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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Celebrex®/Celecoxib

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00038103

PROTOCOL NO.: A3191139 (NQ8-01-02-013)

PROTOCOL TITLE: Open-Label, Multicenter, Controlled Study of Exemestane (Aromasin®) with or without Celecoxib (Celebrex®) in Postmenopausal Women with Advanced Breast Cancer (ABC) Having Progressed on Tamoxifen

Study Centers: Subjects were recruited at 20 centers in 9 countries: 4 in India, 1 in the Philippines, 5 in Belgium, 2 in Peru, 2 in Mexico, 2 in Colombia, 2 in Brazil, 1 in Canada and 1 co-ordinating site in the US.

Study Initiation and Completion Dates: 23 January 2002 to 27 March 2008

Phase of Development: Phase 2

Study Objectives:

Primary

- To evaluate the effect of celecoxib on clinical benefit (defined as the frequency of objective tumor response and disease stabilization for at least 24 weeks) of exemestane in postmenopausal women with advanced breast cancer (ABC) having progressed on tamoxifen.

Secondary

- To evaluate the effect of celecoxib on other efficacy parameters than clinical benefit and on the tolerability (incidence and severity of systemic toxicity) of exemestane in postmenopausal women with ABC having progressed on tamoxifen, and its effect on the exemestane pharmacodynamics and pharmacokinetics (PKs).

METHODS

Study Design: This was an open-label, multicenter, randomized (1:1 randomization ratio) study of exemestane and exemestane combined with celecoxib in postmenopausal women with ABC having progressed on tamoxifen. The study design included administration of

exemestane alone in order to confirm the reproducibility of results from previous studies and to exclude any bias that could have resulted from possible changes in the subject population.

Number of Subjects (Planned and Analyzed): It was planned to include 100 subjects in the study; 111 subjects were enrolled, of which 55 subjects were assigned to the exemestane arm and 56 to the combination arm (exemestane + celecoxib).

Diagnosis and Main Criteria for Inclusion: This study included postmenopausal female subjects with ABC with disease progression who had progressed on tamoxifen. Selected inclusion criteria included: estrogen receptor positive (ER+ve) and/or progesterone receptor positive (PgR+ve) or unknown receptors (if previous response to tamoxifen); and at least 1 measurable tumoral lesion.

Study Treatment: Subjects randomized to exemestane alone received an oral dose taken with food (25 mg tablet once daily); subjects randomized to the combination treatment received oral doses to be taken with food (25 mg tablet exemestane once daily; celecoxib 2 x 200 mg tablets twice daily) throughout the study period. Subjects remained in the study until disease progression, death or unacceptable toxicity.

Efficacy Evaluations: The primary endpoint of the study was to determine antitumor efficacy and was based on objective tumor assessments made according to the Response Evaluation Criteria in Solid Tumors (RECIST) system of unidimensional evaluation. The timing and type of tumor evaluations were carried out at baseline and on Week 8, 16, and 24, every 12 weeks beyond Week 24 up to Week 108, and every 24 weeks afterwards.

Secondary endpoints were as follows:

1. Duration of objective response (in subjects with complete response [CR] or partial response [PR]): the time from the first objective documentation of response until the first objective documentation of tumor progression or death due to tumor progression in the absence of previous documentation of tumor progression.

2. Duration of long-term stable disease (SD) (in subjects with long-term SD): the time from randomization until the first objective documentation of tumor progression or death due to tumor progression in the absence of previous documentation of tumor progression.

3. Duration of clinical benefit (in subjects with CR, PR or long-term SD): the time from randomization until the first objective documentation of tumor progression or death due to tumor progression in the absence of previous documentation of tumor progression.

4. Time to tumor progression (TTP): the time from randomization to first objective documentation of tumor recurrence or progression or death due to tumor progression in the absence of previous documentation of tumor progression.

For subjects who did not have objective evidence of tumor progression and who were removed from the study, or who died of causes not related to cancer, or those subjects who were given antitumor treatment other than the study treatment, duration of objective response, duration of long-term SD, duration of clinical benefit and TTP were to be censored.

Subjects who died of unknown causes were considered to have died due to tumor progression.

5. Time to treatment failure (TTF): the time from the randomization to the date of first objective documentation of tumor recurrence or progression or death due to any cause or withdrawal from study treatment due to any reason, whichever was the earliest event. Subjects who were still on treatment at the time of the analysis were not to be considered to have experienced treatment failure. For those subjects, TTF was censored at last available assessment.

6. Survival: the time from randomization to the date of death due to any cause. Subjects alive at the time of analysis and subjects lost to follow-up were censored at last available assessment.

Pharmacokinetic and Pharmacodynamic Evaluations:

Pharmacokinetics

Plasma concentrations of exemestane and its metabolite 17-hydroexemestane were determined in subjects in selected centers to explore the effect of celecoxib on the exposure to exemestane.

Pharmacodynamics

Evaluations included plasma concentrations of estradiol (E2), estrone (E1), estrone sulfate (E1S) and sex hormone-binding globulin (SHBG).

Safety Evaluations: Safety evaluations included the monitoring of all adverse events (AEs); hematological, biochemical and urinary parameters; vital signs and electrocardiogram (ECG).

Physical examination including the determination of body weight, diastolic and systolic blood pressure (BP) and heart rate (HR) were performed at baseline, before dosing, and at each subsequent visit. Eastern Co-operative Oncology Group (ECOG) performance status was assessed at each visit. An ECG was performed at baseline, before dosing, and after dosing if clinically indicated. Laboratory tests (hematology: hemoglobin, white blood cell [WBC] count with differentials, platelet count; blood chemistry: total serum bilirubin, alkaline phosphatase, alanine transaminase [ALT], aspartate transaminase [AST], gamma glutamyl transferase [GGT], total protein, total calcium, glucose, creatinine, blood urea nitrogen, total cholesterol, high-density lipoprotein cholesterol and triglycerides; and urinalysis: pH and protein) were performed at each scheduled visit.

Statistical Methods: Subjects were randomized according to a minimization procedure to balance major prognostic factors (response to prior tamoxifen, prior chemotherapy and site of metastases) in the 2 treatment arms. The sample size for the combination arm was determined according to the 1 stage Fleming design. The inclusion of the exemestane arm in the study was used as internal control. Overall, 50 subjects per arm were needed to account for an approximately 10% non-evaluability rate.

Efficacy Analyses

The primary endpoint of this study was the evaluation of the clinical benefit rate defined as the proportion of subjects who achieved objective tumor response (CR or PR) or long-term disease stabilization (SD lasting at least 24 weeks) out of the total number of subjects included in the population (evaluable or intent-to-treat [ITT]). The 95% confidence interval (CI) for the clinical benefit rate was calculated using the normal approximation of the binomial distribution. The estimation of the objective response rate was also provided.

Secondary efficacy endpoints (duration of clinical benefit, duration of objective response, duration of long-term SD, TTP, TTF and survival) were estimated by Kaplan and Meier methods and graphically presented both in the evaluable and the ITT populations. Analyses focused on the combination arm, but were also provided for the exemestane arm.

Pharmacokinetic and Pharmacodynamic Analyses

Descriptive statistics were provided for all PK and pharmacodynamic parameters.

Safety Analyses

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA Version 11.1) and were described in terms of severity, seriousness and study treatment relationship. Aggregations according to the System Organ Class were provided. Data were analyzed by subject. The worst severity grade was the one reported during the entire study period.

Laboratory data was graded according to the National Cancer Institute Common Terminology Criteria (NCI CTC; Version 2.0) classification whenever possible. For each parameter, a cross-tabulation of the worst grade observed during treatment versus the baseline was provided.

RESULTS

Subject Disposition and Demography: Subject disposition and subjects analyzed are summarized in Table S1. A total of 111 subjects were randomized (55 subjects in the exemestane arm; 56 subjects in the combination arm); 2 subjects in the exemestane arm were not treated. Eleven subjects were considered non-evaluable for efficacy, either because they were never treated, has less than 4 weeks of treatment or had an early withdrawal. There were 5 subjects who were non-evaluable for safety: 2 subjects (3.6%) were randomized but never treated in the exemestane arm and 3 subjects (5.4%) were treated but never assessed for safety in the combination arm.

Approximately 54% of subjects completed at least Weeks 16-24 of treatment (49.1% in the exemestane arm and 58.9% in the combination arm), and approximately 3% of subjects completed more than 180 weeks of treatment. The median duration of treatment was 16.3 weeks (range 3.3-296.0 weeks) and 18.4 weeks (range 0.3-302.3 weeks) for the exemestane and combination arms, respectively.

Table S1. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Exemestane Arm (Exemestane Alone)	Combination Arm (Exemestane + Celecoxib)
Randomized	55	56
Treated	53	56
Discontinuations	55 (100.0)	56 (100.0)
Adverse events	5 (9.1)	6 (10.7)
Consent withdrawn	0	3 (5.4)
Lack of efficacy	48 (87.3)	41 (73.2)
Lost to follow-up	0	3 (5.4)
Protocol violation	0	2 (3.6)
Randomized/never treated	2 (3.6)	0
Sponsor's Decision	0	1 (1.8)
Subjects died	32	37
Evaluable population for efficacy	49	51
ITT population	55	56
Safety population	53	53

ITT = Intent-to-treat

The demographic characteristics age, race and body mass index were similar in both arms. The distribution of ECOG performance status (0, 1 or 2) was similar for both arms. Other baseline characteristics (postmenopausal status, tumor history, prior antitumor treatment, receptor status and site of disease) were also similar for the 2 treatment arms.

Efficacy Results:

Primary Efficacy Endpoint

Clinical benefit and objective response rates were similar for the 2 treatment arms (Table S2). Clinical benefit was observed in 24 subjects in each arm, showing a clinical benefit rate of 49.0% in the combination arm and 47.1% in the exemestane arm. Objective response was observed in 12 subjects in the combination arm and 11 subjects in the exemestane arm; the resulting objective response rates were 23.5% in the combination arm and 22.4% in the exemestane arm.

Similar results were seen for the ITT population. Tumor response was similar for the 2 arms when stratified for previous response to tamoxifen, previous chemotherapy and site of metastasis and according to receptor status.

Table S2. Summary of Tumor Response – Evaluable for Efficacy Population

Number (%) of Subjects	Exemestane Arm (Exemestane Alone) N=49	Combination Arm (Exemestane + Celecoxib) N=51
Best Tumor Response:		
CR	3.0 (6.1)	2.0 (3.9)
PR	8.0 (16.3)	10.0 (19.6)
SD	19.0 (38.8)	23.0 (45.1)
≥24 weeks	13.0 (26.5)	12.0 (23.5)
<24 weeks and off therapy	6.0 (12.2)	11.0 (21.6)
PD	19.0 (38.8)	16.0 (31.4)
Within Week 4 of therapy	0	0
After Week 4 of therapy	19.0 (38.8)	16.0 (31.4)
Clinical Benefit Rate[a] [95% CI]	24.0 (49.0) [34.4%, 63.7%]	24.0 (47.1) [32.9%, 61.5%]
Objective Response Rate[b] [95% CI]	11.0 (22.4) [11.8%, 36.6%]	12.0 (23.5) [12.8%, 37.5%]

CI = confidence interval; CR = complete response; PR = partial response; SD = stable disease;
PD = progressive disease
[a] Clinical benefit rate = CR + PR + SD ≥24 weeks
[b] Objective response rate = CR + PR

Secondary Efficacy Endpoints

For the evaluable for efficacy population, the subjects with clinical benefit (24 subjects per treatment arm), had a median duration of response of 96.6 weeks in the combination arm and 49.1 weeks in the exemestane arm (Table S3). Confidence intervals (95%) were wide for both arms, with the lower CI similar for both arms (37 weeks).

Approximately 20% of subjects had an objective response in each arm, with the median duration for the combination arm (40.1 weeks) approximately 7 weeks longer than for the exemestane arm (32.7 weeks). Again, CIs were wide and the lower CI was similar for both arms.

Median duration of SD ≥24 weeks was 109.7 weeks in the combination arm (12 subjects) and 52.9 weeks in the exemestane arm (13 subjects); the 95% CI were wide and the lower CI was similar for both treatments.

For both treatments, median TTP and median TTF were similar; approximately 20 weeks.

The number of deaths was similar for both arms: 32 and 37 deaths for the exemestane and combination arms, respectively. Median survival time was approximately 75 weeks for both treatments.

Table S3. Time (Weeks) to Event Endpoints – Evaluable for Efficacy Population

	Exemestane Arm (Exemestane Alone) N=49	Combination Arm (Exemestane + Celecoxib) N=51
Median Duration of (95% CI):		
Clinical Benefit	49.1 (37.0, 85.0)	96.6 (37.0, 147.0)
Objective Response	32.7 (23.1, 68.9)	40.1 (28.3, 169.1)
SD ≥24 weeks	52.9 (36.6 , 110.0)	109.7 (36.6, 147.0)
Median TTP (95% CI)	20.0 (9.4, 36.6)	23.4 (16.3, 36.9)
Median TTF (95% CI)	18.1 (36.6, 49.0)	20.4 (34.6, 51.0)
Median Survival (95% CI)	74.7 (57.7, 101.4)	73.9 (52.3, 106.7)

TTP = time to tumor progression; TTF = time to treatment failure; CI = confidence interval; SD = stable disease

Pharmacokinetic and Pharmacodynamic Results:

Pharmacokinetic Results

Pharmacokinetic samples were available from 13 subjects in the combination arm and from 5 subjects in exemestane arm. After exemestane alone, exemestane concentrations were in reasonable agreement with those obtained in a previous study in subjects with ABC. In both arms, some variability could be observed in the concentrations of both drug and metabolite. After exemestane alone, drug levels were slightly higher than those after the combination arm; 95% CIs suggested no difference in PK parameters between the 2 treatment arms. The metabolite-to-parent ratio after the combination therapy was not altered in comparison to that obtained after exemestane alone.

Pharmacodynamic Results

After exemestane alone, the mean values for inhibition of E2, E1 and E1S ranged between 81% and 89%. Although the 95% CIs of average inhibition for E2 (both Day 29 and 57 values) and E1S (Day 29 only) indicated a difference between exemestane and combination arms, absolute concentrations were similar between the 2 treatment arms for all the 3 hormones. The difference in outcome of the 2 parameters, absolute concentration and percentage inhibition, was probably due to the combination arm baseline concentrations for all estrogens being lower than those measured in the exemestane arm.

After exemestane alone, the mean values for inhibition of SHBG were 29.3% and 41.2% at Day 29 and Day 57, respectively. The 95% CIs for SHBG either expressed in terms of absolute values or in term of percentage inhibition indicated that there were no relevant differences between the 2 treatment arms.

Safety Results: Most subjects reported at least 1 treatment emergent AE (Table S4). Fewer than 30% of subjects reported treatment-related AEs; these were reported by 13 and 15 subjects in the exemestane and combination arms, respectively. Most AEs were Grade 1 or 2 in severity, although for approximately 20% and 8% of subjects (across both treatment

arms) their most severe AE was Grade 3 and 4, respectively. None of the Grade 4 AEs that were reported were considered to be treatment-related.

Table S4. Summary of Frequency of Treatment Emergent Adverse Events

	Exemestane Arm (Exemestane Alone) N=53		Combination Arm (Exemestane + Celecoxib) N=53	
Number (%) Subjects with:	**Any Event**	**Treatment Related**	**Any Event**	**Treatment Related**
At least 1 AE	45 (84.9)	13 (24.5)	43 (81.1)	15 (28.3)
Highest grade of AE:				
Grade 1	6 (11.3)	4 (7.5)	15 (28.3)	9 (17.0)
Grade 2	25 (47.2)	8 (15.1)	13 (24.5)	4 (7.5)
Grade 3	12 (22.6)	1 (1.9)	9 (17.0)	2 (3.8)
Grade 4	2 (3.8)	0	6 (11.3)	0

AE = adverse event

The most common system organ class (SOC) of AE was Musculoskeletal and connective tissue disorders, which were reported by 42% and 49% of subjects in the exemestane and combination arms, respectively (Table S5), most commonly back pain. Most of these AEs were not treatment-related. Other common AEs pertained to the Gastrointestinal disorders and General disorders and administration site conditions SOCs. Incidence of events in each of these SOCs was similar for the exemestane and combination arms. There was a higher incidence of events in the Metabolism and nutrition disorders and in Investigations in the exemestane arm than the combination arm, while the incidence of events in Infections and infestations was higher with the combination treatment.

Cardiac disorders were rare: 1 subject (1.9%) in the combination arm experienced cardiac failure congestive (Grade 3); this was considered to be related to study medication. Bleeding events were also rare: ulcer hemorrhage (1 subject [1.9%]) and vaginal hemorrhage (2 subjects [3.8%]) were reported for the exemestane arm; the ulcer hemorrhage was considered to be related to study medication.

Table S5. Most Common Treatment Emergent Adverse Events by System Organ Class (Reported by >10% Subjects in Either Arm)

	Exemestane Arm (Exemestane Alone) N=53	Combination Arm (Exemestane + Celecoxib) N=53
Musculoskeletal and connective tissue disorders	22 (41.5%)	26 (49.1%)
Gastrointestinal disorders	17 (32.1%)	16 (30.2%)
General disorders and administration site conditions	18 (34.0%)	15 (28.3%)
Vascular disorders	11 (20.8%)	13 (24.5%)
Nervous system disorders	10 (18.9%)	12 (22.6%)
Infections and infestations	7 (13.2%)	13 (24.5%)
Metabolism and nutrition disorders	14 (26.4%)	5 (9.4%)
Investigations	10 (18.9%)	5 (9.4%)
Skin and subcutaneous tissue disorders	8 (15.1%)	7 (13.2%)
Psychiatric disorders	6 (11.3%)	1 (1.9%)
Renal and urinary disorders	6 (11.3%)	1 (1.9%)
Reproductive system and breast disorders	6 (11.3%)	1 (1.9%)

A total of 23 subjects had serious adverse events (SAEs) or death reported (14 in the combination arm and 9 in the exemestane arm). The majority of SAEs were related to the subjects' underlying disease; however, there were 3 SAEs that were reported as related to study drug: 1 subject in the exemestane arm had deep vein thrombosis (DVT) which resolved after 14 days, 1 subject in the combination arm had a hypersensitivity reaction which resolved after 13 days, and subject in the combination arm had congestive cardiac failure, which was ongoing when study treatment was withdrawn.

Five subjects died as a result of SAEs:

- A 57-year old subject died due to a cardiorespiratory arrest.
- A 44-year old subject died due to pulmonary embolism secondary to DVT due to paresis.
- A 46-year old subject died due to acute respiratory failure.
- An 83-year old subject died because of a general deterioration in health due to the disease under study.
- A 68-year old subject died due to respiratory failure.

Most clinical laboratory abnormalities were Grade 1 or 2. Grade 3 and 4 abnormalities are detailed in Table S6. Some of the Grade 3 abnormalities had been present at baseline. Two Grade 4 abnormalities were observed: total bilirubin for 1 subject in the exemestane arm (no grade at baseline) and GGT for 1 subject in the combination arm (was Grade 3 at baseline).

Table S6. Summary of Subjects with Grade 3 or 4 Laboratory Findings

	Exemestane Arm (Exemestane Alone)		Combination Arm (Exemestane + Celecoxib)	
Number (%) Subjects	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematology				
Platelet count	0	0	1 (2.0)	0
Neutrophils	2 (4.1)	0	0 1 (2.0)	0
Lymphocytes	2 (4.1)	0	0	0
Blood Chemistry				
Alkaline phosphatase	3 (6.5)	0	2 (4.1)	0
AST	0	0	2 (4.1)	0
GGT	7 (16.3)	0	5 (10.9)	1 (2.2)
Calcium	0	0	1 (2.2)	0
Total bilirubin	0	1 (2.1)	0	0

AST = aspartate aminotransferase; GGT = gamma glutamyl transferase

CONCLUSIONS:

The demographic characteristics were similar in both arms and the 2 groups appeared balanced with respect to the prognostic factors. The majority of subjects in both groups were affected by visceral metastases, a factor known to be associated with a worse prognosis and a poor outcome.

The duration of clinical benefit was almost twice as long with the combination arm compared to the exemestane arm. The median duration of prolonged stabilization of disease (SD ≥24 weeks) was also almost twice as long in the combination arm. It should be noted that the sample size was relatively small, making the 95% CIs for each of these parameters wide and in some case overlapping for the 2 treatment arms. Median survival time was similar for the 2 treatment arms.

The results of this study indicated that the combination of exemestane plus celecoxib was an effective and tolerated treatment for hormone-dependent ABC. The exploratory nature of this study and the limited sample size did not allow firm conclusions to be drawn regarding the anti-tumor activity of the combination arm; however, the increases in the duration of clinical benefit and objective response suggested the possibility that the addition of celecoxib to exemestane could sustain the stabilization of the disease or the response obtained with the exemestane treatment alone by delaying disease progression.