2. S032 Synopsis

Clinical Study Report Synopsis: Study H6Q-MC-S032

<table>
<tr><td colspan="2">Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study with and without Enzastaurin in Combination with Docetaxel and Prednisone, Followed by Enzastaurin Maintenance as First-Line Treatment in Hormone Refractory Metastatic Prostate Cancer</td></tr>
<tr><td colspan="2">Number of Investigator(s): This multicenter study included 29 principal investigator(s).</td></tr>
<tr><td colspan="2">Study Center(s): This study was conducted at 29 study centers in 3 countries.</td></tr>
<tr><td colspan="2">Publication(s) Based on the Study: None at this time.</td></tr>
<tr><td>Length of Study:
Date of first patient visit: 15 June 2007
Date of last patient visit: 03 June 2010</td><td>Phase of Development: 2</td></tr>
<tr><td colspan="2">Primary Objective: To compare the objective response rate of enzastaurin given in combination with docetaxel and prednisone followed by enzastaurin maintenance therapy (Regimen A) in patients with hormone refractory metastatic prostrate cancer (HRPC) during first-line therapy versus placebo plus docetaxel and prednisone followed by placebo as maintenance (Regimen B).
Secondary Objectives: To assess -
rate of 3-month prostrate specific antigen (PSA) level decline of ≥30% in both treatment arms
PSA velocity at 2 and 3 months in both treatment arms
the following efficacy variables in both treatment arms:
progression-free survival (PFS) time
overall survival (OS)
duration of response (DOR) for responding patients
the safety and adverse event (AE) profile in both treatment arms
biomarkers relevant to enzastaurin and the disease state, as well as their correlation to clinical outcome
the pharmacokinetics (PK) of enzastaurin using intensive sampling in Part 1 (safety lead-in) and a sparse sampling strategy in randomized Part 2 of the trial
if PK of docetaxel is altered when administered in combination with enzastaurin</td></tr>
</table>

Approval Date: 09-Jun-2011 GMT

Study Design: This was a multicenter, double-blind, randomized, Phase 2 study which consisted of 2 parts: a safety lead-in with PK characterization followed by a double-blind randomized study. Both the Part 1 safety lead-in and Part 2 included patients with metastatic, androgen-independent prostate cancer who had a rising PSA value appropriate for first-line chemotherapy.

Part 1: This was an open-label safety lead-in of enzastaurin in combination with docetaxel and prednisone and PK characterization was included. The PK sampling was done from only a selected and limited number of sites. Part 1 was an unblinded study consisting of a total of 12 patients evaluated in 2 cohorts (6 patients per cohort) sequentially. Patients were treated with a modified investigational regimen (Modified Regimen A) with no dose escalation: docetaxel (75 mg/m^2 IV) was administered on Day 1 every 3 weeks for 6 cycles (maximum up to 10 cycles) and prednisone (5 mg by mouth [po] twice a day BID]) every day. Cycles 1 through 6 were planned to each be a 21-day cycle. In Cycle 1, enzastaurin was given as a loading dose of 1125 mg starting on Day 4, followed by enzastaurin 500 mg po once daily (QD) for the remaining Period 2 (chemotherapy) and Period 3 (maintenance). Patients were evaluated after completion of 2 cycles by the Safety Assessment Committee (SAC). The first safety evaluation took place after 6 patients had completed 2 cycles of Modified Regimen A. A final safety evaluation for Part 1 took place after another 6 patients completed 2 cycles.

Part 2: This was a double-blind randomized study. Patients were randomized to either Regimen A or Regimen B. In Cycle 1, enzastaurin (Regimen A) was given as a loading dose of 1125 mg 1 day prior to docetaxel (75 mg/m^2 IV) and prednisone (5 mg po BID) followed by enzastaurin 500 mg po QD for the remaining Period 2 (chemotherapy) and Period 3 (maintenance). Docetaxel (75 mg/m^2 IV) was administered on Day 1 every 3 weeks for 6 cycles (maximum up to 10 cycles) and prednisone (5 mg po BID) every day. Placebo was administered in place of enzastaurin in Regimen B. Two interim analyses were defined and planned in the protocol for Part 2. The objective was to determine if there is sufficient efficacy in terms of objective and PSA response rates to initiate a Phase 3 study. The study would not be stopped for futility; however, it was allowed to stop if there were safety concerns.

Number of Patients:

Part 1 – Modified Regimen A
- Planned: 12
- Entered: 15
- Enrolled: 14
- Evaluable for Full Analysis: 13

Part 2 –
- Planned: 84 (42 per treatment regimen)
- Randomized: 94 total; 48 active drug (Regimen A), 46 placebo (Regimen B)
- Treated (at least 1 dose): 88 total; 47 Regimen A, 41 Regimen B
- Evaluable for Full Efficacy Analysis: 86 total; 46 Regimen A, 40 Regimen B

Diagnosis and Main Criteria for Inclusion: Patients were at least 18 years of age with pathologically confirmed adenocarcinoma of the prostate. Patients had evidence of androgen-independent metastatic prostate cancer, an orchiectomy or castrate levels of testosterone (<50 ng/dL), no prior chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 and adequate organ function (as defined in the protocol).

Study Drug, Dose, and Mode of Administration:

A single 1125 mg loading dose of enzastaurin was administered orally as three 125-mg tablets 3 times in 1 day. Subsequently, the enzastaurin dose was 500 mg/day, administered orally as four 125-mg tablets. Docetaxel was administered intravenously on Day 1 of each 21-day cycle at a dose of 75 mg/m^2. Prednisone was administered orally as a 5-mg tablet twice daily.

Reference Therapy, Dose, and Mode of Administration: Placebo was administered orally as 3 tablets 3 times in 1 day. Subsequently, placebo was administered orally as 4 tablets daily.

Docetaxel was administered intravenously on Day 1 of each 21-day cycle at a dose of 75 mg/m^2.

Prednisone was administered orally as a 5-mg tablet twice daily.

Duration of Treatment:

Patients could receive 6 (up to 10) 21-day cycles of chemotherapy (enzastaurin + docetaxel + prednisone) followed by up to 3 years of maintenance treatment (enzastaurin). Patients could continue treatment until disease progression, unacceptable toxicity, or they required discontinuation from study treatment.

Variables:

Efficacy: The primary efficacy variable was objective response, a composite endpoint that includes both an objective lesion response (per Response Evaluation Criteria In Solid Tumors [RECIST] criteria) and a PSA response (≥50% decline from baseline in absolute value of PSA confirmed by a second value obtained at least 4 weeks later). The secondary variables were proportion of 3-month 30% PSA decline, PSA velocity at 2 and 3 months, PFS, OS, and DOR.

Safety: Physical examination including vital signs, clinical laboratory assessments, Common Terminology for Adverse Events (CTCAE) ratings, and AEs were monitored throughout the study.

Pharmacokinetic: For Part 1, serial plasma samples for quantifying enzastaurin and its major active metabolite LSN326020 were collected at predose, 2, 4, 6, 8, and 24 hours postdose on Cycle 1 Day 21 when enzastaurin was given alone, and predose, 2, 3, 4, 8, and 24 hours postdose on Cycle 2 Day 1 in combination with docetaxel. For quantifying docetaxel, serial plasma samples were collected at predose, 0.5, 1, 1.5, 2, 3, 4, 8, and 24 hours postdose on Cycle 1 Day 1 when docetaxel was given alone, and Cycle 2 Day 1 when docetaxel was given with enzastaurin. For Part 2, samples for quantifying enzastaurin and its major active metabolite LSN326020 were collected at predose, 1 to 3, and 4 to 9 hours after the enzastaurin dose on Day 1 (±3 days) of Cycle 2.

Translational Research: Blood samples were collected for translational research (TR) analysis and stored for possible research on enzastaurin mechanism of action and predictors of response. Samples will be stored for a maximum of 5 years after the last patient visit for the study; any sample remaining at that time will be destroyed. Formalin-fixed and paraffin-embedded (FFPE) pretreatment tumor tissue samples were prepared for disease diagnosis where available

Statistical Evaluation Methods:

Efficacy:

Primary Analysis: Objective Response Rate—The objective response rates and the 90% confidence intervals (CIs) were estimated for the qualified patients using unadjusted normal approximation for binomial proportions (z approximation). A 90% CI for the difference in the rates was computed, along with a p-value for the difference using a $\chi 2$–test.

Secondary Analyses: 3-month PSA level decline ≥30%—The rate (that is, proportion of patients) exhibiting a decline from baseline of ≥30% within the first 3 months of treatment was calculated. The analysis included all patients having baseline and at least 1 postbaseline PSA response within the first 3 months of treatment. The rate (and 90% CI) was calculated for both treatment groups. A 90% CI for the difference in the rates between groups was computed, along with a p-value for the difference using a $\chi 2$–test.

PSA velocity at 2 and 3 months— The per-patient PSA velocity at 2 and 3 months was summarized as a continuous measure in the set of patients with a valid baseline and at least 1 postbaseline PSA measurement within the first 2 and 3 months of treatment, respectively. The geometric mean velocity and 90% CI was reported for each treatment group, along with the median velocity and quartiles. A 90% CI for the difference in the geometric mean velocities was computed, along with a p-value for the difference using a t–test.

Duration of objective response— The duration of objective response was analyzed using Kaplan-Meier methods. If the patient received other poststudy anticancer therapy prior to progression, the patient was censored at the start date of this other therapy. The analysis set for duration of objective response was analyzed only for the set of patients who exhibited an objective response.

Progression-Free Survival—PFS was analyzed using Kaplan-Meier methods. If the patient received other poststudy anticancer therapy prior to progression, the patient was censored at the start date of this other therapy. Quartiles and 90% CIs were reported for each treatment group. PFS was compared between groups using the log-rank test. The hazard ratio estimation was determined using the Cox proportional hazards model.

Overall Survival—OS was analyzed using Kaplan-Meier methods. Quartiles and 95% CIs were reported for each treatment group. PFS was compared between groups using the log-rank test if there is adequate number of deaths. Additional supporting analyses included hazard ratio estimation using the Cox proportional hazards model.

Safety: Enzastaurin, docetaxel, and prednisone mean daily dose were summarized for both Part 1 and Part 2 using descriptive statistics at each tumor assessment visit and over the entire study

AEs that occurred during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality, were summarized for both Part 1 and Part 2. Summaries were done by CTCAE (Version 3.0; NCI 2003) group, CTCAE preferred term, and Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), and preferred terms and CTCAE grade.

Summaries similar to the above were done by study drug relationship: not related, at least possibly related.

Deaths, serious adverse events (SAEs), and discontinuations due to AEs that occurred during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality, were summarized. Frequency counts (and percentages) were done by CTCAE group, CTCAE preferred term, and MedDRA SOC and preferred terms and CTCAE grade. Listings of all AEs, regardless of when they occurred, were completed.

Pharmacokinetic: Part 1: PK parameter estimates were computed using noncompartmental analysis using WinNonlin® Enterprise Version 5.3. The primary parameter for analysis was the area under the concentration versus time curve from zero to infinity (AUC(0-∞)) for docetaxel. The maximum observed drug concentration (C_{max}), total body clearance of drug calculated after intravenous administration (CL), time of maximum observed drug concentration (t_{max}), volume of distribution at steady state following IV administration (V_{ss}), and terminal elimination half-life ($t_{1/2}$) were also estimated. AUC(0-∞) was compared between Day 1 of Cycle 1 and Day 1 of Cycle 2 for docetaxel to determine if enzastaurin has any influence on docetaxel. For enzastaurin, the maximum observed drug concentration at steady state ($C_{max,ss}$), average concentration at steady state during multiple dosing ($C_{av,ss}$), time of maximal observed concentration at steady state ($t_{max,ss}$), area under the concentration versus time curve during 1 dosing interval at steady state ($AUC_{\tau,ss}$), and apparent clearance (CL/F) were estimated. The $C_{max,ss}$, $C_{av,ss}$, $t_{max,ss}$, $AUC_{\tau,ss}$, and metabolic ratio (calculated as $AUC_{\tau,ss}$ LSN326020/ $AUC_{\tau,ss}$ enzastaurin) were estimated for LSN326020. $C_{max,ss}$, $C_{av,ss}$, $t_{max,ss}$, and $AUC_{\tau,ss}$ were estimated for total analyte (enzastaurin + LSN326020). The dosing interval (τ) for enzastaurin was 24 hours.

For Part 2, plasma concentration versus time data, together with information about dosing and patient characteristics, were pooled and analyzed using a population PK (PopPK) analysis approach. Due to the limited plasma concentration data, individual post hoc estimates of PK parameters for enzastaurin and its metabolite were calculated using a previously developed PopPK model using NONMEM® VII, ICON Development Solutions. Post hoc PopPK estimates of $AUC_{\tau,ss}$ of enzastaurin and LSN326020, as well as CL_{ss}/F of enzastaurin were determined. The $C_{av,ss}$ was determined by dividing $AUC_{\tau,ss}$ by the dosing interval of 24 hours.

Exposure-response modeling combining PK data with the safety and efficacy (for example, PFS) data was not performed due to insufficient data.

Bioanalytical: Plasma samples were analyzed at [redacted]. located in [redacted], USA. The samples were analyzed for LY317615 and its metabolite LY326020 using the validated liquid chromatography mass spectrometry (LC/MS/MS) method, "Determination of LY317615, LY326020, LY485912, and LY2406799 in Human Plasma by Turbo Ion Spray LC/MS/MS" (05207VTJO_EII_R4.DOC). The bioanalytical laboratory used the prefix LY for enzastaurin analytes in the bioanalytical report, notebook references, and documentation and, therefore, this notation is used in this section of the report. In other sections of this report, LY317615 and LY326020 are referred to as enzastaurin and LSN326020, respectively. For docetaxel, plasma samples were analyzed at [redacted], located in [redacted] USA. The samples were analyzed for docetaxel using a validated LC/MS/MS method (report # [redacted]).

Translational Research: These analyses were not completed due to a limited number of samples and lack of efficacy in the experimental arm.

Summary:

Part 1:

Based on safety review of Part 1, the SAC recommended opening Part 2 of the study without modifications.

Protocol Violations:

There were no protocol violations in Part 1 of the study.

Disposition:

Of the 15 patients who entered this study, 14 patients received at least 1 dose of study drug, and 13 had a valid baseline PSA assessment and at least 1 valid postbaseline PSA assessment and were considered the evaluable patient population. Table S032.2.1 provides a summary of reasons for discontinuation from study treatment for all patients who received at least 1 dose of study drug.

Table S032.2.1. Summary of Reasons for Discontinuation from Study Treatment – Part 1 (All Treated Patients)[a]

	Doc+Pred+Enz (N=14)
Reasons	**n (%)**
Adverse event	1 (7.1%)
Lost to follow-up	0 (0.0%)
Physician decision	0 (0.0%)
Protocol entry Criteria not met	0 (0.0%)
Protocol violation	0 (0.0%)
Sponsor decision	0 (0.0%)
Patient decision	0 (0.0%)
Progressive disease	13 (92.9%)
Death	1 (7.1%)
Death due to study disease	0 (0.0%)
Death due to study drug related	0 (0.0%)
Death due to procedural related	0 (0.0%)
Death due to adverse events	1 (7.1%)

Abbreviations: Doc = docetaxel; Enz = enzastaurin; N=total population size; n=number of patients with discontinuation; Pred = prednisone.

a Defined as all enrolled patients who received at least 1 dose of study drug.

Demographics: Major patient demographics and baseline characteristics are shown inTable S032.2.2.

Table S032.2.2. Summary of Patient Demographics and Baseline Characteristics-Part 1, (All Treated Patients[a])

Parameter	Doc+Pred+Enz (N=14)
Age (years)[b]	
No. of Patients	14
Median	65.1
Minimum	56.0
Maximum	78.0
Race	**[n (%)]**
No. of Patients	14
Caucasian	14 (100.0%)
African	0 (0.0%)
Hispanic	0 (0.0%)
Native American	0 (0.0%)
East Asian	0 (0.0%)
West Asian (Indian sub continent)	0 (0.0%)
ECOG Performance Status	**[n %]**
0=Fully active and asymptomatic	8 (57.1%)
1=Ambulatory with symptoms	6 (42.9%)
Testosterone (ng/dL)	
n	3
Median	0.0
PSA (microgram/Liter)[c]	
n	14
Median	114.5
Minimum	9.5
Maximum	2142.8

Parameter	Doc+Pred+Enz (N=14)
Gleason Grade	**[n %]**
Primary	
Low, <=4	12 (85.7%)
Intermediate, 5-7	2 (14.3%)
High, > 7	0 (0.0%)
Secondary	
Low, <=4	6 (42.9%)
Intermediate, 5-7	7 (50.0%)
High, > 7	0 (0.0%)
Gleason Score	
n	14
Median	8.0
Minimum	6.0
Maximum	10.0

Abbreviations: dL=deciliter; Doc = docetaxel; ECOG=Eastern Cooperative Oncology Group; Enz = enzastaurin; N=total population size; n = number of patients evaluated for parameter; ng=nanogram; Pred = prednisone; PSA=prostate specific antigen.

[a] Defined as all enrolled patients who received at least 1 dose of study drug.

[b] Age in years is calculated as (date of informed consent - date of birth +1)/365.25.

[c] Only patients with PSA in SI unit are summarized.

Treatment Exposure and Safety:

Nine (64.3%) of 14 patients completed at least 6 cycles of treatment and 2 (14.3%) completed 10 months of treatment. Median number of cycles received was 8.5.

Summary of Adverse Event Information: Of the 14 patients included in the safety population, all (100%) experienced at least 1 treatment-emergent adverse event (TEAE), and 12 (85.7%) experienced at least 1 TEAE possibly related to study drug. Nine patients (64.3%) experienced at least 1 Grade 3/4 TEAE and 7 (50%) experienced at least 1 Grade 3/4 TEAE possibly related

to study drug. Eight patients (57.1%) experienced at least 1 SAE, 5 (35.7%) of which were study drug related. One patient discontinued due to an AE or SAE of sepsis, which was not attributed to study drug and later lead to patient death. Table S032.2.3 summarizes AEs experienced by >10% of patients by frequency and maximum CTCAE Grade 3/4, and Table S032.2.4 summarizes SAEs.

Table S032.2.3. Summary of Adverse Events in >10% of Patients by Frequency and Maximum CTCAE Grade 3/4a – Part 1 (All Treated Patients[b])

Adverse Event	**Doc+Pred+Enz Safety Population (N = 14)**
	Regardless of Causality and Possibly Drug Related[c]
Grade 3/4 CTCAE Term that occurred in > 10%	**Grade 3 n (%)**
Lymphopenia	4 (28.6%)
Leukocytes (Total WBC)	3 (21.4%)
Fatigue	2 (14.3%)
Febrile Neutropenia	2 (14.3%)
Neutrophils/Granulocytes (ANC/AGC)	2 (14.3%)
Thrombosis/Thrombus/Embolism	2 (14.3%)

Abbreviations: AGC = absolute granulocyte count; ANC = absolute neutrophils count; CTCAE=Common Terminology Criteria for Adverse Events; Doc = docetaxel; Enz = Enzastaurin; N=total population size; n=number of patients; Pred = prednisone; TEAE = treatment-emergent adverse event; WBC = white blood cell.

[a] No Grade 4 adverse events occurred at a frequency > 10%.

[b] Defined as all enrolled patients who received at least 1 dose of study drug.

[c] The events for regardless of causality and possibly related to study drug resulted in the same number of events and percentages for all listed events in the table.

Table S032.2.4. Summary of Serious Adverse Events - Part 1 (All Treated Patients[a])

	Doc+Pred+Enz (N=14)		
	Regardless of Causality		**Possibly related to Study Drug**
MedDRA Preferred Term	**n (%)**	**MedDRA Preferred Term**	**n (%)**
Patients with at least 1 SAE	8 (57.1%)	**Patients with at least 1 SAE**	5 (35.7%)
EXTRAVASATION	2 (14.3%)	FEBRILE NEUTROPENIA	2 (14.3%)
FEBRILE NEUTROPENIA	2 (14.3%)	THROMBOSIS	2 (14.3%)
THROMBOSIS	2 (14.3%)	EXTRAVASATION	1 (7.1%)
INFECTION	1 (7.1%)	INFECTION	1 (7.1%)
OESOPHAGEAL CARCINOMA	1 (7.1%)	OESOPHAGEAL CARCINOMA	0 (0.0%)
RENAL FAILURE	1 (7.1%)	RENAL FAILURE	0 (0.0%)
SEPSIS	1 (7.1%)	SEPSIS	0 (0.0%)
SYNCOPE	1 (7.1%)	SYNCOPE	0 (0.0%)
URINARY TRACT OBSTRUCTION	1 (7.1%)	URINARY TRACT OBSTRUCTION	0 (0.0%)

Abbreviations: Doc = docetaxel; Enz = enzastaurin; N=total population size; n=number of patients with discontinuation; Pred = prednisone.

[a] Defined as all enrolled patients who received at least 1 dose of study drug.

Pharmacokinetics:

Enzastaurin, LSN326020, and Total Analyte Pharmacokinetics

Steady-state noncompartmental PK parameter estimates of enzastaurin, its major active metabolite LSN326020, and total analyte (enzastaurin + LSN326020) were estimated for 9 patients during Cycle 1 (enzastaurin alone) and 7 patients during Cycle 2 (enzastaurin with docetaxel). Patient profiles excluded from the analysis are listed below:

- Patient [redacted] Cycle 1, incorrect sample collection time data. C_{max} and t_{max} reported.
- Patient [redacted] Cycle 2, excluded due to incorrect sample collection time data.
- Patient [redacted] Cycle 2, excluded due to incorrect sample collection time data.
- Patient [redacted] Cycle 2, incorrect sample collection time data. C_{max} and t_{max} reported.
- Patient [redacted] Cycle 2, excluded due to incorrect sample collection time data.
- Patient [redacted] Cycle 1 and Cycle 2 due to incorrect sample collection time data.
- Patient [redacted] Cycle 1, excluded due to incorrect sample collection time data.
- Patient [redacted] Cycle 1, excluded due to missing dosing data.
- Patient [redacted] Cycle 2, excluded due to missing dosing data.

Table S032.2.5 provides the PK parameter estimates for enzastaurin, LSN326020, and total analyte when enzastaurin was given as 500 mg once daily doses alone on Cycle 1 Day 21 and with docetaxel on Cycle 2 Day 1. Figure S032.2.1 shows the mean total analyte concentration versus time plots for enzastaurin alone and with docetaxel. Figure S032.2.2 shows ping pong plots of total analyte $C_{av,ss}$ of enzastaurin alone and with docetaxel (75 mg/m^2) in the 5 patients with complete profiles in both Cycle 1 and Cycle 2.

Table S032.2.5. Summary of Steady-State Plasma Pharmacokinetic Parameters of Enzastaurin, LSN326020, and Total Analyte (Enzastaurin + LSN326020) in Prostate Cancer Patients following 500 mg Daily Doses of Enzastaurin Alone and with Docetaxel (75 mg/m^2)

	Geometric Mean (CV%)					
	Enzastaurin 500 mg QD Alone			Enzastaurin 500 mg QD + Docetaxel 75 mg/m^2		
	Enzastaurin	LSN326020	Total Analyte	Enzastaurin	LSN326020	Total Analyte
N	9	9	9	7	7	7
$C_{max,ss}$ (nmol/L)	870 (84)	664 (45)	1540 (62)	778 (39)	667 (30)	1450 (32)
$t_{max,ss}$[a] (h)	4.00 (1.83 – 5.87)	4.03 (1.83 – 5.92)	4.00 (1.83 – 5.87)	3.75 (2.05 – 24.00)	7.92 (2.92 – 24.00)	3.43 (2.05 – 24.00)
$AUC_{\tau,ss}$[b] (nmol•h/L)	12900[c] (79)	15200[c] (35)	28700[c] (49)	13100[d] (26)	15700[d] (20)	29000[d] (18)
$C_{av,ss}$ nmol/L	536[c] (79)	631[c] (35)	1200[c] (49)	545[d] (26)	654[d] (20)	1210[d] (18)
CL_{ss}/F L/h	75.4[c] (79)	NC	NC	74.1[d] (26)	NC	NC
MR	NC	1.18[c] (51)	NC	NC	1.20[d] (29)	NC

Abbreviations: $AUC_{\tau,ss}$ = area under the concentration versus time curve during 1 dosing interval at steady state; $C_{av,ss}$ = average drug concentration under steady state conditions during multiple dosing; CL_{ss}/F = apparent total body clearance of drug calculated after extra-vascular administration at steady-state; $C_{max,ss}$ = maximum observed drug concentration during a dosing interval at steady state; CV = coefficient of variation; MR = metabolic ratio; N = number of subjects; $t_{max,ss}$ = time of maximum observed drug concentration during a dosing interval at steady state.

a Median (range).

b τ equals 24 hours.

c N=7

d N=6

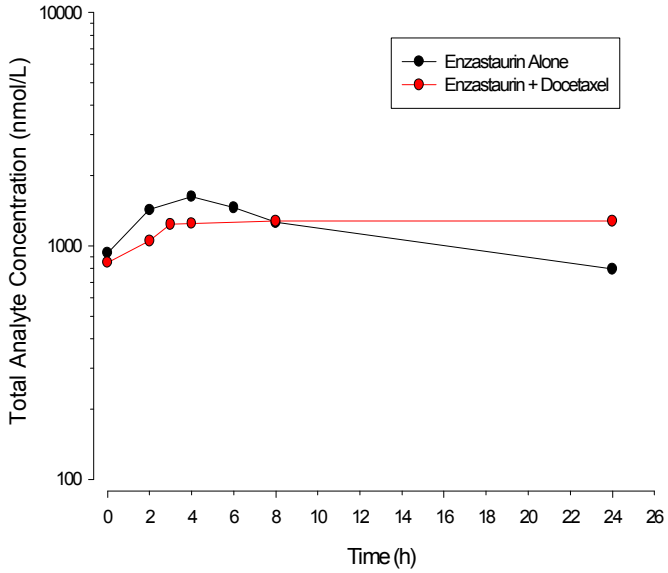

Figure S032.2.1. **Mean steady-state total analyte (enzastaurin + LSN326020) concentration versus time plots following once-daily 500-mg doses of enzastaurin alone and with docetaxel (75 mg/m^2).**

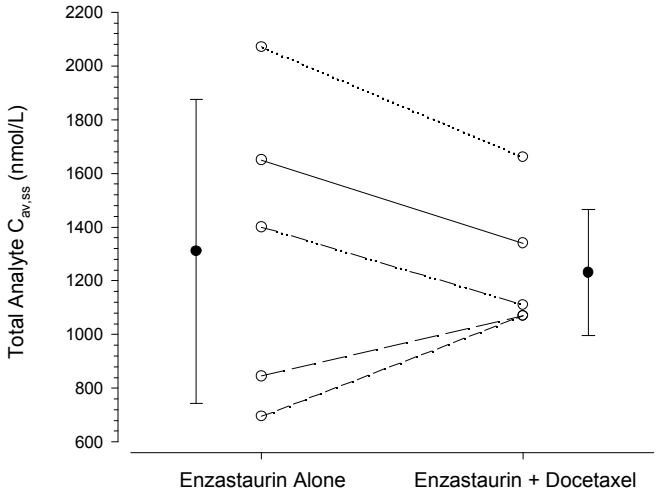

Figure S032.2.2. **Individual steady-state total analyte (enzastaurin + LSN326020) $C_{av,ss}$ values for Cycle 1 (enzastaurin alone) and Cycle 2 (enzastaurin + docetaxel).**

The mean total analyte $AUC_{\tau,ss}$ and $C_{av,ss}$ in this study (Table S032.2.5) were virtually identical when patients received 500 mg QD oral doses of enzastaurin alone or with docetaxel.

Docetaxel Pharmacokinetics

The docetaxel noncompartmental PK parameters were estimated for 13 patients on Cycle 1 Day 1 when docetaxel was given alone and 10 patients on Cycle 2 Day 1 when docetaxel was given with 500 mg daily doses of enzastaurin. The Cycle 2 Day 1 profile for Patient [redacted] was excluded due to incorrect sampling, and sample data were not available for Patients [redacted] and [redacted]. Table S032.2.6 provides the PK parameter estimates for docetaxel alone for Cycle 1 and docetaxel with enzastaurin for Cycle 2. Figure S032.2.3 shows the mean docetaxel concentration versus time plots for docetaxel alone and docetaxel with enzastaurin. Figure S032.2.4 shows docetaxel AUC(0-∞) ping pong plots of docetaxel alone and docetaxel with enzastaurin in the 10 patients with complete profiles for both Cycle 1 and Cycle 2. As seen in Figure S032.2.3 docetaxel exhibits a tri-exponential decline in concentration. Only 3 patients had quantifiable concentrations (below quantifiable limit [BQL] < 10 ng/mL) at 24 hours postdose, so the $t_{1/2}$ was calculated using the final 3 points in the terminal elimination phase. This was generally 3 to 8 hours postdose, which is generally reported as the β terminal elimination half-life for docetaxel.

Table S032.2.6. Summary of Noncompartmental Pharmacokinetic Parameter Estimates Following a 1.0-Hour IV Infusion of 75 mg/m^2 of Docetaxel during Cycle 1 (Docetaxel Alone) and Cycle 2 (Enzastaurin + Docetaxel)

	Geometric Mean (CV%)	
Parameter	**Docetaxel Alone**	**Enzastaurin + Docetaxel**
N	13	10
C_{max} (ng/mL)	2230 (21)	1840 (22)
t_{max}[a] (h)	0.53 (0.48 - 1.00)	0.51 (0.42 - 1.00)
AUC(0-∞) (ng□h/mL)	2350 (26)	1750 (20)
CL (L/h)	67.2 (26)	90.3 (19)
V_{ss} (L)	89.8 (73)	71.0 (38)
$t_{1/2}$[c] (h)	4.63 (80)	2.60 (56)

Abbreviations: AUC (0-∞) = area under the plasma concentration time curve from time zero to infinity; CL = systemic clearance; C_{max} = maximum plasma concentration; $t_{1/2}$ = half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis; t_{max} = time of maximal plasma concentration; V_{ss} = Volume of distribution at steady-state.

[a] Median (range).

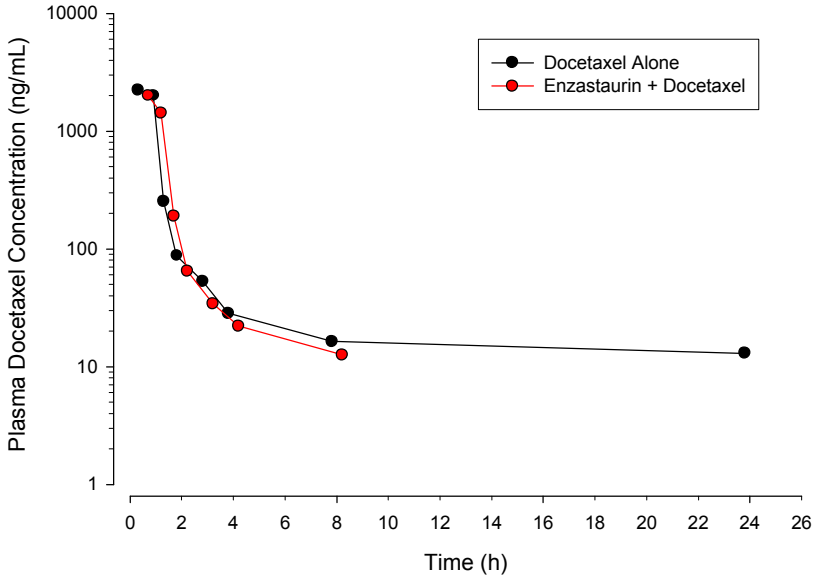

Figure S032.2.3. **Docetaxel mean concentration-time profiles following a 1.0-hour IV infusion of 75 mg/m^2 of docetaxel during Cycle 1 (docetaxel alone) and Cycle 2 (enzastaurin + docetaxel).**

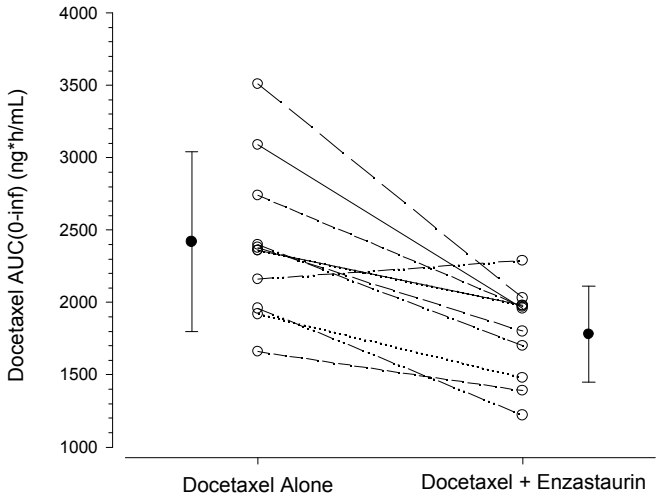

Figure S032.2.4. **Individual AUC(0-∞) values following a 1.0-hour IV infusion of 75 mg/m^2 of docetaxel during Cycle 1 (docetaxel alone) and Cycle 2 (enzastaurin + docetaxel).**

Mean docetaxel AUC(0-∞) was about 25% lower in Cycle 2 with docetaxel + enzastaurin (1750 ng•h/mL) than in Cycle 1 with docetaxel alone (2350 ng•h/mL). This difference was statistically significant when using a mixed-effects model comparing the ratio of docetaxel parameters with and without enzastaurin (Table S032.2.7). The reason for docetaxel's reduced AUC(0-∞) is unknown. Docetaxel is predominately metabolized by CYP3A4 and CYP3A5, and therefore induction of these enzymes by enzastaurin is 1 potential scenario that could explain this, but to date no evidence exists to suggest that enzastaurin induces these enzymes. On the contrary, there is evidence that enzastaurin moderately *inhibits* CYP3A in vivo. Clinical study H6Q-LC-JCAV (Lilly study on file) has shown that the AUC(0-∞) of midazolam, a probe CYP3A substrate, was 2.5 times higher in the presence of enzastaurin 500-mg/day at steady state in cancer patients than when midazolam was given alone.

Table S032.2.7. Summary of Pharmacokinetic Ratio of Geometric Means Following a 1.0-Hour IV Infusion of 75 mg/m^2 of Docetaxel during Cycle 1 (Docetaxel Alone) and Cycle 2 (Enzastaurin + Docetaxel)

	Ratio of Geometric Mean (90% CI)		
Parameter	**Cycle 1 Docetaxel Alone**	**Cycle 2 Enzastaurin + Docetaxel**	**Ratio (With Enzastaurin 90% CI) versus (Without Enzastaurin 90% CI) [p-value]**
C_{max} (ng/mL)	2231 (2094, 2643)	1747 (1543, 1978)	0.820 (0.744, 0.904) [0.004]
AUC(0-∞) (ng□h/mL)	2353 (2016, 2470)	1829 (1639, 2041)	0.743 (0.669, 0.824) [<0.001]

Abbreviations: AUC (0-∞) = area under the plasma concentration time curve from time zero to infinity; CI = confidence interval; C_{max} = maximum plasma concentration.

Part 2:

Protocol Violations: For all treated patients, 9 (9.6%) major protocol violations occurred because patients were inadvertently admitted to Part 2 of the study despite not meeting 1 of the inclusion/exclusion criteria [5 (10.4%) for enzastaurin arm; 4 (8.7%) for placebo arm]. For all treated patients, 12 (12.8%) patients experienced a major protocol violation related to the study drug (7 [14.6%] for enzastaurin arm; 5 [10.4%] for placebo arm). The remainder of the protocol violations (total [49%]) were listed as other (25 [52.1%] for enzasataurin arm; 24 [52.2%] for placebo arm).

Disposition: A total of 106 patients entered the trial and 94 were randomized, 48 patients to the docetaxel, prednisone, and enzastaurin (enzastaurin arm) and 46 patients to docetaxel, prednisone, and placebo (placebo arm), and 12 patients failed initial screening. Forty-seven and 41 patients received at least 1 dose of medication in the enzastaurin and placebo arm, respectively. Six patients who were randomized did not receive at least 1 dose as follows: 3 of the 6 were removed due to entry criteria exclusion, 2 physician decision, and 1 sponsor decision. Forty-six and 40 patients were evaluable for the full analysis.

Thirty-four (70.8%) patients in enzastaurin arm and 31 (67.4%) patients in the placebo arm were discontinued due to progressive disease. Table S032.2.8 provides a summary of reasons for discontinuation from study treatment for all patients randomized.

Table S032.2.8. Summary of Reasons for Discontinuation from Study Treatment – Part 2 (ITT Population)[a]

	Doc+Pred+Enz (N=48)	Doc+Pred+Plc (N=46)	Total (N=94)
Reasons	**n (%)**	**n (%)**	**n (%)**
Adverse event	5 (10.4%)	2 (4.3%)	7 (7.4%)
Lost to follow-up	1 (2.1%)	0 (0.0%)	1 (1.1%)
Physician decision	2 (4.2%)	5 (10.9%)	7 (7.4%)
Protocol entry criteria not met	0 (0.0%)	4 (8.7%)	4 (4.3%)
Protocol violation	0 (0.0%)	0 (0.0%)	0 (0%)
Sponsor decision	0 (0.0%)	2 (4.3%)	2 (2.1%)
Patient decision	5 (10.4%)	2 (4.3%)	7 (7.4%)
Progressive disease	34 (70.8%)	31 (67.4%)	65 (69.1%)
Death	2 (4.2%)	0 (0.0%)	2 (2.%)
Death due to study disease	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death due to study drug related	1 (2.1%)	0 (0.0%)	1 (1.1%)
Death due to procedural related	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death due to adverse events	1 (2.1%)	0 (0.0%)	1 (1.1%)

Abbreviations: Doc = docetaxel; Enz = enzastaurin; ITT = intent to treat; N=total population size; n=number of patients with discontinuation; Plc = placebo; Pred = prednisone.

[a] Defined as all patients enrolled or randomized to study drug.

Demographics: Demographic and baseline characteristics for all randomized are provided inTable S032.2.9. It appears the 2 arms were balanced, however, the median PSA level was higher in the placebo arm (enzastaurin, 51.8 mcg/L; placebo, 158.9 mcg/L).

Table S032.2.9. Demographic and Baseline Characteristics – Part 2 (ITT Population)[a, b]

Parameter	Doc + Pred + Enz (N=48), n (%)	Doc + Pred +Plc (N=46), n (%)	Total (N=94), n (%)
Age (years)[c]			
No. of Patients	48	46	94
Median	69.4	71.2	70.1
Minimum	53.7	46.3	46.3
Maximum	88.6	88.2	88.6
Race (n [%])			
No. of Patients	48	46	94
Caucasian	39 (81.3)	33 (71.7)	72 (76.6)
African	8 (16.7)	7 (15.2)	15 (16.0)
Hispanic	0 (0)	6 (13.0)	6 (6.4)
Native American	0 (0)	0 (0)	0 (0)
East Asian	1 (2.1)	0 (0)	1 (1.1)
West Asian (Indian sub continent)	0 (0)	0 (0)	0 (0)
ECOG Performance Status (n [%])			
0=Fully active and asymptomatic	27 (56.3)	26 (56.5)	53 (56.4)
1=Ambulatory with symptoms	19 (39.6)	15 (32.6)	34 (36.2)
2=In bed <50% of the time	1 (2.1)	0 (0)	1 (1.1)
3= In bed>=50% of the time	0 (0)	0 (0)	0 (0)
4=bedridden	0 (0)	0 (0)	0 (0)
5=dead	0 (0)	0 (0)	0 (0)
Gleason Grade			
Primary			
Low, <=4	35 (72.9%)	26 (56.5%)	61 (64.9%)
Intermediate, 5-7	4 (8.3%)	7 (15.2%)	11 (11.7%)
High, > 7	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	9 (18.8%)	13 (28.3%)	22 (23.4%)
Secondary			
Low, <=4	28 (58.3%)	28 (60.9%)	56 (59.6%)
Intermediate, 5-7	11 (22.9%)	5 (10.9%)	16 (17.0%)
High, > 7	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	9 (18.8%)	13 (28.3%)	22 (23.4%)
Gleason Score			
No. of Patients	39	33	72
Median	8.0	8.0	8.0
Minimum	5.0	6.0	5.0
Maximum	10.0	9.0	10.0

Demographic and Baseline Characteristics – Part 2 (ITT Population)[a, b]

PSA (microgram/Liter)[d]			
No. of Patients	48	45	93
Median	51.8	158.9	73.4
Minimum	3.7	3.6	3.6
Maximum	2833.1	4804.1	4804.1
Testosterone (nanomole/Liter)			
No. of Patients	45	42	87
Median	0.6	0.6	0.6
Minimum	0.6	0.6	0.6
Maximum	1.4	10.5	10.5

Abbreviations: dL=deciliter; Doc = docetaxel; ECOG=Eastern Cooperative Oncology Group; Enz = enzastaurin; ITT = intent to treat; N=total population size; n = number of patients evaluated for parameter; ng=nanogram; Plc = placebo; Pred = prednisone; PSA=Prostate-Specific Antigen; SD=standard deviation.

[a] Defined as all patients enrolled or randomized to study drug.

[b] Percentages are based on the total number of patients in the ITT population (all treated patients population).

[c] Age in years is calculated as (date of informed consent - date of birth +1)/365.25.

[d] Only patients with PSA in SI unit are summarized.

A majority of patients in both arms, 89.6% in the enzastaurin arm and 84.8% placebo arm, had prior systemic treatment that included adjuvant, neoadjuvant, or palliative therapy (Table S032.2.10).

Table S032.2.10. Summary of Reported Prior Therapies – Part 2 (ITT Population)[a]

	Doc+Pred+Enz	**Doc+Pred+Plc**	**Total**
	(N=48)	**(N=46)**	**(N=94)**
Parameter	**n(%)**	**n(%)**	**n(%)**
Prior Therapies[b]	47 (97.9%)	40 (87.0%)	87 (92.6%)
Surgery	21 (43.8%)	21 (45.7%)	42 (44.7%)
Radiotherapy	25 (52.1%)	22 (47.8%)	47 (50.0%)
Systemic Therapy (includes hormonal)	43 (89.6%)	39 (84.8%)	82 (87.2%)
No. of Prior Systemic Therapy Regimen			
0	5 (10.4%)	7 (15.2%)	12 (12.8%)
1-3	30 (62.5%)	34 (73.9%)	64 (68.1%)
>3	13 (27.1%)	5 (10.9%)	18 (19.1%)

Abbreviations: Doc = docetaxel; Enz = enzastaurin; ITT = intent to treat; N=total population size; n = number of patients evaluated for parameter; No. = number; Plc = placebo; Pred = prednisone.

[a] Defined as all patients enrolled or randomized to study drug.

[b] Patients may [may not] have received more than 1 prior therapy.

Drug Exposure: Median number of cycles received in enzastaurin arm was 7 and for the placebo arm was 6. Fifteen patient (31.9%) in the enzastaurin arm completed 10 cycles of treatment versus 8 (19.5%) in the placebo arm. More patients in the enzastaurin arm required dose

reductions compared to placebo: enzastaurin and docetaxel, respectively (9 [19.1%] and 11 [23.4%]) versus placebo and docetaxel, respectively (2 [4.9%] and 6 [14.6%]) (Table S032.2.11). The most common reason for dose reductions in the enzastaurin arm was thrombocytopenia, fatigue, and febrile neutropenia. Compliance was high in both treatment arms.

Table S032.2.11. Summary of Drug Exposure, Actual Mean Dose and Dose Adjustments – Part 2 (All Treated Patients)[a]

	Doc+Pred+Enz (N=47)		Doc+Pred+Plc (N=41)	
	Enzastaurin mg/day	**Docetaxel mg/m^2/cycle**	**Placebo mg/day**	**Docetaxel mg/m^2/cycle**
Parameter	(N=47)	(N=47)	(N=41)	(N=41)
Number of Days/Cycles on Drug				
N	47	47	41	41
Median (minimum, maximum)	195.0 (4.0, 511.0)	7.0 (1.0, 10.0)	190.0 (6.0, 371.0)	6.0 (1.0, 10.0)
Patients completed at least n(%)				
1 cycle		47 (100.0%)		41 (100.0%)
2 cycles		46 (97.9%)		38 (92.7%)
3 cycles		42 (89.4%)		38 (92.7%)
4 cycles		36 (76.6%)		34 (82.9%)
5 cycles		35 (74.5%)		32 (78.0%)
6 cycles		32 (68.1%)		31 (75.6%)
7 cycles		25 (53.2%)		20 (48.8%)
8 cycles		23 (48.9%)		17 (41.5%)
9 cycles		16 (34.0%)		12 (29.3%)
10 cycles		15 (31.9%)		8 (19.5%)
Median (minimum, maximum)		7.0 (1.0, 10)		6.0 (1.0, 10)
Dose Adjustments n(%)	13 27.7%	15 (31.9%)	7 (17.1%)	11 (26.8%)
Infusion Delay due to AE	NA	9 (19.1%)	NA	7 (17.1%)
Dose Omitted	8 (17.0%)	NA	5 (12.2%)	NA
Dose Escalation	2 (4.3%)	1 (2.1%)	3 (7.3%)	0 (0.0%)
Dose Reduction	9 (19.1%	11 (23.4%)	2 (4.9%)	6 (14.6%)
Actual Mean Dose[c]				
Median	505.9	73.5	500.7	75.0

Abbreviations: AE = adverse event; Doc= docetaxel; Enz = enzastaurin; N = total population size; n = number of patients; NA = not applicable; Plc = placebo; Pred = prednisone.

a Percentage is based on the total number of patients in the safety population per treatment group. Safety population or all treated patients defined as all enrolled patients who received at least 1 dose of study drug.

b The planned dose for enzastaurin took into account dose adjustments. The planned dose for docetaxel was 75mg/m^2 per cycle.

[c] Actual mean dose for enzastaurin is calculated as total actual dose received minus total doses returned divided by number of days. Actual mean dose for docetaxel is calculated as total actual dose received divided by number of study cycles.

Efficacy:

Primary: There was no difference in the objective response rate between the enzastaurin and placebo arms (7 [15.2%] for enzastaurin arm 6 [15.0%]; p=1.00).

Secondary:

There was no statistically significant difference in median PFS time between the 2 groups (229.0 and 213.0 days for enzastaurin and placebo arms, respectively; p=0.524) (Figure S032.2.5). There was no significant difference in the 1-year OS rate (76.7% for the enzastaurin and 75.1% for the placebo arm; [90% CI enzastaurin: 61.4% , 86.6% and 90 % CI placebo: 58.1% , 86.0%]) (Figure S032.2.6). Furthermore, there was statistically no difference in PFS and OS in various subgroups, including Stage (III versus IV), baseline ECOG (0-1 versus 2) and age (≤65 versus >65). There was no difference in the median DOR (242.0 and 204.0 days for enzastaurin and placebo arms, respectively; p=.6088). In addition, there was no statistically difference between the 2 arms in PSA level decline >30% at 3 months or >50% decline.

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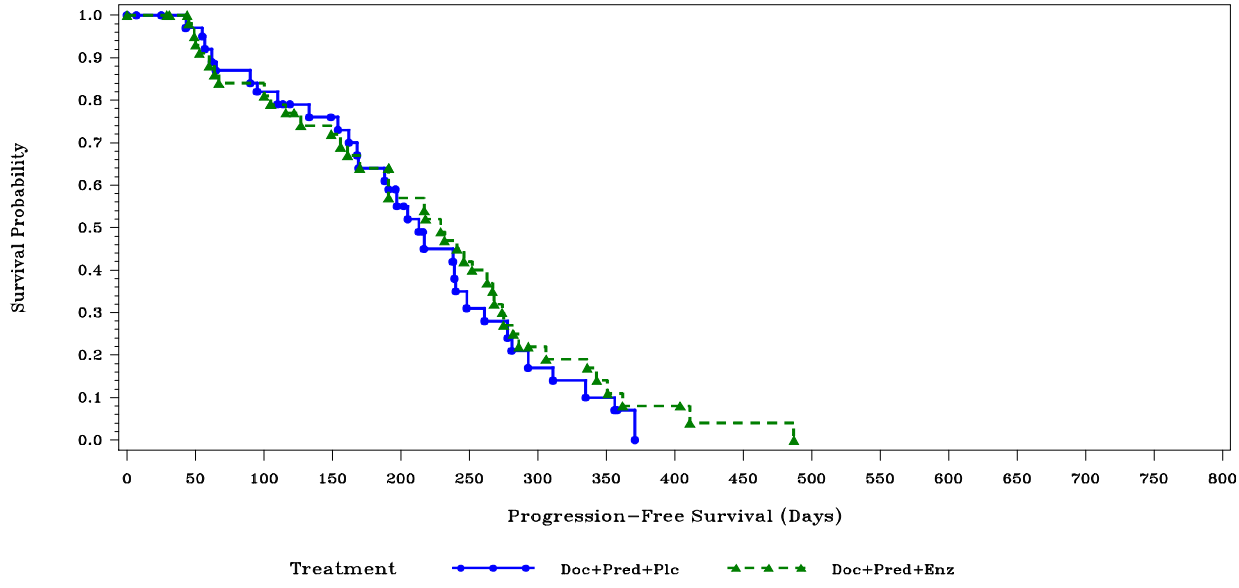
Figure 1.1 Kaplan-Meier Curves for Progression-Free Survival Time - FA Population



Doc+Pred+Enz patients at risk: 45 (Day 30), 36 (Month 3), 26 (Month 6), 3 (Year 1), 0 (Year 2)
Doc+Pred+Plc patients at risk: 38 (Day 30), 32 (Month 3), 22 (Month 6), 1 (Year 1), 0 (Year 2)
Logrank p-value = 0.5240
Abbreviation: FA = full analysis set

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Abbreviations: Doc= docetaxel; Enz = enzastaurin; FA = full analysis; Plc = placebo; Pred = prednisone; PSA = prostate specific antigen.

[a] Patients enrolled, received at least 1 dose, valid baseline PSA assessment, and > 1 post-baseline PSA assessment.

Figure S032.2.5. Kaplan-Meier curves for progression free survival time – Part 2 (FA population)[a].

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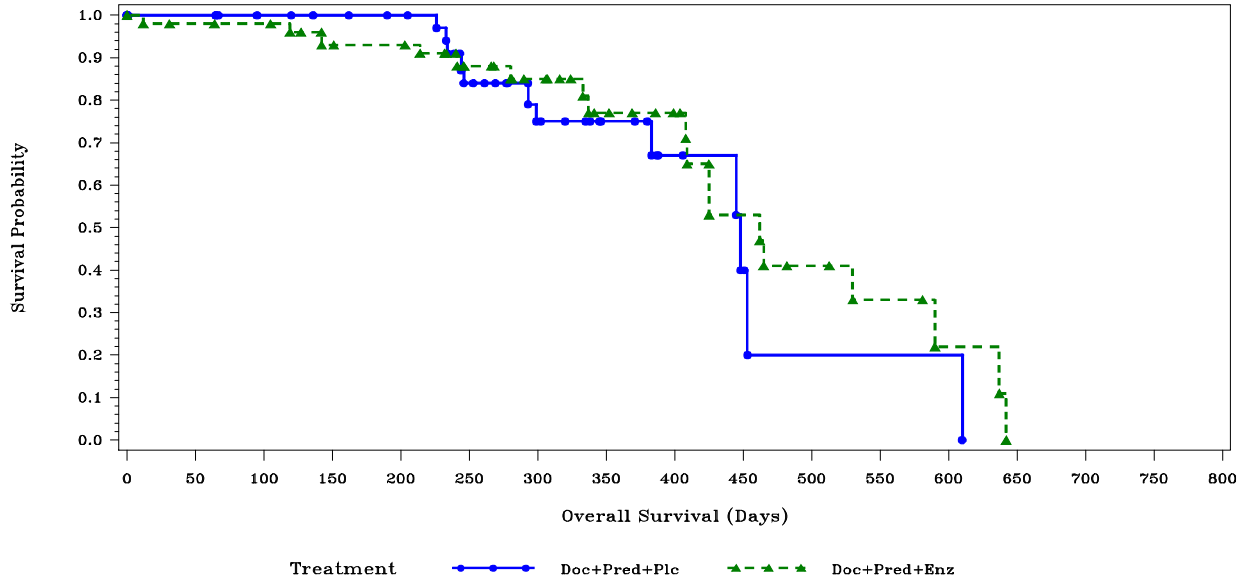
Figure 1.2 Kaplan-Meier Curves for Overall Survival Time - ITT Population



Doc+Pred+Enz patients at risk: 46 (Day 30), 44 (Month 3), 38 (Month 6), 17 (Year 1), 0 (Year 2)
Doc+Pred+Plc patients at risk: 41 (Day 30), 38 (Month 3), 34 (Month 6), 11 (Year 1), 0 (Year 2)
Logrank p-value = 0.4407
Abbreviation: ITT = intent to treat

Data Version Date: 02AUG2010 Execution Date: 26OCT2010 12:36

Abbreviations: Doc= docetaxel; Enz = enzastaurin; ITT = intent to treat; Plc = placebo; Pred = prednisone.

[a] All randomized patients.

Figure S032.2.6. Kaplan-Meier curves for overall survival time – Part 2 (ITT population).

Safety: Of the 47 patients in the enzastaurin arm and 41 in the placebo arm included in the safety population, all (100%) experienced at least 1 TEAE, and 45 (95.7%) and 39 (95.1%) experienced at least 1 TEAE possibly related to study drug. Forty (85.1%) and 28 (68.3%) patients in the enzastaurin and placebo arm, respectively, experienced at least 1 Grade 3/4 TEAE, of which, 30 (63.8%) and 24 (58.5%) TEAEs were considered possibly related to study drug. Table S032.2.12 provides a summary of TEAEs possibly related to study drug according to CTCAE, Grades 1 through 4. Sixteen (34.0%) in the enzastaurin arm and 14 (34.1%) patients in the placebo arm experienced at least 1 SAE, and 12 (25.5%) and 9 (22.0%), respectively, experienced at least 1 SAE possibly related to study drug. Two possibly drug-related SAEs occurred in greater than 5% of patients in the enzastaurin arm (febrile neutropenia: 6 [12.8%] and diarrhea: 3 [6.4%]). No SAEs occurred in greater than 5% of patients in the placebo arm.

Table S032.2.12. Summary of Adverse Events in >10% of Patients by Maximum CTCAE Grade 1 to 4 – Part 2, Possibly Related (All Treated Patients[a])

Grade	Doc + Pred + Enz (N=48) CTCAE[b], n (%)	Doc + Pred +Plc (N=46) CTCAE, (n (%)
Grade 1	Diarrhea, 14 (29.8%) Hair Loss/Alopecia, 14 (29.8%) Nausea, 13 (27.7%) Hemoglobin, 10 (21.3%) Fatigue, 8 (17.0%) Taste Alteration (Dysgeusia), 8 (17.0%) AST, SGOT, 7 (14.9%) Vomiting, 7 (14.8%) Dizziness, 6 (12.8%) Nail Changes, 6 (12.8%) Constipation, 5 (10.6%) Edema: Limb, 5 (10.6%)	Hair Loss/Alopecia, 14 (34.1%) Nail Changes, 11 (26.8%) Constipation, 7 (17.1%) Fatigue, 7 (17.1%) Nausea, 7 (17.1%) Neuropathy: Sensory, 7 (17.1%) Dizziness, 6 (14.6%) Vomiting, 5 (12.2%)
Grade 2	Fatigue, 10 (21.3%) Diarrhea, 6 (12.8%) Nausea, 6 (12.8%) Neuropathy: Sensory, 6 (12.8%) Hemoglobin, 5 (10.6%)	Fatigue, 12 (29.3%) Anorexia, 5 (12.2%) Hair Loss/Alopecia, 5 (12.2%)
Grade 3	Fatigue, 8 (17.0%) Neutrophils/Granulocytes, 7 (14.9%) Leukocytes (Total WBC), 5 (10.6%)	Lymphopenia, 5 (12.2%)
Grade 4	---	Neutrophils/Granulocytes, 6 (14.6%)

Abbreviations: CTCAE = Common Terminology for Adverse Events; Doc = docetaxel; Enz = enzastaurin; N=total population size; n = number of patients evaluated for parameter; Pred = prednisone.

[a] Defined as all enrolled patients who received at least 1 dose of study drug.

[b] There are 25 events with missing grade that were excluded from this analysis.

Three (6.4%) patients in the enzastaurin arm and 0 (0.0%) in the placebo arm discontinued due to a nonserious AE, of which, 2 (4.3%) were considered related to study drug in the enzastaurin arm (1 electrocardiogram QT prolonged, 1 nausea). Two (4.3%) patients in the enzastaurin arm and 2 (4.9%) in the placebo arm discontinued due to an SAE, of which 1 (2.1%) and 2 (4.9%) were considered related to study drug, respectively (enzastaurin: 1 colitis; placebo: 1 hypersensitivity and 1 pulmonary fibrosis). Two (4.3%) patients died on therapy in the enzastaurin arm, both due to cardiac ischemia/infarction, 1 of which (2.1%) was considered related to study drug. No patients died on therapy in the placebo arm.

Pharmacokinetics: For Part 2, 36 patients received enzastaurin 500 mg QD and had samples analyzed. Twenty-seven patients were excluded from the analysis for the following reasons:

- Patients [redacted], [redacted], [redacted], [redacted], and [redacted] were excluded due to incorrect or missing sample data.
- Patients [redacted] and [redacted] were excluded due to dose reductions on the day of sampling, so that samples were not collected at steady state.
- Twenty patients were excluded due to missing or incorrect dose records.

Table S032.2.13 provides a summary of the PK parameter estimates of enzastaurin and its major active metabolite derived by post hoc estimation in the 9 evaluable patients.

Table S032.2.13. Summary of Steady-State Plasma Pharmacokinetic Parameter Estimates of Enzastaurin, LSN326020, and Total Analytes (Enzastaurin + LSN326020) in Prostate Cancer Patients following Once-Daily 500-mg Doses of Enzastaurin with Docetaxel

	Geometric Mean (%CV)		
Parameter	**Enzastaurin**	**LSN326020**	Total Analytes
N	9	9	9
$C_{av,ss}$ (nmol/L)	868 (104)	1030 (52)	1990 (74)
$AUC_{\tau,ss}$ (nmol*h/L)	20800 (104)	24800 (52)	47800 (74)
CL/F (L/h)	34.9 (104)	NC	NC
MR	NC	1.19 (74)	NC

Abbreviations: $AUC_{\tau,ss}$ = area under the concentration versus time curve during 1 dosing interval at steady state; Cav,ss = average concentration under steady state conditions during multiple dosing; CL/F = apparent total body clearance of drug calculated after extra-vascular administration; CV = coefficient of variation; MR = metabolic ratio; N = number of subjects, NC = not calculable.

Conclusions:

Part 1:

- No unusual or unexpected AE or SAEs were noted when enzastaurin 500 mg was administered with standard treatment of docetaxel and prednisone. One patient discontinued therapy due to sepsis unrelated to study drug, which ultimately lead to patient death. The SAC recommended to open Part 2 of the study.
- Enzastaurin and LSN326020 mean $C_{av,ss}$ concentrations were virtually identical when enzastaurin was given as 500 mg QD doses alone or with docetaxel.
- Enzastaurin significantly reduced the AUC(0-∞) of docetaxel by about 25%. The reason for this effect is unknown.

Part 2:

- There were no statistical differences in PFS, OS, objective response rate, or DOR when enzastaurin 500 mg was given in combination with docetaxel and prednisone as compared with docetaxel, prednisone, and placebo.
- There were no differences in safety between the 2 arms. There was a slight increase in number of patients who discontinued due to AEs in the enzastaurin arm. Two patients died on therapy in the enzastaurin arm; 1 was considered related to drug (cardiac ischemia/infarction). No patients died on therapy in the placebo arm.
- The pharmacogenomic component of the study was canceled due to a limited number of samples and lack of efficacy in the experimental arm.