains unknown. Therefore, your percent retention analysis will be considered as exploratory.

Please note that your proposed fixed margin and analysis will not be acceptable for a non-inferiority claim.

Discussion:

The sponsor will submit the study discussed as a phase 4 commitment. The sponsor will provide further data to support the 21 day regimen and dosage with the sNDA.

The sponsor will request an application orientation presentation.

The FDA requested that the DMC recommendations be submitted with the sNDA.

2. Since Study JMDB is a Phase IV Commitment study, Lilly understands that the current accelerated approval status of Alimta will be converted to regular approval if FDA's review concludes that Study JMDB demonstrates the clinical benefit of Alimta. Does FDA agree?

   FDA Response: No, please see response to question #1.

   Discussion: There was no further discussion.

3. In addition to the advantages in certain subgroups observed, significant improvements in toxicity were observed in the overall population for patients treated with Alimta plus cisplatin. Lilly believes these results provide significant advances in the initial treatment of NSCLC. Lilly plans to request priority review of this sNDA. Is FDA open to consideration of this application for priority review?

   FDA Response: No, please see response to question #1.

   Discussion: There was no further discussion.

4. Does the FDA have any comments on particular issues or analyses that it feels the sponsor needs to address in the sNDA?

   FDA Response: Please see response to question #1.

   Discussion: There was no further discussion.

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II. Structure and Format

5. Lilly will submit this sNDA as an eCTD. However, Lilly proposes submitting the Clinical Study Reports as a single file in .PDF format rather than the granular modules. Is the FDA agreeable to this proposal?

   FDA Response:

   Please see response to question #1.

   Discussion:

   FDA requested that the annotated blank CRFs be submitted with the sNDA. The CRFs for notable patients will be submitted as previously agreed.

6. Does FDA agree with the proposal to present safety data in the label using Adverse Reactions?

   FDA Response: Please see response to question #1.

   Discussion:

   FDA confirmed that the label should be submitted using adverse reactions.

7. Does FDA agree with the proposed safety update and cases to be included in the section for Post-Marketing experience including waiver of the 4-month safety update as outlined?

   FDA Response: Please see response to question #1.

   Discussion: FDA agreed with the sponsor proposal.

8. Does the Agency agree with this proposal to request pediatric waiver?

   FDA Response: Please see response to question #1.

   Discussion: FDA agreed with the sponsor proposal.

General discussion:

1. FDA requested that the CRF be submitted with the sNDA.
2. The sponsor will submit the SAP for the JMEN study.

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ACTION ITEMS:

1. The sponsor will submit the study discussed as a phase 4 commitment. The sponsor will provide further data to support the 21 day regimen and dosage with the sNDA.

2. The sponsor will request an application orientation presentation.

3. The FDA requested that the DMC recommendations be submitted with the sNDA.

4. FDA requested that the annotated blank CRFs be submitted with the sNDA. The CRFs for notable patients will be submitted as previously agreed.

5. The sponsor will submit the SAP for the JMEN study.

There was no unresolved issue. The meeting concluded at 10:47 a.m.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Senior Regulatory Project Manager

Concurrence Chair:

{See appended electronic signature page}

John Johnson, M.D.
Medical Team Leader

Attachment: Sponsor slide presentations

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JUL - 5 2007

Soto- Gem cis 21 vs 28 day Phase 2 trial

	4 week n= 54	3 week n=53	p value
ORR	38%	42%	NR
Med OS mo	9.2	12.1	p = 0.49
Dose Intensity (mg/week)	Gem (592.8) Cisplatin (16.7)	Gem (589.9) Cisplatin (21.5)	p = 0.89 p = 0.0001
G3/4 neutropenia	22.5%	27.8%	p = 0.69
G3/4 platelets	29.5%	5.5%	p = 0.14

Gemcitabine 1000 mg/m2 and cisplatin 70 mg/m2 on each arm

Gemcitabine plus Cisplatin in Phase-3 Trials

	Study Reference	Pts (#)	ORR (%)	Med TTP (mo)	Med Surv (mo)	1-Yr OS (%)
28-day Regimens (4 trials)	Crino et al. 1999	155	38	5.0	8.6	33
	Sandler et al. 2000	260	30	5.6	9.1	39
	Schiller et al. 2002	301	22	4.2	8.1	36
	Gebbia et al. 2003	138	30	4.0	8.2	20
	Total number of Pts	**854**				
21-day Regimens (12 trials)	Cardenal et al. 1999	69	41	6.9	8.7	32
	Comella et al. 2001	118	28	4.4	8.8	-
	Scagliotti et al. 2002	205	30	5.3	9.8	37
	Alberola et al. 2003	182	42	6.3	9.3	38
	Smit et al. 2003	160	37	5.1	8.9	33
	Wachters et al. 2003	119	46	6.0	9.9	45
	Zatloukal et al. 2003	87	41	5.9	8.8	33
	Giaccone et al. 2004	363	47	6.0	10.9	44
	Bissett et al. 2005	181	26	5.5	10.8	38
	Paz-Ares et al. 2006	328	35	6.0	10.4	45
	Gatzemeier et al. 2007	579	30	5.7	10.2	42
	JMDB	863	28	5.1	10.3	42
	Total number of Pts	**3254**				

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/s/

Patricia Garvey
6/29/2007 11:47:06 AM

John Johnson
6/29/2007 12:04:21 PM

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/s/

Patricia Garvey
6/29/2007 01:28:57 PM

CHERYL BEAL ANDERSON

JUL - 5 2007

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

IND 40,061

Eli Lilly and Company
Attention: Colleen Mockbee, R.Ph., RAC.
Associate Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Mockbee:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alimta™ (pemetrexed).

We also refer to the meeting between you and the FDA on January 11, 2007, the purpose of this meeting was to discuss your proposed sNDA submission in support of converting the approval status of Alimta from accelerated approval to full approval and completion of the Phase 4 comments.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions me at (301)796-1356.

Sincerely,

{See appended electronic signature page}

Patricia N. Garvey, R.Ph.
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

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MEETING MINUTES

MEETING DATE: January 11, 2007 **TIME:** 1:00 p.m.

IND 40,061 **Meeting Request Submission Date:** 10-18-06; sn920
Briefing Document Submission: 12-8-06; sn935

DRUG: Alimta® (pemetrexed)

SPONSOR/APPLICANT: Eli Lilly and Company

TYPE OF MEETING:

1. Pre-sNDA (Type B)

2. **Proposed Indication:**
   a. Alimta as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.
   b. Alimta in combination with platinum-based therapy or as a single agent used as maintenance therapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer.

FDA PARTICIPANTS:

Robert Justice, M.D.	--	Director, Division of Drug Oncology Products (DDOP)
John Johnson, M.D.	--	Medical Team Leader, DDOP (Chair)
Martin Cohen, M.D.	--	Medical Reviewer, DDOP
Rajeshwari Sridhara, Ph.D.	--	Statistical Team Leader, Division of Biometrics I (DBI)
Shenghui Tang, Ph.D.	--	Statistical Reviewer, DBI
Patty Garvey, R.Ph.	--	Senior Regulatory Project Manager, DDOP (Facilitator)
Pre-meeting: Ann Farrell, M.D.	--	Acting Deputy Director, DDOP
Laurie Burke, R.Ph, MPH	--	Director, Study Endpoint and Labeling Development (SEALD) Team
Melissa Furness	--	Endpoint Reviewer, SEALD

INDUSTRY PARTICIPANTS:

Richard Gaynor, M.D.	--	Vice President, Cancer Research and Oncology Platform Team
Cheryl Beal Anderson, Pharm.D.	--	Director, U.S. Regulatory Affairs
Allen Melemed, M.D.	--	Medical Director, Oncology
Coleman Obasaju, M.D.	--	Medical Director, Oncology
Katherine Posther Sugarman,M.D.	--	Clinical Research Physician, Oncology
Susumu Adachi	--	Clinical Research Physician, Oncology
Patrick Peterson	--	Statistician, Oncology
Colleen Mockbee, R.Ph.	--	Associate Director, U.S. Regulatory Affairs

MEETING OBJECTIVES:

1. To seek FDA input on the proposed contents of the sNDA.
2. To seek FDA input on the use of PFS as an endpoint in the maintenance treatment of patients with locally advanced or metastatic lung cancer.

BACKGROUND:

On August 19, 2004, Alimta received accelerated approval for Alimta as a single agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy. As a condition of the approval, as per Subpart H, studies JMDB and JMEN were required to confirm and describe the clinical benefit of Alimta. Study JMDB is indicated for 1st line non-small cell lung cancer and will be completed in first quarter 2007. Study JMEN is indicated for maintenance treatment for advanced non-small cell lung cancer.

The purpose of this meeting is to discuss the sponsor proposed sNDA submission in support of converting the approval status of Alimta from accelerated approval to full approval and completion of the Phase 4 commitments.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

I. Status of Postmarketing Study Commitments

1. Does FDA require the results of each study required under Subpart H be submitted as an sNDA with a PDUFA User Fee regardless of study outcome (i.e., whether a label claim is sought or not)?

   FDA Response:

   Study JMDB and study JMEN seek different indications, the former being first line therapy of previously untreated advanced/metastatic NSCLC, the latter being maintenance therapy of non-progressing advanced/metastatic NSCLC patients after 4 cycles of a platinum regimen. Therefore, they should be submitted as separate sNDA's.

   Discussion:

   The sponsor will submit Study JMDB when complete as a separate sNDA. Please also refer to the discussion for question 2.

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II. sNDA Second-Line Regular Approval

2a. Does FDA agree the proposed submission package is sufficient to file this sNDA for FDA review for conversion of Alimta's approval in second-line lung cancer to regular approval?

FDA Response:

We remind Lilly that the 21 day Gemzar/Cisplatin study did not show a statistically significant survival effect, p=0.18 (See Gemzar PI). In addition we have concerns with the proposed SAP for JMDB and further discussions will be necessary. Please see comments on the submission serial number 918 to IND 40061.

Filing decisions are not made until after the application is submitted.

Discussion:

The sponsor will follow-up with the FDA once the results of study JMDB are available approximately April/May 2007.

The FDA added that the 21 day gemzar/cisplatin regimen used in study JMDB is not the same as the 21 day gemzar/cisplatin regimen referred to in the gemzar label.

In response to serial number 918 FDA comments, the sponsor clarified that the interim analyses were for futility and therefore no type I error adjustment was considered. The sponsor clarified that first interim was prespecified in the protocol and the second interim was specified as optional based on DSMB recommendations.

The sponsor intends to submit the clarification and DSMB minutes with the results of the study.

2b. Does FDA agree, given a successful outcome of Study JMDB, that the proposed submission package is sufficient to support FDA review of Alimta for the treatment of patients with previously untreated, locally advanced or metastatic lung cancer?

FDA Response: Please see response to question 2a.

Discussion: There was no further discussion.

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3. Does the FDA agree with the proposal for inclusion of Financial Disclosure, Case Report Forms, and Patient Narratives as outlined?

   FDA Response:

   Regarding study JMDB, the CRFs for "notable patients" as defined in the meeting package must be submitted with the sNDA.

   Regarding study JMEN, the requirement for financial disclosure and CRFs submission will be the same as for study JMBD, if the results support a labeling change in Alimta dose.

   Discussion:

   FDA clarified that JMEN referenced in the second bullet should be JMGX as followed:

   > *Regarding study JMGX, the requirement for financial disclosure and CRFs submission will be the same as for study JMBD, if the results support a labeling change in Alimta dose.*

4. Does FDA agree with the proposed submission of CT Scans for the independently reviewed cohort upon agency request?

   FDA Response:

   Regarding the independent review since you potentially plan to include both PFS and RR data in the label, tumor measurements, by cycle, should also be independently reviewed. What was the basis for the selection of only 400 patients and how are these patients selected for review?

   Lilly's proposal to submit CT scans for the independently reviewed cohort upon Agency request is acceptable.

   Discussion:

   The sponsor clarified that the 400 patients were randomly selected from the first thousand randomized patients.

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III. JMEN Maintenance sNDA

5. Does FDA agree PFS is an appropriate primary endpoint to measure the clinical benefit of Alimta in this patient population?

FDA Response:

No. As indicated in the FDA End of Phase 2 (EOP2) meeting minutes, survival should be the primary efficacy endpoint.

Discussion:

The FDA referred to the June 10, 2004 EOP2 meeting minutes discussion points to question 1a regarding the potential for PFS to support approval.

6a. Does FDA agree with the proposed gate-keeping approach for analysis of PFS as the primary endpoint and survival as a secondary endpoint as described?

FDA Response: Please see response to question 5.

Discussion: There was no further discussion.

6b. Does FDA agree a successful outcome of the Phase 3 study, JMEN, in demonstrating superiority of pemetrexed in PFS for the maintenance treatment of patients completing initial treatment for non-small cell lung cancer is sufficient for filing a supplemental NDA for regular approval?

FDA Response: Please see response to question 5.

Discussion: There was no further discussion.

6c. Does FDA agree an updated study report including the final survival analysis would be adequate for FDA review to fulfill the Phase IV commitment and incorporate the survival results into the Alimta label?

FDA Response: Please see response to question 5.

Discussion: There was no further discussion.

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7. Does FDA agree that the analyses plans for assessment of time to worsening of symptoms (TWS) are adequate to further characterize and support the benefit derived by patients from a longer PFS time?

   FDA Response: Please see response to question 5.

   We remind you that your proposed PRO analyses will be considered as exploratory because the analysis plan did not specify allocation of alpha to control a family-wise type I error at a level of 0.025 (one-sided).

   In addition, the LCSS has not been adequately developed to measure worsening of the individual symptoms of fatigue, pain, dyspnea, cough, anorexia, and hemoptysis.

   Imbalanced dropout or missing data between treatment arms may introduce a bias in statistical analysis. If that happens, the results may not be interpretable. Please pre-specify methods to handle missing data. Also statistically significant differences may not necessarily be clinically meaningful.

   Discussion: There was no further discussion.

ACTION ITEMS:

1. The sponsor will submit Study JMDB when complete as a separate sNDA.

2. The sponsor will follow-up with the FDA once the results of study JMDB are available approximately April/May 2007.

3. Regarding study JMDB, the sponsor will submit a clarification that the first interim was prespecified in the protocol and the second interim was specified as optional based on DSMB recommendations. The DSMB minutes with also be submitted with the results of the study.

There was no unresolved issue. The meeting concluded at 1:50 p.m.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Senior Regulatory Project Manager

Concurrence Chair:

{See appended electronic signature page}

John Johnson, M.D.
Medical Team Leader

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/s/

Patricia Garvey
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John Johnson
1/30/2007 11:30:59 AM

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/s/

Patricia Garvey
1/31/2007 10:01:58 AM

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