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PROPRIETARY DRUG NAME/INN: Celebrex/Celecoxib

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

- Relief of signs and symptoms of osteoarthritis
- Relief of signs and symptoms of rheumatoid arthritis in adults
- Management of acute pain in adults
- Treatment of primary dysmenorrhea
- Reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis as an adjunct to usual care

PROTOCOL NO. IQ5-97-02-001

PROTOCOL TITLE: A Double-Blind, Randomized, Placebo-Controlled, Comparative Study Of Celecoxib (SC-58635) For The Inhibition Of Progression Of Alzheimer's Disease

Study Center(s): 30 centers: 9 USA (1 did not enroll any subjects), 3 Australia, 3 Belgium, 4 Finland, 5 France, 1 Germany, 1 Netherlands, and 4 UK.

Study Initiation and Completion Dates: 1 Jul 1997 - 24 Jun 1999

Phase of Development: Phase 2

Study Objective(s):

The primary objectives were to:

- Assess whether treatment with celecoxib 200 mg twice daily (BID) would statistically significantly limit or attenuate the progression of Alzheimer's Disease as measured by the change in the Alzheimer's Disease Assessment Scale-Cognitive Behavior (ADAS-Cog) composite score and the Clinician's Interview-Based Impression of Change Plus (CIBIC-Plus) score;
- Evaluate the safety of celecoxib at 200 mg BID in the elderly population suffering from Alzheimer's Disease during long-term treatment.

The secondary objectives were to:

- Evaluate the change from Baseline after one year of treatment in the Behavioral Pathology in Alzheimer's Disease (Behave-AD) score, the Nurses Observation Scale for Geriatric Patients (NOSGER) score, the scores for the recall and recognition scales of the ADAS, the Mini-

Mental State Exam (MMSE) score, and the scores of the Pharmacoeconomic (PE) and Quality of Life surveys (QOL) [SF-36].

- Additional assessments included the Montgomery-Asbers Depression Rating Scale (MADRS) to confirm that depression was not playing an interfering role.

METHODS

Study Design: Patients meeting the entry criteria were randomized to receive 52 weeks of double-blind celecoxib 200 mg BID or matching placebo in a 2:1 ratio. Clinic visits occurred at Screening, Baseline, and Weeks 13, 26, 39, and 52 after the first dose of study medication. There was an interim analysis and review by an independent data safety monitoring board after all patients completed the Week 26 visit or had withdrawn earlier and after 50% of the patients had completed the Week 52 visit. This interim analysis was conducted in February 1999.

Diagnosis and Main Criteria for Inclusion: Early to moderate Alzheimer's Disease confirmed by MMSE and Global Deterioration Scale (GDS) scores, meeting the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) or Diagnostic and Statistical Manual-IV (DSM-IV) criteria for probable Alzheimer's Disease, with symptoms present for at least one year. Decline in intellectual function of a progressive (not stepwise) type, and values for B12, folate, thyroid-stimulating hormone (TSH), T4, and serology within normal limits.

Study Treatment: The double-blind treatment period was 52 weeks in duration. Celecoxib 200 mg capsules -patients received two doses per day for 52 weeks, one dose with breakfast and the other with the evening meal. Matching placebo capsules -patients received two capsules per day for 52 weeks, one capsule with breakfast and the other with the evening meal.

Efficacy Evaluations: The primary efficacy measures were assessed by ADAS-Cog composite scores and CIBIC-Plus scores. The secondary efficacy measures were assessed by the Behave-AD scale, NOSGER score, ADAS recall and recognition subtests, the MMSE score, the MADRS score, and the scores derived from the PE/QOL (SF-36) surveys.

Safety Evaluations: Safety was evaluated by assessment of the incidence of adverse events (AEs) and the incidence of clinically relevant laboratory values.

Statistical Methods: A total of 375 patients were planned to be randomized. A total of 425 patients were enrolled and randomized to receive double-blind medication: 140 to placebo and 285 to celecoxib 200 mg BID. All patients who received at least one dose of study medication, had Baseline measurements, and had at least one posttreatment evaluation were included in two Intent-to-Treat (ITT) efficacy analyses: at Week 26, 135 placebo patients (96.4% of all patients randomized to placebo) and 274 celecoxib patients (96.1% of all patients randomized to celecoxib) were included for analysis, and at Week 52, 135 placebo patients (96.4%) and 278 celecoxib patients (97.5%) were included for analysis.

All statistical tests were two-sided of size α=0.05. All analyses were performed using SAS®. All efficacy analyses were limited to randomized patients who received at least one dose of study medication and had Baseline measurements (except for CIBIC-Plus) and at least one posttreatment evaluation. Six populations were identified for analysis: Week 26 intent-to-treat

(ITT), observed cases (OC), and traditional Last Observation Carried Forward (LOCF) populations; and Week 52 ITT, OC, and traditional LOCF.

The primary efficacy analyses were carried out for the Week 52 ITT population. The primary efficacy measures included change from Baseline in Week 52 ADAS-Cog composite score and Week 52 CIBIC-Plus score.

All randomized patients who received at least one dose of study medication were included in the safety analysis. All AEs were coded and summarized by treatment group. The incidence of treatment-emergent AEs (using the World Health Organization Adverse Reaction Terms [WHOART] preferred term) were tabulated.

RESULTS

Subject Disposition and Demography:

Of the 97 patients withdrawn from the study, most (celecoxib 200 mg BID, 52 patients [18.2% of all patients randomized] and placebo, 26 patients [18.6%]) withdrew during the first 26 weeks of treatment.

Reasons for Study Termination - All Randomized Patients

	Placebo		Celecoxib 200 mg bid		Total	
Randomized	140	(100%)	285	(100%)	425	(100%)
Reason (a)						
Lost to follow-up	1	(1%)	3	(1%)	4	(1%)
Violation of entry criteria	0	(0%)	1	(<1%)	1	(<1%)
Protocol noncompliance	16	(11%)	27	(9%)	43	(10%)
Adverse event	15	(11%)	34	(12%)	49	(12%)
Total	32	(23%)	65	(23%)	97	(23%)
Completed study	108	(77%)	220	(77%)	328	(77%)

(a) Mutually exclusive and exhaustive categories.

For the All Randomized patient population, there were no statistically significant differences between treatment groups for age, race, gender, height (male and female), weight (male and female), years of education, duration of Alzheimer's Disease, estrogen treatment (females only), number of alcoholic drinks (current and former), smoking, anti-psychotic drugs, vitamin E use, APOE genotype, and screening scores for MMSE, MADRS, GDS, and MHS. In the All Randomized population, 59% and 53% of the patients were female, 99% and 96% were Caucasian, and the mean ages were 73 and 74 years for the placebo and celecoxib 200 mg BID groups, respectively. The mean durations of time since diagnosis of Alzheimer's Disease were 1.31 years for the placebo group and 1.37 years for the celecoxib 200 mg BID group.

Imbalances existed between treatment groups in baseline medical history (eg, hypertension for 22% of patients treated with placebo versus 32% of patients treated with celecoxib 200 mg BID; diabetes mellitus in 7% of patients treated with placebo versus 10% of patients treated with celecoxib 200 mg BID; previous aorto-coronary bypass surgery in 0.7% of patients treated with placebo versus 3.2% of patients treated with celecoxib 200 mg BID).

Efficacy Results:
The results of the primary efficacy variables are summarized below.

Primary Efficacy Results - Week 52 ITT

	ADAS-Cog Change From Baseline			CIBIC-Plus		
Mean (n)	**Week 13**	**Week 26**	**Week 52**	**Week 13**	**Week 26**	**Week 52**
Placebo	0.69 (124)	2.15 (135)	5.00 (135)	4.30 (122)	4.40 (135)	4.83 (135)
Celecoxib	0.77 (263)	1.64 (274)	4.39 (278)	4.25 (261)	4.51 (276)	4.92 (279)
P_{ANCOVA}	0.897	0.461	0.541	0.571	0.277	0.446
P_{CMH}	0.821	0.643	0.262	0.492	0.495	0.584

The results of the secondary efficacy variables are summarized below.

Secondary Efficacy Results - Week 52 ITT
Adjusted Mean Behave-AD and NOSGER Change From Baseline

	Behave-AD1			Behave-AD2			NOSGER		
Mean (n)	**Week 13**	**Week 26**	**Week 52**	**Week 13**	**Week 26**	**Week 52**	**Week 13**	**Week 26**	**Week 52**
Placebo	0.30 (124)	0.28 (135)	1.18 (135)				1.97 (124)	3.31 (135)	5.25 (135)
Celecoxib	0.25 (266)	1.01 (275)	1.46 (276)				1.86 (266)	3.89 (275)	6.59 (276)
P_{ANCOVA}	0.897	0.122	0.655				0.915	0.633	0.348
P_{CMH}	0.666	0.339	0.117	0.986	0.590	0.270	0.535	0.846	0.395

The ADAS-Cog mean changes from Baseline and mean CIBIC-Plus scores over time were similar in the two treatment groups for all analysis populations, and increased (worsened) in both treatment groups over time. There were no statistically significant differences between treatments in these scores for the Week 52 ITT population. Similar results were observed in the other populations. There were no statistically significant differences between treatment groups in the change from Baseline in ADAS-Cog components, MMSE and MADRS scores, and QOL (SF-36) health survey as rated by the caregiver. For the QOL (SF-36) health survey as rated by the caregiver's "proxy", except for the statistically significant differences in favor of placebo in the mean change from Baseline at Week 52 for Role-Physical (p=0.022) and Role-Emotional (p=0.043), there were no differences between treatment groups. In general, the results of the PE questionnaire support structure (Week 52 ITT population) were similar in the two treatment groups. Across the study for both treatment groups, most patients lived in their own homes, with

the majority cared for by spouses. Relatively low proportions of patients in both treatment groups required paid caregiver activities.

Safety Results: Overall, 334 (78.6%) of the patients in this study experienced an adverse event(s). A total of 105 (24.7%) patients reported serious adverse events. A total of 17 (4.0%) patients died during this study. Forty-eight (11.3%) patients withdrew from the study because of adverse events. Rates of overall incidence of treatment-emergent adverse events, serious adverse events, deaths, and adverse event-related withdrawals were similar between the 2 treatment groups.

Summary of Adverse Events Reported

N (%) of Patients Experiencing	Placebo (n = 140)		Celecoxib 200 mg BID (n = 285)		Total (n = 425)	
At Least 1 Treatment-Emergent AE	105	(75.0%)	229	(80.3%)	334	(78.6%)
Serious Adverse Events	32	(22.9%)	73	(25.6%)	105	(24.7%)
Death	4	(2.9%)	13	(4.6%)	17	(4.0%)
Withdrawals Due to Adverse Events	14	(10.0%)*	34	(11.9%)	48	(11.3%)

*One patient randomized to the placebo group, was withdrawn >28 days after receiving the last dose of study medication and is therefore not included here.

Adverse events that occurred with a frequency of ≥5% of patients in either treatment group are shown below.

Adverse Events Reported for ≥5% of the Patients in Either Treatment Group

	Placebo (n = 140)		Celecoxib 200 mg BID (n = 285)	
Total Patients With Any AE	105	(75.0%)	229	(80.3%)
Urinary tract infection	13	(9.3)	24	(8.4)
Insomnia	5	(3.6)	20	(7.0)
Upper resp tract infection	7	(5.0)	18	(6.3)
Dizziness	11	(7.9)	18	(6.3)
Headache	10	(7.1)	17	(6.0)
Diarrhea	5	(3.6)	17	(6.0)
Agitation	4	(2.9)	16	(5.6)
Abdominal pain	6	(4.3)	16	(5.6)
Nausea	6	(4.3)	16	(5.6)
Confusion	5	(3.6)	15	(5.3)
Constipation	10	(7.1)	14	(4.9)
Arthralgia	7	(5.0)	14	(4.9)
Male Patients	(n=58)		(n=134)	
Prostatic Disorder	4	(6.9%)	7	(5.2%)

Individual cardiovascular adverse events did not differ significantly between the celecoxib and placebo treatment groups. A statistically significant difference favoring placebo in adverse events was observed for certain CV-related body system terms (Cardiovascular Disorders, General; Heart Rate and Rhythm Disorders; Myo, Endo, Pericardial & Valve Disorders). These differences were primarily driven by the individual terms cardiac failure, fibrillation atrial, and angina pectoris. Adverse events for other body system terms (eg, Extracardiac Vascular Disorders; Platelet, Bleeding and Clotting Disorders; Autonomic Nervous System Disorders) did not differ significantly between treatment groups.

The 4 most frequently reported serious adverse events were respite care, confusion, fracture accidental, and cerebrovascular disorder. Such events are not unexpected with this patient population. All Serious adverse events which were reported in more than one patient are shown below.

Serious Adverse Events Occurring in More than One Patient (Number of Patients/Episodes)

Adverse Event	Placebo (n = 140)	Celecoxib 200 mg BID (n = 285)
Confusion	3 (3)	7 (8)
Urinary Tract Infection	1 (1)	7 (7)
Fracture Accidental	3 (3)	6 (8)
Cerebrovascular Disorder	3 (5)	6 (8)
Pneumonia	1 (1)	6 (6)
Respite Care	5 (5)	5 (5)
Cardiac Failure	0 (0)	5 (5)
Convulsions	0 (0)	4 (4)
Prostatic Disorder	2 (2)	4 (4)
Angina Pectoris	0 (0)	4 (4)
Fracture Pathological	0 (0)	3 (5)
Fibrillation Atrial	0 (0)	3 (4)
Treatment-Emergent Surgery	1 (1)	3 (3)
Carcinoma	1 (1)	3 (3)
Agitation	0 (0)	3 (3)
Syncope	0 (0)	2 (2)
Back Pain	0 (0)	2 (2)
Injury-Accidental	1 (1)	2 (2)
Abdominal Pain	1 (1)	2 (2)
Constipation	0 (0)	2 (2)
Diarrhea	0 (0)	2 (2)
Peptic Ulcer	0 (0)	2 (2)
Myocardial Infarction	0 (0)	2 (2)
Aggressive Reaction	0 (0)	2 (2)
Anemia	1 (1)	2 (2)
Infection	1 (1)	2 (2)
Dyspnea	0 (0)	2 (2)
Pulmonary Edema	0 (0)	2 (2)
Urinary Retention	1 (1)	2 (2)
Cataract	3 (3)	1 (1)

Adverse Event	Placebo (n = 140)	Celecoxib 200 mg BID (n = 285)
Total Patients With SAEs	32 (22.9%)	73 (25.6%)

Deaths that occurred during the study are described in the table below.

Listing of Deaths

Patient No.	Age/Gender	Date of Death	Cause of death [WHOART (Investigator Term)]
Placebo (n = 140)			
0088	84/male	25 Dec 1998	Cerebrovascular disorder (cerebrovascular disorder), pneumonia (pneumonia), ileus (ileus), renal failure acute (renal failure acute)
0211	74/female	24 Dec 1997	Sepsis (sepsis)
0412	72/male	20 Nov 1998	Cerebrovascular disorder (stroke)
0503	81/male	15 Feb 1998	Intestinal gangrene (intestinal gangrene), volvulus (volvulus)
Celecoxib 200 mg BID (n = 285)			
0022	79/male	17 Dec 1997	Aneurysm (ruptured aortic aneurysm)
0087	86/male	04 Oct 1998	Emphysema (exacerbation of emphysema increased), respiratory insufficiency (respiratory failure with pneumonia), heart block (3rd degree heart block), cardiac failure (congestive heart failure), bowel disease (bowel ischemia)
0179	83/male	03 Apr 1998	Cerebrovascular disorder (stroke), cardiac failure (cardiac failure)
0219	73/female	17 Jul 1998	Embolism pulmonary (lung emboli)
0308	74/male	11 Oct 1998	Myocardial infarction (myocardial infarction)
0402	72/male	23 Dec 1998	Pneumonia (pneumonia)
0411	87/female	29 Oct 1998	Fibrillation atrial (atrial fibrillation)
0472	79/female	01 Feb 1998	Cerebrovascular disorder (cerebrovascular ischemic accident)
0501	75/male	30 Nov 1998	Pulmonary fibrosis (pulmonary fibrosis), pneumonia (bilateral pneumonia), cardiac failure (cardiac failure)
0592	71/male	16 Jan 1999	Pneumonia (bronchial pneumonia)
0593	83/male	10 Apr 1998	Subdural hematoma (subdural hematoma)
0637	75/female	17 Aug 1998	Cerebrovascular disorder (cerebrovascular disorder)
9631	81/male	13 Nov 1998	Rectal carcinoma (rectum cancer), pneumonia (pneumonia)

There were no clinically significant alterations in vital signs. BUN and creatinine increased slightly and hemoglobin decreased slightly in the celecoxib 200 mg BID group after up to 1 year of treatment.

Conclusion(s): In conclusion, the results of this study demonstrate the following:

- Oral doses of celecoxib 200 mg BID for a 52-week period did not statistically significantly limit or attenuate the symptomatic progression of Alzheimer's Disease as assessed by the change in ADAS-Cog and the CIBIC-Plus scores in this patient population.
- There were 17 deaths during the study, with an imbalance in deaths between the groups, however the causes of death were typical of this patient population.
- Interpretation of differences in adverse events for certain CV-related body system terms in this study is complicated by marked imbalances in baseline medical history and by the complex medical condition of many of these patients. In addition, the small sample size in this Phase 2 study and the imbalanced randomization results in decreased power to detect relatively rare cardiovascular events, especially in the smaller placebo-treated arm.
- Based on the imbalances between treatment groups in baseline medical history and the complex medical condition of many of these patients, the safety and tolerability of celecoxib 200 mg BID, compared to placebo, in this elderly, debilitated population cannot be decisively concluded.

Based on a reports completed on: 22 December 2000 and 22 December 2004