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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Torisel® / Temsirolimus

PROTOCOL NO.: 3066A1-303-WW (B1771034)

PROTOCOL TITLE: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study of Oral CCI-779 Administered in Combination With Letrozole vs. Letrozole Alone as First Line Hormonal Therapy in Postmenopausal Women With Locally Advanced or Metastatic Breast Cancer

Study Centers: A total of 261centers took part in the study and enrolled subjects.

Study Initiation and Final Completion Dates: January 2004 to October 2006.

The study was terminated prematurely after the second interim analysis following the recommendation by the Independent Data Monitoring Committee (IDMC) which showed that the conditional power of continuing the study to full accrual and finding a statistically significant difference in favor of the experimental (temsirolimus/letrozole) arm was <10% and that there was also an excess number and severity of adverse events (AEs) in the temsirolimus/letrozole group.

Phase of Development: Phase 3

Study Objectives:

Primary Objectives:

To compare the efficacy of the combination of temsirolimus and letrozole versus letrozole alone as first-line treatment of metastatic breast cancer, using progression-free survival (PFS) as the primary efficacy endpoint.

Secondary Objectives:

Included determination of secondary efficacy endpoints, safety, health outcomes, prognostic markers, and pharmacogenomics.

METHODS

Study Design: This was a Phase 3, randomized, placebo-controlled, double-blind study comparing 2 treatments (temsirolimus/placebo once daily (QD) for 5 days every 2 weeks in combination with letrozole 2.5 mg QD; temsirolimus/placebo were blinded, letrozole was open-label) in subjects with locally advanced or metastatic breast cancer.

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Subjects could continue treatment until disease progression or withdrawal of consent, provided that the treatment was well tolerated. Subjects were followed up every 3 months for survival until disease progression (for subjects who withdrew for reasons other than documented progressive disease) or until initiation of another anticancer treatment.

Two (2) interim analyses evaluating safety and efficacy were planned to be conducted by the IDMC based on the occurrence of 20% and 50% of the expected PFS events using the Investigator's assessment of progression.

The estimated duration of study participation was 34 months. The planned study duration included approximately 16.4 months for subject accrual, 2 years of treatment after the last subject was enrolled, and up to 3 years for the collection of survival data.

The schedule of activities is summarized in Table 1.

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Table 1. Study Flowchart

Study Procedures	Screening (-14 to –1 Days)	Treatment Cycles (14 Day Cycles)				End of Treatment (Within 4 Weeks After Last Dose of Test Article)	Long Term Follow-Up Period (Approximately Every 3 Months)
		Cycle 1	Cycle 2	Cycle 3	Every 4 Cycles, Beginning With Cycle 5 (ie Cycle 5, 9, etc)		
		Day 1			Day 1		
Informed consent (may be within 28 days prior to Day 1)	X						
Inclusion/exclusion criteria	X						
Medical history	X						
Demographics, including race and ethnicity	X						
Prior and current medications	X						
Health outcomes assessment	X				X[a]	X	
Physical examination	X				X	X	
Vital signs	X	X	X	X	X	X	
KPS	X	X	X	X	X	X	X[b]
ECG	X				X[c]	X	
Chest x-ray	X					X	
CBC with differential[d]	X	X	X	X	X	X	
Chemistry panel[e]	X[f]	X	X	X	X	X	
Optional whole blood sample (PBMC)		X	X		X[g]	X	
Tissue slides/block for testing (if available)	X[h]						
Optional tumor biopsy	X[i]						
Tumor sites/assessments[j]	X[k]				X[j]	X[l]	X[b]
Telephone call[m]					X		
Randomization via CORE[n]		X					
Subject diaries		X	X	X	X		
Temsirolimus /placebo administration		X	X	X	X		
Letrozole administration		----------Daily----------					
Monitor adverse events	----------Continuously----------						X[o]
Concomitant medications	----------Continuously----------						
Tumor assessments, anti-cancer Tx, survival							X[b]

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AEs = adverse events; CBC = complete blood count; CORE = computer randomization/enrollment system; DNA = deoxyribonucleic acid; ECG =electrocardiogram; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D = European Quality of Life-5 Dimensions; HER-2 = human epidermal growth factor receptor; IVRS = interactive voice response system; KPS = Karnofsky performance status; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PI3 = phosphatidylinositol 3-kinase; PTEN = phosphatase and tensin homolog; SAEs = serious adverse events.

a. Health outcomes (EORTC QLQ C-30 and EQ-5D) assessments were administered at Screening, and on Day 1 of every 4 cycles starting with Cycle 5 (ie, Cycle 5, 9, etc) ±3 days and at the End of Treatment Visit. Assessments were administered at the time of withdrawal of a subject for any reason and at visits (if possible) where a report was made of at least 1 symptomatic Grade 3 or 4 AEs not requiring hospitalization during the treatment period.
b. **For Subjects Who Discontinued the Active Treatment Phase for Reasons Other Than PD:** 1) Tumor assessments and KPS every 8 weeks from the date of the last tumor assessment until documented PD or until beginning a new cancer treatment; 2) Survival information collected approximately every 3 months from last day of test article administration (eg, end of active treatment phase; 3) SAEs that were considered related to test article; 4) New cancer treatment with available current response.
For Subjects Who Discontinued the Active Treatment Phase for PD: 1) Survival information collected approximately every 3 months from last day of test article administration (eg, end of active treatment phase); 2) New cancer therapy with available current response; 3) SAEs related to test article.
c. ECG was performed at the end of every 12 cycles (approximately every 6 months) ±3 days.
d. CBC with differential: white blood cell count, differential, platelets, red blood count, hemoglobin and hematocrit (if not collected within past 72 hours).
e. Chemistry Panel: sodium, potassium, chloride, blood urea nitrogen or urea, creatinine, glucose, carbon dioxide or bicarbonate, calcium, phosphorus, total protein, albumin, uric acid, lactic dehydrogenase, asparatate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase, total bilirubin, and fasting (at Screening only) serum cholesterol and triglycerides (if not collected within past 72 hours).
f. Fasting was required at Screening only for cholesterol and triglyceride level.
g. If consent was given, whole blood samples were obtained prior to test article administration on Day 1 of Cycles 1, 2, and 5, and End of Treatment Visit.
h. If available, archived tumor biopsy or tumor tissue from glass slides or from paraffin blocks (preferred) were obtained for testing including Cyclin D_1, PTEN, cyclin dependent kinase inhibitor (p27), Her-2/neu receptor status. If optional consent was given, gene alteration tests on DNA, including for testing for PI3 mutation may have been also performed.
i. If consent was given, subjects had a tumor biopsy performed within 4 weeks prior to Day 1 of treatment. The biopsy was analyzed for testing including Cyclin D_1, PTEN, p27, Her-2/neu receptor status. If optional consent was given, gene alteration tests on DNA, including for testing for PI3 mutation may have been performed.
j. Tumor assessments were performed every 4 cycles (approximately every 8 weeks) and were not postponed for test article delays.
k. Screening tumor assessments were performed within 4 weeks prior to Day 1 of treatment on study.
l. Tumor assessments did not need performed at End of Treatment visit if <8 weeks have been passed since last assessment and/or progression of disease has already been documented.
m. An effort was made to contact the subject prior to the start of any new cycle to review any AEs with the subject.
n. Once all eligibility criteria were confirmed, randomization via the CORE IVRS system was performed not more than 1 business day prior to Day 1.
o. In addition to the End of Treatment visit, all subjects were followed for AEs of test article related toxicity for 30 days after stopping test article. SAEs of test article related toxicity were followed until resolution or stabilization. SAEs that occured during the long-term follow-up period that were considered related to test article and were collected.

Number of Subjects (Planned and Analyzed): It was planned to enroll approximately 1236 subjects (1050 subjects evaluable) in the study. A total of 1112 subjects were enrolled in this study: 555 subjects in each of the 2 treatment arms and 2 subjects were randomized in error but were not treated.

Diagnosis and Main Criteria for Inclusion and Exclusion: Women aged ≥18 years and postmenopausal subjects with histologically and/or cytologically confirmed diagnosis of locally advanced (not amenable to curative surgery and/or radiation) or metastatic breast cancer (Stage 3B or 4 respectively, by American Joint Committee on Cancer Criteria), documented estrogen receptor positive and/or progesterone positive tumors based on most recently analyzed biopsy, at least 1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors and received no more than 1 regimen of chemotherapy (including antibody, immunotherapy, biologic therapy, and/or cytotoxic therapy) and no more than 14 consecutive days of hormonal treatment (including aromatase inhibitors) in the locally advanced or metastatic setting were included in the study.

Exclusion Criteria: Subjects with bone as the only site of disease, have extensive visceral disease including bilateral diffuse lymphangitic and extensive hepatic involvement, prior radiation therapy to the site of measurable disease for subjects with solitary measurable lesion were excluded from the study.

Study Treatment: Subjects were randomly assigned to receive either temsirolimus 30 mg tablets or placebo tablets QD orally for 5 days every 2 weeks in combination with letrozole 2.5 mg tablets QD orally. Subjects in both treatment groups took letrozole daily at approximately the same time every day. Subjects received temsirolimus or placebo tablets concomitantly with letrozole during the 5 first days of each cycle and letrozole alone during the 9 last days of each cycle. All subjects were treated as long as the treatment was tolerated or until evidence of disease progression or withdrawal of consent.

No dose reduction of letrozole was permitted. If letrozole-associated toxicities occurred, administration of letrozole was held at the Investigator's discretion for a maximum of 3 consecutive weeks while temsirolimus administration was continued. If temsirolimus/placebo-associated toxicities occurred, dose delay and/or schedule reduction was authorized as described in Table 2.

Table 2. Reduced Schedules According to Dose Modification Requirements

Dose and schedule per study	30 mg temsirolimus/placebo daily for 5 days every 2 weeks
Reduced schedule (-1)	30 mg temsirolimus/placebo daily for 4 days every 2 weeks
Reduced schedule (-2)	30 mg temsirolimus/placebo daily for 3 days every 2 weeks

Other dose modifications were also specified for temsirolimus-/placebo-related hematologic and nonhematologic toxicities. For subjects with Grade 3 or 4 neutropenia or thrombocytopenia, the next dose was to be held until recovery to an absolute neutrophil count of $\geq 1.0 \times 10^9$/L and a platelet count to $\geq 50 \times 10^9$/L. For subjects with Grade 3 or 4 toxicities, the next dose was to be held until recovery to at least Grade 2 (or within 1 grade of screening for preexisting laboratory abnormalities; except for alopecia).

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Efficacy Endpoints:

Primary Efficacy Endpoint: PFS which was based on an independent assessment of progression. A sensitivity analysis of Investigator PFS was also planned.

Secondary Efficacy Endpoints: It included overall survival (OS), objective response rate (ORR), duration of response, clinical benefit rate, time to tumor progression (TTP), time to treatment failure (TTF), and time to initiation of subsequent anticancer therapy.

The primary endpoint was to be based on a retrospective independent assessment of progression which was not complete at the time the trial was stopped. As such, only data on PFS based on Investigator assessment, OS, and ORR were available.

Safety Evaluations: Included physical examination, measurement of weight and vital signs, laboratory assessments, AEs, and serious adverse events (SAEs). AEs were graded according to the National Cancer Institute Common Terminology Criteria, version 3.0.

Statistical Methods: The primary efficacy analyses were based on the intent-to-treat (ITT) population. The ITT population was defined as all subjects randomized in the study.

All subjects who received at least 1 dose of test article were included in the analysis of safety.

PFS rates and survival were estimated using the Kaplan-Meier method. Hazard ratios and corresponding 95% confidence intervals (CIs) between the 2 treatment arms were calculated using the stratified Cox proportional hazard model. Other time-to-event endpoints (survival, TTP, duration of response, and TTF) were evaluated using the same methods. Tumor response and clinical benefit rates were compared using the Mantel-Haenszel test. Observed rates and the associated 95% CIs were calculated.

RESULTS

Subject Disposition and Demography: A total of 1112 subjects were enrolled in the study, including 556 subjects in the temsirolimus/letrozole group and 556 subjects in the letrozole-alone group. The study population included 2 subjects who were randomly assigned to treatment by mistake and did not receive treatment (1 subject randomly assigned to the temsirolimus/letrozole arm and 1 subject randomly assigned to the letrozole alone arm).

All 1112 subjects were included in the efficacy analysis, whereas 550 and 553 subjects in the combination arm and letrozole-alone arm, respectively, were included in safety analysis.

None of the subjects completed the study. All subjects discontinued from the study mainly due to the Sponsor's request regarding the early termination of the study as well as other reasons including disease progression. The reasons for discontinuation from the treatment phase of the study are summarized in Table 3.

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Table 3. Number (%) of Reasons for Conclusion of Subject Participation, Treatment Phase

Conclusion Status Reason[a]	Treatment		
	Unknown (n=2)[b]	Temsirolimus 30 mg Letrozole 2.5 mg (n=555)	Temsirolimus Placebo Letrozole 2.5 mg (n=555)
Discontinued	0	555 (100)	555 (100)[c]
Other[d]	0	273 (49)	264 (48)
Disease progression	0	193 (35)	229 (41)
Subject request	0	26 (5)	19 (3)
AEs related to test article	0	19 (3)	6 (1)
Death	0	13 (2)	9 (2)
Symptomatic deterioration	0	8 (1)	10 (2)
Investigator request	0	9 (2)	7 (1)
AEs not related to test article	0	5 (1)	4 (1)
Protocol violation	0	5 (1)	3 (1)
Failed to return	0	4 (1)	2 (0)

AEs = adverse events; n = number of subjects in each treatment group.

a. Total discontinued was the sum of individual reasons because they were mutually exclusive by subject.
b. These 2 randomly assigned subjects were screen failures.
c. One hundred (100) was a rounding up number.
d. The majority of the other reasons were the discontinuations due to the termination of the study.

The demographic characteristics of the 1112 women with locally advanced or metastatic breast cancer randomly assigned in this study are summarized in Table 4.

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Table 4. Demographic Characteristics

Characteristics	Treatment		
	Unknown[a] (n=2)	Temsirolimus 30 mg Letrozole 2.5 mg (n=555)	Temsirolimus Placebo Letrozole 2.5 mg (n=555)
Sex, n (%)			
Female	0	555 (100)	555 (100)
Missing	2	0	0
Age, years			
N	0	555	555
Mean	0.00	62.80	63.01
Standard deviation	0.00	10.93	10.60
Minimum	0.00	36.00	28.00
Maximum	0.00	98.00	91.00
Median	0.00	63.00	63.00
Missing	2	0	0
Ethnic origin, n (%)			
Hispanic or Latino	0	95 (17.12)	114 (20.54)
Non-Hispanic and Non-Latino	0	460 (82.88)	441 (79.46)
Missing	2	0	0

N = number of subjects in specific driteria; n = number of subjects in each treatment group.
a. These 2 randomly assigned subjects were screen failures.

Efficacy Results: As the study was terminated prematurely, only data on PFS based on Investigator assessment, OS, and ORR were available and these are presented below.

Progression-Free Survival: The primary endpoint was based on a retrospective independent assessment of progression, which was not complete at the time the trial was stopped. As such, only data on PFS based on Investigator assessment, OS, and ORR are presented. Results are presented for ITT population, which represents all 1112 subjects randomly assigned to treatment. PFS was defined as the time from the first dose of treatment to disease progression, symptomatic deterioration, or death. Investigator PFS results are presented in Table 5. Median PFS was 8.9 months in the temsirolimus/letrozole group versus 9.0 months in the letrozole-alone group. There was no significant difference in PFS between the treatment groups (hazard ratio 0.90; p-value 0.2469).

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Table 5. Kaplan-Meier Estimate of PFS - IIT, Population

Characteristics	Treatment		
	Temsirolimus 30 mg Letrozole 2.5 mg (n=556)	Temsirolimus Placebo Letrozole 2.5 mg (n=556)	All Subjects (N=1112)
Investigator's assessment[a]			
No. subjects with follow-up tumor assessment (n, %)	493 (88.7)	503 (90.5)	996 (44.8)
Median PFS in months (95% CI)	8.9 (7.4, 9.6)	9.0 (7.2, 9.4)	8.9 (7.4, 9.2)
Hazard ratio (95% CI)[b]	----------0.90 (0.76, 1.07)----------		
p-Value[c]	----------0.2469----------		
No. of subjects with PD/death (n, %)	266 (47.8)	286 (51.4)	552 (24.8)
No. of censored subjects (n, %)	290 (52.2)	270 (48.6)	560 (25.2)

CI = confidence interval; ITT = intent-to-treat; n = number of subjects in each treatment group; N = total number of subjects; No. = number; PD = progressive disease; PFS = progression-free survival.

a. Progressive disease was determined based on radiographic review or diagnosis of symptomatic deterioration by Investigator.
b. Compared with letrozole alone, based on Cox proportional hazard model stratified by prior bone disease status and geographic region.
c. Compared with letrozole alone, based on log rank test stratified by prior bone disease status and geographic region.

Survival: Per study, collection of survival data could have lasted up to 7 years. Owing to the early termination of the study, collection of survival data was stopped prematurely. The available data are provided in Table 6. Owing to early termination of the study, few subjects had died at the time of the analysis. Thus, the majority of subjects were censored and median survival could not be calculated.

Table 6. Kaplan-Meier Estimate of Overall Survival, Intent-To-Treat Population

Characteristics	Treatment		
	Temsirolimus 30 mg Letrozole 2.5 mg (n=556)	Temsirolimus Placebo Letrozole 2.5 mg (n=556)	All Subjects (N=1112)
No. subjects with follow-up tumor assessment (n, %)	493 (88.7)	503 (90.5)	996 (44.8)
Median survival in months (95% CI)	NA (NA, NA)	NA (NA, NA)	NA (NA, NA)
Hazard ratio (95% CI) [a]	----------0.89 (0.65, 1.23)----------		
p-Value[b]	----------0.4927----------		
No. of subjects with Death (n, %)	73 (13.1)	81 (14.6)	154 (6.9)
No. of censored subjects (n, %)	483 (86.9)	475 (85.4)	958 (43.1)

CI = confidence interval; n = number of subjects in each treatment group; N = total number of subjects; NA = not applicable; No. = number.

a. Compared with letrozole alone, based on Cox proportional hazard model stratified by prior bone disease status and geographic region.
b. Compared with letrozole alone, based on log rank test stratified by prior bone disease status and geographic region.

Best Tumor Response: The best overall tumor responses are presented in Table 7. The treatment combination did not improve the best tumor response compared with letrozole alone. The percentage of subjects with a best tumor response of complete response or partial

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response was 27.1% in the temsirolimus/letrozole group versus 26.8% in the letrozole-alone group.

Table 7. Best Overall Response by Treatment Group, IIT Population

Characteristics	Treatment		
	Temsirolimus 30 mg Letrozole 2.5 mg (n=556)	Temsirolimus Placebo Letrozole 2.5 mg (n=556)	All Subjects (N=1112)
Complete response	14 (2.5)	10 (1.8)	24 (2.2)
Partial response	137 (24.6)	139 (25.0)	276 (24.8)
Stable disease ≥24 weeks[a]	97 (17.4)	106 (19.1)	203 (18.3)
Stable disease ≥16 weeks[a]	63 (11.3)	40 (7.2)	103 (9.3)
Stable disease ≥8 weeks[a]	95 (17.1)	98 (17.6)	193 (17.4)
Progressive disease	85 (15.3)	109 (19.6)	194 (17.4)
Indeterminate	2 (0.4)	1 (0.2)	3 (0.3)
No post screening evaluation	63 (11.3)	53 (9.5)	116 (10.4)

ITT = intent-to-treat; n = number of subjects in each treatment group; N = total number of subjects.
a. Included a 2-week window.

Safety Results:

Serious Adverse Events: SAEs are summarized in Table 8. SAEs were reported for 93 (16.9%) subjects in the temsirolimus/letrozole arm and for 75 (13.6%) subjects in the letrozole-alone arm. The most frequently SAEs affected the Body as a Whole system and the Respiratory system categories. Treatment-related SAEs were reported for 33 (5.9%) subjects in the temsirolimus/letrozole arm and for 12 (2.2%) subjects in the letrozole-alone arm.

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Table 8. Number (%) of Subjects Reporting Serious Adverse Events in Descending Order of Incidence

Body System[a] Serious Adverse Event	Treatment	
	Temsirolimus 30 mg Letrozole 2.5 mg (n=550)	Temsirolimus Placebo Letrozole 2.5 mg (n=553)
Any adverse event	93 (16.9)	75 (13.6)
Classification unknown	1 (0.2)	0
Classification unknown	1 (0.2)	0
Body as a whole	29 (5.3)	32 (5.8)
Accidental injury	2 (0.4)	6 (1.1)
Carcinoma	5 (0.9)	4 (0.7)
Abdominal pain	4 (0.7)	4 (0.7)
Infection	3 (0.5)	3 (0.5)
Pain	3 (0.5)	0
Back pain	1 (0.2)	3 (0.5)
Chest pain	0	3 (0.5)
General physical health deterioration	1 (0.2)	3 (0.5)
Fever	2 (0.4)	2 (0.4)
Headache	2 (0.4)	1 (0.2)
Asthenia	0	2 (0.4)
Cellulitis	1 (0.2)	2 (0.4)
Abscess	1 (0.2)	0
Ascites	1 (0.2)	1 (0.2)
Neck pain	1 (0.2)	1 (0.2)
Neoplasm	1 (0.2)	0
Sepsis	1 (0.2)	1 (0.2)
Chills	0	1 (0.2)
Generalized edema	0	1 (0.2)
Hernia	0	1 (0.2)
Cardiovascular system	21 (3.8)	9 (1.6)
Congestive heart failure	4 (0.7)	1 (0.2)
Pulmonary embolus	4 (0.7)	1 (0.2)
Heart failure	3 (0.5)	1 (0.2)
Deep vein thrombosis	2 (0.4)	0
Hypertension	2 (0.4)	1 (0.2)
Myocardial infarct	2 (0.4)	1 (0.2)
Atrial fibrillation	1 (0.2)	0
Cerebrovascular accident	1 (0.2)	0
Pericardial effusion	1 (0.2)	0
Shock	1 (0.2)	0
Syncope	1 (0.2)	0
Thrombophlebitis	1 (0.2)	0
Thrombosis	1 (0.2)	1 (0.2)
Bradycardia	0	1 (0.2)
Cardiac tamponade	0	1 (0.2)
Cerebral infarct	0	1 (0.2)
Hemorrhage	0	1 (0.2)
Tachycardia	0	1 (0.2)
Digestive system	15 (2.7)	12 (2.2)
Diarrhea	5 (0.9)	0
Vomiting	2 (0.4)	3 (0.5)
Hepatic failure	2 (0.4)	1 (0.2)

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Table 8. Number (%) of Subjects Reporting Serious Adverse Events in Descending Order of Incidence

Body System[a] Serious Adverse Event	Treatment	
	Temsirolimus 30 mg Letrozole 2.5 mg (n=550)	Temsirolimus Placebo Letrozole 2.5 mg (n=553)
Mucositis	2 (0.4)	1 (0.2)
Tongue edema	2 (0.4)	0
Intestinal obstruction	1 (0.2)	2 (0.4)
Nausea	1 (0.2)	2 (0.4)
Gastrointestinal hemorrhage	1 (0.2)	1 (0.2)
Ileus	1 (0.2)	0
Liver damage	1 (0.2)	0
Cholangitis	0	1 (0.2)
Cholecystitis	0	1 (0.2)
Gamma glutamyl transpeptidase increased	0	1 (0.2)
Hematemesis	0	1 (0.2)
Jaundice	0	1 (0.2)
Pancreatitis	0	1 (0.2)
Endocrine system	0	1 (0.2)
Diabetes mellitus	0	1 (0.2)
Hemic and lymphatic system	4 (0.7)	6 (1.1)
Anemia	2 (0.4)	4 (0.7)
Neutropenia	2 (0.4)	1 (0.2)
Lymphopenia	1 (0.2)	0
Thrombocytopenia	1 (0.2)	1 (0.2)
Leukopenia	0	1 (0.2)
Metabolic and nutritional	17 (3.1)	6 (1.1)
Dehydration	6 (1.1)	2 (0.4)
Hyperglycemia	3 (0.5)	0
Hypercalcemia	2 (0.4)	1 (0.2)
Hypokalemia	2 (0.4)	1 (0.2)
Electrolyte abnormality	1 (0.2)	0
Failure to thrive	1 (0.2)	0
Gout	1 (0.2)	0
Hypophosphatemia	1 (0.2)	0
Peripheral edema	1 (0.2)	0
Hyperuricemia	0	1 (0.2)
Hypoglycemia	0	1 (0.2)
Musculoskeletal system	4 (0.7)	2 (0.4)
Arthralgia	1 (0.2)	0
Myasthenia	1 (0.2)	0
Pathological fracture	1 (0.2)	1 (0.2)
Spinal fracture	1 (0.2)	0
Bone pain	0	1 (0.2)
Nervous system	5 (0.9)	3 (0.5)
Vertigo	2 (0.4)	0
Confusion	1 (0.2)	0
Convulsion	1 (0.2)	0
Neuropathy	1 (0.2)	0
Spinal cord compression	1 (0.2)	0
Anxiety	0	1 (0.2)
Nerve compression	0	1 (0.2)

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Table 8. Number (%) of Subjects Reporting Serious Adverse Events in Descending Order of Incidence

Body System[a] Serious Adverse Event	Treatment	
	Temsirolimus 30 mg Letrozole 2.5 mg (n=550)	Temsirolimus Placebo Letrozole 2.5 mg (n=553)
Neuralgia	0	1 (0.2)
Subdural hematoma	0	1 (0.2)
Respiratory system	33 (6.0)	14 (2.5)
Pneumonia	9 (1.6)	2 (0.4)
Dyspnea	8 (1.5)	7 (1.3)
Pleural effusion	7 (1.3)	5 (0.9)
Respiratory failure	5 (0.9)	2 (0.4)
Respiratory distress syndrome	2 (0.4)	1 (0.2)
Chronic obstructive airways disease	1 (0.2)	0
Interstitial pneumonia	1 (0.2)	0
Lung disorder	1 (0.2)	0
Pneumonitis	1 (0.2)	0
Respiratory disorder	1 (0.2)	0
Skin and appendages	4 (0.7)	2 (0.4)
Angioedema	1 (0.2)	0
Fungal dermatitis	1 (0.2)	0
Herpes zoster	1 (0.2)	0
Pustular rash	1 (0.2)	0
Rash	1 (0.2)	0
Contact dermatitis	0	1 (0.2)
Skin ulcer	0	1 (0.2)
Special senses	0	1 (0.2)
Blindness	0	1 (0.2)
Urogenital system	7 (1.3)	8 (1.4)
Breast carcinoma	2 (0.4)	2 (0.4)
Urinary tract infection	2 (0.4)	0
Kidney function abnormal	0	2 (0.4)
Cervix carcinoma	1 (0.2)	0
Kidney calculus	1 (0.2)	1 (0.2)
Pyelonephritis	1 (0.2)	0
Breast neoplasm	0	1 (0.2)
Hematuria	0	1 (0.2)
Hydronephrosis	0	1 (0.2)
Mastitis	0	1 (0.2)
Ovarian carcinoma	0	1 (0.2)

n = number of subjects in each treatment group.

a. Body system totals were not necessarily the sum of the individual adverse events since a subject may have been reported ≥2 different adverse events in the same body system.

Adverse Events: Summary tabulations of treatment-emergent adverse events (TEAEs) regardless of causality are provided in Table 9.

The overall incidence of TEAEs was 90.7% (499/550) in the temsirolimus/letrozole arm and 79.4% (439/553) in the letrozole-alone arm. In the temsirolimus/letrozole arm, the main body systems affected were digestive system, body as a whole, metabolic and nutritional, and respiratory system. The most frequent TEAEs (incidence ≥10%) were asthenia, diarrhea,

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headache, nausea, cough increased, peripheral edema, rash and pain, anorexia, and mucositis and fever. In the letrozole-alone arm, the main body systems affected were body as a whole, digestive system, and metabolic and nutritional. The most frequent TEAEs were asthenia, nausea, and arthralgia.

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Table 9. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events With an Incidence of ≥5%

Body System[a] Adverse Event	Treatment	
	Temsirolimus 30mg Letrozole 2.5 mg (n=550)	Temsirolimus Placebo Letrozole 2.5 mg (n=553)
Any AE	499 (90.7)	439 (79.4)
Body as a whole	337 (61.3)	296 (53.5)
Asthenia	148 (26.9)	115 (20.8)
Headache	102 (18.5)	66 (11.9)
Pain	82 (14.9)	59 (10.7)
Fever	78 (14.2)	41 (7.4)
Infection	62 (11.3)	43 (7.8)
Back pain	57 (10.4)	60 (10.8)
Abdominal pain	56 (10.2)	50 (9.0)
Chest pain	41 (7.5)	44 (8.0)
Flu syndrome	23 (4.2)	31 (5.6)
Cardiovascular system	111 (20.2)	120 (21.7)
Vasodilatation	28 (5.1)	59 (10.7)
Hypertension	28 (5.1)	28 (5.1)
Digestive system	345 (62.7)	224 (40.5)
Diarrhea	115 (20.9)	52 (9.4)
Nausea	87 (15.8)	90 (16.3)
Anorexia	81 (14.7)	39 (7.1)
Mucositis	78 (14.2)	11 (2.0)
Stomatitis	65 (11.8)	13 (2.4)
Vomiting	63 (11.5)	50 (9.0)
Constipation	51 (9.3)	33 (6.0)
Gamma glutamyl transpeptidase increased	31 (5.6)	20 (3.6)
Mouth ulceration	28 (5.1)	6 (1.1)
Hemic and lymphatic system	143 (26.0)	70 (12.7)
Anemia	59 (10.7)	27 (4.9)
Thrombocytopenia	39 (7.1)	9 (1.6)
Neutropenia	37 (6.7)	11 (2.0)
Leukopenia	36 (6.5)	8 (1.4)
Metabolic and nutritional	266 (48.4)	166 (30.0)
Peripheral edema	83 (15.1)	33 (6.0)
Hyperglycemia	72 (13.1)	26 (4.7)
Hypercholesteremia	67 (12.2)	33 (6.0)
Hyperlipemia	61 (11.1)	28 (5.1)
SGOT increased	30 (5.5)	22 (4.0)
SGPT increased	28 (5.1)	19 (3.4)
Musculoskeletal system	128 (23.3)	143 (25.9)
Arthralgia	60 (10.9)	78 (14.1)
Myalgia	37 (6.7)	33 (6.0)
Bone pain	33 (6.0)	32 (5.8)
Nervous system	147 (26.7)	123 (22.2)
Insomnia	48 (8.7)	34 (6.1)
Dizziness	35 (6.4)	33 (6.0)
Respiratory system	220 (40.0)	148 (26.8)
Cough increased	84 (15.3)	56 (10.1)
Dyspnea	69 (12.5)	54 (9.8)
Epistaxis	55 (10.0)	11 (2.0)

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Table 9. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events With an Incidence of ≥5%

Body System[a] Adverse Event	Treatment	
	Temsirolimus 30mg Letrozole 2.5 mg (n=550)	Temsirolimus Placebo Letrozole 2.5 mg (n=553)
Pharyngitis	37 (6.7)	19 (3.4)
Skin and appendages	205 (37.3)	101 (18.3)
Rash	82 (14.9)	23 (4.2)
Pruritus	66 (12.0)	29 (5.2)
Nail disorder	36 (6.5)	3 (0.5)
Urogenital system	88 (16.0)	72 (13.0)
Breast pain	20 (3.6)	31 (5.6)

Non SAE/SAE results are not separated out.
AEs = adverse events; n = number of subjects in each treatment group; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.
a. Body system totals were not necessarily the sum of the individual AEs since a subject may have been reported ≥2 different AEs in the same body system.

The overall incidence of treatment-related TEAEs was 75.8% (417/550) in the temsirolimus/letrozole arm and 50.8% (281/553) in the letrozole-alone arm. Number (%) of subjects reporting treatment-related TEAEs with an incidence of ≥5% is presented in Table 10.

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Table 10. Number (%) of Subjects Reporting Treatment-Related Treatment-Emergent Adverse Events With an Incidence of ≥5%

Body System[a] Adverse Event	Treatment	
	Temsirolimus 30mg Letrozole 2.5 mg (n=550)	Temsirolimus Placebo Letrozole 2.5 mg (n=553)
Any AE	417 (75.8)	281 (50.8)
Body as a whole	188 (34.2)	130 (23.5)
Asthenia	101 (18.4)	70 (12.7)
Headache	56 (10.2)	24 (4.3)
Fever	30 (5.5)	9 (1.6)
Cardiovascular system	47 (8.5)	61 (11.0)
Vasodilatation	20 (3.6)	50 (9.0)
Digestive system	272 (49.5)	125 (22.6)
Diarrhea	75 (13.6)	16 (2.9)
Mucositis	71 (12.9)	8 (1.4)
Nausea	64 (11.6)	54 (9.8)
Stomatitis	63 (11.5)	9 (1.6)
Anorexia	56 (10.2)	20 (3.6)
Vomiting	31 (5.6)	25 (4.5)
Constipation	28 (5.1)	11 (2.0)
Hemic and lymphatic system	104 (18.9)	29 (5.2)
Anemia	39 (7.1)	10 (1.8)
Thrombocytopenia	38 (6.9)	5 (0.9)
Leukopenia	35 (6.4)	7 (1.3)
Neutropenia	35 (6.4)	6 (1.1)
Metabolic and nutritional	174 (31.6)	82 (14.8)
Hypercholesteremia	56 (10.2)	24 (4.3)
Hyperlipemia	54 (9.8)	17 (3.1)
Hyperglycemia	42 (7.6)	13 (2.4)
Peripheral edema	33 (6.0)	8 (1.4)
Musculoskeletal system	50 (9.1)	55 (9.9)
Arthralgia	28 (5.1)	30 (5.4)
Respiratory system	85 (15.5)	27 (4.9)
Epistaxis	39 (7.1)	5 (0.9)
Skin and appendages	154 (28.0)	60 (10.8)
Rash	69 (12.5)	15 (2.7)
Pruritus	45 (8.2)	18 (3.3)
Nail disorder	30 (5.5)	3 (0.5)

Non SAE/SAE results are not separated out.
AEs = adverse events; n = number of subjects in each treatment group.
a. Body system totals were not necessarily the sum of the individual AEs since a subject may have been reported ≥2 different AEs in the same body system.

Discontinuations due to Adverse Events: The AEs leading to treatment discontinuation are summarized in Table 11; no AE had an incidence of ≥1%. Thirty-five (35, 6.4%) subjects had AEs leading to temsirolimus/letrozole discontinuation and 21 (3.8%) subjects had AEs leading to letrozole discontinuation. In the temsirolimus/letrozole arm, the most commonly reported AEs leading to discontinuation (incidence ≥2 subjects) were stomatitis (3 subjects, 0.5%) and pulmonary embolus, γ-glutamyl transpeptidase increased, pneumonitis, and respiratory failure (2 subjects, 0.4% each). In the letrozole-alone arm, back pain and

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pneumonia were the most commonly reported AEs leading to discontinuation (2 subjects, 0.4% each).

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Table 11. Number (%) of Subjects Reporting Adverse Events Leading to Test Article Discontinuation

Body System[a] Adverse Event	Treatment	
	Temsirolimus 30mg Letrozole 2.5mg (n=550)	Temsirolimus Placebo Letrozole 2.5mg (n=553)
Any adverse event	35 (6.4)	21 (3.8)
Body as a whole	9 (1.6)	7 (1.3)
Back pain	0	2 (0.4)
Allergic reaction	1 (0.2)	0
Ascites	1 (0.2)	0
Asthenia	1 (0.2)	0
Carcinoma	1 (0.2)	1 (0.2)
Cellulitis	1 (0.2)	0
General physical health deterioration	1 (0.2)	0
Infection	1 (0.2)	0
Pain	1 (0.2)	0
Sepsis	1 (0.2)	0
Abdominal pain	0	1 (0.2)
Accidental injury	0	1 (0.2)
Chills	0	1 (0.2)
Headache	0	1 (0.2)
Cardiovascular system	4 (0.7)	4 (0.7)
Pulmonary embolus	2 (0.4)	0
Congestive heart failure	1 (0.2)	0
Deep vein thrombosis	1 (0.2)	0
Heart failure	0	1 (0.2)
Thrombosis	0	1 (0.2)
Vascular disorder	0	1 (0.2)
Vasodilatation	0	1 (0.2)
Digestive system	9 (1.6)	4 (0.7)
Stomatitis	3 (0.5)	0
Gamma glutamyl transpeptidase increased	2 (0.4)	1 (0.2)
Abdominal distension	1 (0.2)	0
Anorexia	1 (0.2)	0
Hepatic failure	1 (0.2)	0
Mucositis	1 (0.2)	0
Intestinal obstruction	0	1 (0.2)
Liver function tests abnormal	0	1 (0.2)
Nausea	0	1 (0.2)
Hemic and lymphatic system	0	2 (0.4)
Lymphedema	0	1 (0.2)
Thrombocytopenia	0	1 (0.2)
Metabolic and nutritional	2 (0.4)	4 (0.7)
Dehydration	1 (0.2)	0
Failure to thrive	1 (0.2)	0
BUN increased	0	1 (0.2)
Creatinine increased	0	1 (0.2)
Edema	0	1 (0.2)
Hypokalemia	0	1 (0.2)
Peripheral edema	0	1 (0.2)
Musculoskeletal system	1 (0.2)	0
Myasthenia	1 (0.2)	0

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Table 11. Number (%) of Subjects Reporting Adverse Events Leading to Test Article Discontinuation

Body System[a] Adverse Event	Treatment	
	Temsirolimus 30mg Letrozole 2.5mg (n=550)	Temsirolimus Placebo Letrozole 2.5mg (n=553)
Nervous system	1 (0.2)	1 (0.2)
Confusion	1 (0.2)	0
Nerve compression	0	1 (0.2)
Respiratory system	6 (1.1)	3 (0.5)
Pneumonitis	2 (0.4)	0
Respiratory failure	2 (0.4)	0
Pneumonia	0	2 (0.4)
Dyspnea	1 (0.2)	1 (0.2)
Lung infiltration (not other specified)	1 (0.2)	0
Respiratory distress syndrome	0	1 (0.2)
Skin and appendages	2 (0.4)	0
Pruritus	1 (0.2)	0
Pustular rash	1 (0.2)	0
Special senses	1 (0.2)	0
Taste perversion	1 (0.2)	0
Urogenital system	3 (0.5)	1 (0.2)
Breast carcinoma	1 (0.2)	0
Cervix carcinoma	1 (0.2)	0
Kidney calculus	1 (0.2)	0
Kidney function abnormal	0	1 (0.2)

Events leading to treatment discontinuation were determined using the action code of D (discontinuation) or W (withdrawal).
BUN = blood urea nitrogen; n = number of subjects in each treatment group.
a. Body system totals were not necessarily the sum of the individual adverse events since a subject may have been reported ≥2 different adverse events in the same body system.

The treatment-related AEs leading to treatment discontinuation are reported in Table 12; no AE had an incidence of ≥1%. Twenty-four ([24], 4.4%) subjects discontinued treatment because of temsirolimus/letrozole-related AEs and 7 (1.3%) subjects because of letrozole-related AEs.

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Table 12. Number (%) of Subjects Reporting Treatment-Related Adverse Events in Descending Order of Incidence Where Action Code Indicated Permanent Discontinuation of Test Article

Body System[a] Adverse Event	Treatment	
	Temsirolimus 30mg Letrozole 2.5mg (n=550)	Temsirolimus Placebo Letrozole 2.5mg (n=553)
Any adverse event	24 (4.4)	7 (1.3)
Body as a whole	4 (0.7)	2 (0.4)
Allergic reaction	1 (0.2)	0
Ascites	1 (0.2)	0
Asthenia	1 (0.2)	0
Pain	1 (0.2)	0
Back pain	0	1 (0.2)
Chills	0	1 (0.2)
Cardiovascular system	4 (0.7)	2 (0.4)
Pulmonary embolus	2 (0.4)	0
Congestive heart failure	1 (0.2)	0
Deep vein thrombosis	1 (0.2)	0
Thrombosis	0	1 (0.2)
Vasodilatation	0	1 (0.2)
Digestive system	8 (1.5)	1 (0.2)
Stomatitis	3 (0.5)	0
Gamma glutamyl transpeptidase increased	2 (0.4)	0
Abdominal distension	1 (0.2)	0
Anorexia	1 (0.2)	0
Mucositis	1 (0.2)	0
Nausea	0	1 (0.2)
Metabolic and nutritional	1 (0.2)	3 (0.5)
Dehydration	1 (0.2)	0
Creatinine increased	0	1 (0.2)
Edema	0	1 (0.2)
Hypokalemia	0	1 (0.2)
Musculoskeletal system	1 (0.2)	0
Myasthenia	1 (0.2)	0
Nervous system	1 (0.2)	0
Confusion	1 (0.2)	0
Respiratory system	4 (0.7)	0
Pneumonitis	2 (0.4)	0
Dyspnea	1 (0.2)	0
Lung infiltration (not other specified)	1 (0.2)	0
Skin and appendages	2 (0.4)	0
Pruritus	1 (0.2)	0
Pustular rash	1 (0.2)	0
Special senses	1 (0.2)	0
Taste perversion	1 (0.2)	0
Urogenital system	0	1 (0.2)
Kidney function abnormal	0	1 (0.2)

n = number of subjects in each treatment group.

a. Body system totals were not necessarily the sum of the individual adverse events since a subject may have been reported ≥2 different adverse events in the same body system.

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Deaths: Within 30 days after the last dose of test article, 71 subjects in the temsirolimus/ letrozole arm died and 80 subjects in the letrozole-alone arm died. The main cause of death was disease progression as displayed in Table 13. Three (3) subjects died because of treatment-related AEs.

Table 13. Summary of Reason of Death Categories

Characteristics	Treatment	
	Temsirolimus 30mg Letrozole 2.5 mg (n=71)	**Temsirolimus Placebo Letrozole 2.5 mg (n=80)**
Cause of death		
Adverse events related to test article	1 (1.43)	2 (2.60)
Disease progression	55 (78.57)	68 (88.31)
Other	14 (20.00)	6 (7.79)
Other: general physical deterioration	0	1 (1.30)
Missing[a]	1	3

n = number of subjects died in each treatment group.
a. These 4 deaths did not occur during the study.

Physical Examination, Vital Signs and Laboratory Assessments: Data not available.

CONCLUSIONS:

After review of the second interim analysis of 382 events in 992 subjects, the IDMC unanimously recommended termination of the study because the conditional power of finding a statistically significant difference in favor of the temsirolimus/letrozole arm was <10% with full accrual. In addition, there was an excess number and severity of AEs in the temsirolimus/letrozole group. Based on this recommendation, the Sponsor terminated the study and discontinued clinical development of oral temsirolimus for the treatment of locally advanced or metastatic breast cancer.

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