2. S021 Synopsis

Clinical Study Report Synopsis: Study H6Q-MC-S021

Title of Study: Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of Pemetrexed and Cisplatin plus Enzastaurin versus Pemetrexed and Cisplatin plus Placebo in Chemonaive Patients with Advanced, Unresectable, or Metastatic (Stage IIIB or IV) Nonsquamous Non-Small Cell Lung Cancer

Number of Investigators: This multicenter study included 6 principal investigators.

Study Centers: This study was conducted at 6 study centers in 3 countries.

Publication(s) Based on the Study: None at this time.

Length of Study:
Date of first patient visit: 14 September 2007
Date last patient completed: 26 November 2008

Phase of Development: 2

Objectives:

Part 1

- To evaluate the safety of enzastaurin plus pemetrexed and cisplatin in terms of toxicities, serious adverse events (SAEs), and reasons for discontinuation.

Part 2

- To compare progression-free survival (PFS) of enzastaurin, pemetrexed, and cisplatin, followed by maintenance enzastaurin (Arm A), to that of placebo, pemetrexed, and cisplatin, followed by maintenance placebo (Arm B).
- To compare response and disease control rates between treatment arms; to evaluate time-to-efficacy variables (overall survival [OS], duration of disease control [DDC], duration of response [DoR], and time to worsening of symptoms [TWS]) of treatment arms; to examine the safety and toxicity profiles of treatment arms; and to assess biomarkers relevant to enzastaurin, pemetrexed, and the disease state, as well as their correlation to clinical outcome.

Study Design: This was a Phase 2 study in chemonaive patients with advanced, unresectable, or metastatic (Stage IIIB or IV) non-small cell lung cancer (NSCLC) conducted in 2 parts. Part 1 was a single-arm, open-label safety lead-in of enzastaurin with pemetrexed and cisplatin. Part 2 was a multicenter, double-blind, randomized, placebo-controlled study of pemetrexed and cisplatin with either enzastaurin (Arm A) or placebo (Arm B).

Number of Patients:

Planned: Part 1 = 8; Part 2 = 120

Enrolled: Part 1 = 13 (9 Cohort 1, 4 Cohort 2); Part 2 = 23 entered, 22 enrolled (11 Arm A, 11 Arm B), 1 patient was not randomized but received pemetrexed and cisplatin

Treated (the number of patients who received at least 1 dose of study treatment [enzastaurin or placebo] or cisplatin and pemetrexed): Part 1 = 13 (9 Cohort 1, 4 Cohort 2); Part 2 = 22 (11 Arm A, 10 Arm B, and 1 patient who was not randomized due to early study closure but was treated with pemetrexed and cisplatin)

Completed: Part 1 = 9 completed 4 or more cycles, 8 entered into maintenance therapy; Part 2 = Early study termination

Diagnosis and Main Criteria for Inclusion: Patients were at least 18 years of age with advanced (Stage IIIB or IV) NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and no prior systemic chemotherapy. For Part 2, the patient population was restricted to advanced NSCLC of nonsquamous histology (adenocarcinoma, large cell carcinoma, and not otherwise specified [NOS] NSCLC histologies).

Study Drug, Dose, and Mode of Administration:

Part 1

Cohort 1: Cycle 1: Enzastaurin loading dose 500 mg orally (po) on Day 1 of a 28-day cycle and 125 mg po twice daily (BID), with pemetrexed 500 mg/m^2 intravenous (iv) and cisplatin 75 mg/m^2 iv on Day 8. Cycles 2-6: Enzastaurin 125 mg po BID, with pemetrexed 500 mg/m^2 iv and cisplatin 75 mg/m^2 iv on Day 1 of 21-day cycle. Maintenance therapy with enzastaurin 125 mg BID was planned to begin on the day combination chemotherapy ended and continue until disease progression (PD).

Cohort 2: Cycle 1: Enzastaurin loading dose 375 mg po 3 times daily (TID) on Day 1 of a 28-day cycle and 250 mg po BID thereafter, with pemetrexed 500 mg/m^2 iv and cisplatin 75 mg/m^2 iv on Day 8. Cycles 2-6: Enzastaurin 250 mg po BID, with pemetrexed 500 mg/m^2 iv and cisplatin 75 mg/m^2 iv on Day 1 of 21-day cycle. Maintenance therapy with enzastaurin 250 mg daily BID was planned to begin on the day combination chemotherapy ended and continue until PD.

Part 2 (Arm A)

Cycle 1: Enzastaurin loading dose 375 mg po TID on Day 1 of a 28-day cycle and enzastaurin 250 mg po BID thereafter, with pemetrexed 500 mg/m^2 iv and cisplatin 75 mg/m^2 iv on Day 8. Cycles 2-6: Enzastaurin 250 mg po BID, with pemetrexed 500 mg/m^2 iv and cisplatin 75 mg/m^2 iv on Day 1 of a 21-day cycle. Maintenance therapy with enzastaurin 250 mg daily BID was planned to begin on the day combination chemotherapy ended and continue until PD.

Reference Therapy, Dose, and Mode of Administration (Part 2; Arm B): Cycle 1: Placebo TID on Day 1 of a 28-day cycle and placebo BID thereafter, with pemetrexed 500 mg/m^2 iv and cisplatin 75 mg/m^2 iv on Day 8. Cycles 2-6: Placebo BID, with pemetrexed 500 mg/m^2 iv and cisplatin 75 mg/m^2 iv on Day 1 of a 21-day cycle. Maintenance therapy with placebo BID was planned to begin on the day combination chemotherapy ended and continue until PD.

Duration of Treatment: Combination chemotherapy with enzastaurin or placebo consisted of 4 cycles if the patient's best study response was stable disease (SD) or up to 6 cycles if the patient's best study response was complete response (CR) or partial response (PR), unless the patient discontinued due to PD or for any other reason. Upon completion of combination chemotherapy, patients who did not have PD continued to maintenance therapy with enzastaurin or placebo. Maintenance treatment with either enzastaurin or placebo was planned to continue until PD or discontinuation for any other reason.

Variables:

Safety: Primary endpoint of Part 1 was a safety assessment (toxicities, adverse events, and reasons for discontinuation). Part 2 assessed whether any unusual or unexpected adverse events occurred beyond the known safety profile of pemetrexed, cisplatin and enzastaurin, assessed any unusual toxicity observed from any patient, and recorded deaths and discontinuations.

Efficacy: The primary efficacy endpoint was to evaluate and compare PFS in Arms A and B (Part 2) after a minimum of 90 events (PD or deaths). Secondary endpoints were response (CR, PR, or SD), OS, DDC, DoR, and TWS.

Bioanalytical: Biomarkers relevant to enzastaurin, pemetrexed, and the disease state were to be assessed, as was their correlation to clinical outcome.

Evaluation Methods:

Safety: Safety was summarized by the number of deaths, adverse events as evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) rating scale, Version 3.0 (NCI 2006), and the number of discontinuations.

Efficacy: No statistical evaluations were performed for the primary and secondary endpoints.

Bioanalytical: No statistical evaluations were performed.

Summary:

Demographic and baseline characteristics for all enrolled patients are provided in Table S021.1, below.

Table S021.1. Demographic and Baseline Characteristics by Treatment Group – Enrolled and Treated Patients

	Part 1			Part 2			
	Cohort 1 (N = 9)	**Cohort 2 (N = 4)**	**Total (N = 13)**	**Arm A (N = 11)**	**Arm B (N = 10)**	**Other[c] (N = 1)**	**Total (N = 22)**
Sex, Female/Male, n	1/8	2/2	3/10	6/5	6/4	1/0	13/9
Age (years), mean (SD)	58.3 (9.32)	61.2 (6.85)	59.2 (8.46)	58.6 (9.62)	59.5 (9.39)	49.1 (NA)	58.6 (9.30)
Diagnosis Adeno/ Large/Other[a], n	7/1/1	3/0/1	10/1/2	6/3/2	7/2/1	1/0/0	14/5/3
Disease Stage IIIb/IV, n	0/8[b]	0/4	0/12[b]	1/10	2/8	0/1	3/19
Time Since Diagnosis (days), mean (SD)	23.0 (24.6)	8.3 (9.98)	18.5 (21.9)	28.7 (49.2)	19.2 (12.1)	21.0 (NA)	24.0 (35.2)
ECOG PS 0/1, n	1/8	1/3	2/11	4/7	3/7	0/1	7/15

Abbreviations: Adeno = adenocarcinoma; Arm A = enzastaurin with pemetrexed/cisplatin; Arm B = placebo with pemetrexed/cisplatin; ECOG PS = Eastern Cooperative Oncology Group performance status; Large = large cell lung carcinoma; N = number of enrolled patients; n = number of patients in each category; NA = not applicable; NOS = not otherwise specified; SD = standard deviation; TNM = tumor, nodal involvement, metastases.

[a] Other diagnoses included squamous cell carcinoma (2 Part 1 [1 Cohort 1, 1 Cohort 2]), and NOS non-small cell carcinoma (3 Part 2 [2 Arm A, 1 Arm B]).

[b] No disease stage was derived for Patient [redacted] in Part 1 (Cohort 1); the patient had the TNM classification T4N3MX.

[c] Patient [redacted] was not randomized to Arm A or Arm B but was treated with pemetrexed and cisplatin.

Sources: t_demo, t_patdis, t_pathdiag, t_physcar, t_diseasebl.

Part 1

Of the 10 patients entered in Cohort 1, 9 patients were enrolled and 1 patient was considered a screen failure. One patient discontinued before completing Cycle 1 due to the serious adverse event (SAE) of ileus paralytic (related to study drugs) and that patient was replaced according to protocol. Eight patients in Cohort 1 completed Cycle 1.

Five patients were initially enrolled in Cohort 1 and completed Cycle 1. Three of those patients each experienced 1 SAE in Cycle 1 considered by the investigator to be possibly related to study drug(s): pulmonary embolism, amylase elevated, and venous thrombosis. One patient experienced Grade 3 arthralgia and myalgia during Cycle 1, possibly related to enzastaurin. No relevant toxicities were observed in 1 patient in Cycle 1. After these data were reviewed, the decision was made to extend enrollment to further evaluate the

safety of the combination therapy. Three additional patients were enrolled in Cohort 1, none of whom experienced a Grade 2 to 4 study-drug-related adverse event (AE) in Cycle 1. Table S021.2 summarizes Grade 3/4 AEs for Cycle 1.

Table S021.2. Adverse Events by Cohort Grade 3 or 4 CTCAE Treatment Emergent Cycle 1, Part 1

	Cohort 1 (N = 9)	Cohort 2 (N = 4)	Total (N = 13)
Nonlaboratory			
Pericardial effusion, n (%)	1 (11.1)	0	1 (7.7)
Respiratory tract infection, n (%)	1 (11.1)	0	1 (7.7)
Oxygen saturation decreased, n (%)	1 (11.1)	0	1 (7.7)
Arthralgia, n (%)	1 (11.1)	0	1 (7.7)
Myalgia, n (%)	1 (11.1)	0	1 (7.7)
Dyspnea, n (%)	2 (22.2)	0	2 (15.4)
Pleural effusion, n (%)	1 (11.1)	0	1 (7.7)
Pulmonary embolism, n (%)	1 (11.1)	0	1 (7.7)
Laboratory			
Hyponatremia, n (%)	1 (11.1)	0	1 (7.7)
Amylase elevated, n (%)	1 (11.1)	0	1 (7.7)
Number of Patients ≥ 1 Event (%)	**4 (44.4)**	**0**	**4 (44.4)**

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events (NCI 2006); N = number of enrolled patients; n = number of patients with event; NCI = National Cancer Institute.
Sources: l_ae, t_aeall.

All patients (N = 4) enrolled in Cohort 2 completed Cycle 1. There were no SAEs or study-drug-related Grade 2 to 4 AEs in Cycle 1 for Cohort 2. One patient in Cohort 2 was discontinued at Cycle 4 due to myalgia.

For all cycles in Part 1 and through the 30-day postdiscontinuation follow-up visit, there were 14 Grade 3 or 4 (3/4) treatment-emergent nonlaboratory AEs (12 in Cohort 1 and 2 in Cohort 2; Table S021.3) and 4 Grade 3/4 treatment-emergent laboratory AEs (3 in Cohort 1 and 1 in Cohort 2; Table S021.4). Of the 14 Grade 3/4 nonlaboratory AEs, 4 were considered possibly related to study drug(s): pulmonary embolism, arthralgia, and both events of myalgia. Of the 4 Grade 3/4 laboratory AEs, only amylase elevated was considered possibly related to study drug(s).

One abnormal baseline electrocardiogram (ECG) was reported in Cohort 1 (atrial fibrillation). No patient required a transfusion.

Table S021.3. Adverse Events by Treatment Group
Grade 3 or 4 CTCAE
Nonlaboratory – Treatment Emergent
On Therapy or Within 30 Days of Discontinuation

	Part 1			Part 2			
	Cohort 1 (N = 9)	Cohort 2 (N = 4)	Total (N = 13)	Arm A (N = 11)	Arm B (N = 10)	Other (N = 1)	Total[a] (N = 22)
Pericardial effusion, n (%)	1 (11.1)	0	1 (7.7)	0	0	0	0
Chest pain, n (%)	2 (22.2)	0	2 (15.4)	0	0	0	0
Fatigue, n (%)	1 (11.1)	0	1 (7.7)	0	0	0	0
Lung infection, n (%)	0	0	0	1 (9.1)	0	0	1 (4.5)
Respiratory tract infection, n (%)	1 (11.1)	0	1 (7.7)	0	0	0	0
Oxygen saturation decreased, n (%)	1 (11.1)	0	1 (7.7)	0	0	0	0
Arthralgia, n (%)	1 (11.1)	0	1 (7.7)	0	0	0	0
Myalgia, n (%)	1 (11.1)	1 (25.0)	2 (15.4)	0	0	0	0
Dyspnea, n (%)	2 (22.2)	0	2 (15.4)	1 (9.1)	0	0	1 (4.5)
Pleural effusion, n (%)	1 (11.1)	0	1 (7.7)	0	1 (10.0)	0	1 (4.5)
Pulmonary embolism, n (%)	1 (11.1)	0	1 (7.7)	0	0	0	0
Arterial occlusive disease, n (%)	0	1 (25.0)	1 (7.7)	0	0	0	0
Number of Patients ≥ 1 Event (%)	**5 (55.6)**	**1 (25.0)**	**6 (46.2)**	**2 (18.2)**	**1 (10.0)**	**0**	**3 (13.6)**

Abbreviations: Arm A = enzastaurin with pemetrexed/cisplatin; Arm B = placebo with pemetrexed/cisplatin; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2006); N = number of enrolled patients; n = number of patients with event; NCI = National Cancer Institute.

[a] Patient [redacted] was not randomized to Arm A or Arm B but was treated with pemetrexed and cisplatin.

Sources: l_all, t_aeall.

Table S021.4. Adverse Events by Treatment Group
Grade 3 or 4 CTCAE
Laboratory – Treatment Emergent
On Therapy or Within 30 Days of Discontinuation

	Part 1			Part 2			
	Cohort 1 (N = 9)	**Cohort 2 (N = 4)**	**Total (N = 13)**	**Arm A (N = 11)**	**Arm B (N = 10)**	**Other[a] (N = 1)**	**Total (N = 22)**
Anemia, n (%)	1 (11.1)	0	1 (7.7)	3 (27.3)	0	0	3 (13.6)
Neutropenia, n (%)	0	1 (25.0)[b]	1 (7.7)	0	1 (10.0)	0	1 (4.5)
Thrombocytopenia, n (%)	0	0	0	0	1 (10.0)	0	1 (4.5)
Amylase elevated, n (%)	1 (11.1)	0	1 (7.7)	0	0	0	0
Hyponatremia, n (%)	1 (11.1)	0	1 (7.7)	0	0	0	0
Number of Patients ≥ 1 Event (%)	**2 (22.2)**	**1 (25.0)**	**3 (23.1)**	**3 (27.3)**	**2 (20.0)**	**0**	**5 (22.7)**

Abbreviations: Arm A = enzastaurin with pemetrexed/cisplatin; Arm B = placebo with pemetrexed/cisplatin; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2006); N = number of enrolled patients; n = number of patients with event; NCI = National Cancer Institute.

[a] Patient [redacted] was not randomized to Arm A or Arm B but was treated with pemetrexed and cisplatin.

[b] This event of Grade 4 neutropenia was deemed unrelated to study drug but was reported after start of chemotherapy. Patient recovered and continued with a reduced dose of cisplatin and pemetrexed, as per protocol.

Sources: l_all.

Nine patients (69%) remained on combination therapy for at least 4 cycles (1 of those patients was discontinued from enzastaurin due to Grade 3 myalgia in Cycle 1 and continued only with pemetrexed and cisplatin for 3 more cycles; the patient also had Grade 3 arthralgia), and 6 patients (46%) received the maximum 6 cycles of combination therapy. Eight patients started maintenance treatment with enzastaurin, receiving between 1 and 6 cycles of maintenance treatment. There were 5 dose omissions (3 in Cohort 1 and 2 in Cohort 2) and 4 dose reductions (3 in Cohort 1 and 1 in Cohort 2) of enzastaurin in Part 1, all due to AE except 1 dose reduction due to patient decision (Cohort 1).

All patients in Part 1 received the planned supplementation of folic acid, vitamin B_{12}, and dexamethasone.

For patients in Cohort 1, best tumor response was PR for 4 patients, SD for 2 patients, and PD for 2 patients; 1 patient was not assessed after baseline. For patients in Cohort 2, 4 patients were assessed with PR; 1 of those responses was not confirmed.

Part 2

According to the amended protocol, only patients with advanced NSCLC of nonsquamous histology were enrolled in Part 2. Of the 22 patients treated in Part 2, 14 had advanced NSCLC with nonsquamous histology of adenocarcinoma, 5 had large cell carcinoma, and 3 had NOS NSCLC.

Of the 23 patients entered in the study, 1 patient failed to meet protocol criteria after randomization and did not receive any study drugs and 1 patient was not randomized to either arm but did receive pemetrexed and cisplatin. Therefore, there were 21 patients treated with the 3 study drugs (enzastaurin or placebo, pemetrexed, and cisplatin) and 22 patients evaluable for safety.

Two patients experienced at least 1 possibly drug-related SAE (duodenal ulcer and candidiasis and tachyarrhythmia, respectively), both in Arm B. There was 1 discontinuation due to the study drug(s)-related AE of hypertension (Arm A). Also, 1 patient discontinued due to disease progression (Arm A), 2 patients were discontinued because of death due to study disease (1 in each arm), and 1 patient discontinued due to investigator decision (Arm B). The remaining 17 patients of the 21 who received treatment with enzastaurin or placebo discontinued due to early study closure.

In Part 2, there were 3 Grade 3/4 treatment-emergent nonlaboratory AEs (2 in Arm A and 1 in Arm B; Table S021.3) and 5 Grade 3/4 treatment-emergent laboratory AEs (3 in Arm A and 2 in Arm B; Table S021.4). Three patients required transfusions (packed red blood cells) and 2 patients had abnormal ECGs reported from baseline, all in Arm A.

The decision to close the study was based on the interim results from 2 Phase 2 studies of enzastaurin in NSCLC. Interim analyses were conducted for both studies and no additional benefit for the patients treated with enzastaurin was shown. Due to the lack of

efficacy for enzastaurin in these 2 studies, the decision was made by Lilly, in agreement with the principal investigators, to close Study H6Q-MC-S021.

Conclusions:

- The combination of enzastaurin, pemetrexed, and cisplatin was found to be safe and well tolerated in Part 1. Safety data were reviewed for the 8 patients in Cohort 1 who completed at least 1 cycle of treatment. One clinically relevant event, pulmonary embolism, occurred in 1 of the 8 patients. No clinically relevant safety issues were identified in Cohort 2.
- In Part 1, most patients (9; 69%) received at least 4 cycles of treatment, and approximately half (6; 46%) received the maximum 6 cycles. Eight patients (62%) reached a best study response of PR.
- There were no safety findings for Part 2 patients. No patient received more than 1 cycle of enzastaurin or placebo. Enzastaurin and placebo doses were discontinued due to early study closure before being administered to any patient in a second cycle, thereby limiting assessment of enzastaurin tolerability in Part 2.

Efficacy objectives were not analyzed because of lack of data due to early study closure.