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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. EQ5-98-02-002

PROTOCOL TITLE: A Placebo-Controlled Evaluation Of The Long-Term Efficacy And Safety Of Celecoxib (SC-58635) In Alzheimer's Disease

Study Center(s): One study site in Finland.

Study Initiation and Completion Dates: 1 September 1998 - 7 January 2000

Phase of Development: Phase 2

- **Study Objective(s):** This trial was terminated early based on results from the antecedent Revised Protocol IQ5-97-12-001 in which oral doses of celecoxib 200 mg BID for a 52-week period did not significantly limit or attenuate the symptomatic progression of Alzheimer's Disease. Since the study was terminated early, efficacy variables were not assessed.

The primary objectives of this study were to:

- Assess the long-term treatment effect of celecoxib versus placebo on brain size as determined by magnetic resonance imaging (MRI).
- Assess the long-term treatment effect of celecoxib versus placebo on Alzheimer's Disease-associated proteins and inflammatory mediators.

The secondary objectives of this study were to:

- Assess the long-term treatment effect of celecoxib versus placebo on Alzheimer's Disease as measured by the change in the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) (28) score and the Clinician's Interview - Based Impression of Change plus (CIBIC plus) (29) score, and Nurse's Observation Scale for Geriatric Patients (NOSGER) (30).
- Evaluate the extended use and safety of celecoxib at 200 mg BID in the elderly population suffering with Alzheimer's Disease during long-term treatment.

METHODS

Study Design: This was to be a randomized, placebo-controlled, site-specific study comparing the efficacy of long-term treatment with celecoxib (200 mg BID) plus vitamin E (400 IU QD) to placebo plus vitamin E (400 IU QD) in treating patients with dementia of the Alzheimer type to slow the progression of the disease.

A total of up to 42 patients were to be enrolled in this long-term trial, including 30 patients previously enrolled in the antecedent Revised Protocol IQ5-97-12-001 and who completed the Week 52 assessment, and up to 12 additional subjects to be randomized *de novo* to receive celecoxib 200 mg BID or matching placebo in the ratio 2:1. In addition, all patients were to receive 400 IU of vitamin E in an open-label manner.

The total duration of treatment was planned to be 156 weeks (3 years), with visits occurring at Baseline and every 3 months (at Weeks 13, 26, 39, 52, 65, 78, 91, 104, 117, 130, 143, and 156).

Diagnosis and Main Criteria for Inclusion: Early to Moderate (MMSE 12-26 and GDS 3-5) Alzheimer's Disease meeting NINCDS or DSM-IV criteria for probable Alzheimer's Disease with presence of symptoms for at least one year.

Study Treatment: Celecoxib 200 mg capsule or matching placebo to be taken orally by Alzheimer's Disease Patients, in the morning at breakfast and with evening meal. Vitamin E (400 IU) to be taken orally once at breakfast. The total duration of treatment was planned to be 156 weeks (3 years).

Efficacy Evaluations: No efficacy assessments were reported due to early study termination.

Safety Evaluations: Safety measurements were treatment-emergent signs and symptoms and clinical laboratory tests. Clinical laboratory data were summarized and analyzed using Fisher's exact test. Values outside the normal range were identified.

Statistical Methods: Descriptive statistics only were used.

RESULTS

Subject Disposition and Demography: A total of 36 patients were enrolled into the study at one study center and randomized to receive double-blind medication: 13 patients to placebo and 23 patients to celecoxib 200 mg BID. Twenty-four of the 36 patients were randomized *de novo* from study IQ5- 97-02-001, 15 patients were randomized to the celecoxib treatment group and 9 patients to the placebo treatment group. All patients received at least one dose of study medication and were included in the safety analyses. Prior to study termination, six of 36 patients (16.7%) were withdrawn from the study: three (23.1%) patients in the placebo group and three (13.0%) patients in the celecoxib 200 mg BID group. Two patients in the placebo group were lost to follow-up. Two patients in the celecoxib group were withdrawn due to noncompliance. One patient was withdrawn due to an adverse event (dementia - celecoxib) and one patient died (pulmonary embolism - placebo).

Safety Results: One or more adverse events (AEs) were reported for 12/13 (92.3%) patients receiving placebo and 20/23 (87.0%) patients receiving celecoxib. Adverse events reported in over 10% of patients in any treatment arm included the following:

Adverse Events

	Placebo (n=13)		**Celecoxib 200 mg BID (n=23)**	
Adverse Events	**n**	%	**n**	%
Total patients with any AE	12	(92.3)	20	(87.0)
Anxiety	4	(30.8)	3	(13.0)
Respite care	3	(23.1)	3	(13.0)
Influenza-like symptoms	0	(0.0)	3	(13.0)
Cystitis	5	(38.5)	2	(8.7)
Insomnia	2	(15.4)	2	(8.7)
Arthralgia	2	(15.4)	1	(4.3)
Male Patients		(n=7)		(n=7)
Prostatic disorder	3	(42.9)	0	(0.0)

Serious adverse events (SAEs) were reported for 6/13 (46%) patients receiving placebo and 10/23 (43%) patients receiving celecoxib; one patient in the placebo group died during the study due to a pulmonary embolus.

Incidence of Serious Adverse Events During the Study

	Placebo (n=13)		Celecoxib 200 mg BID (n=23)	
Body System				
Adverse Event	**N**	**(e)**	**N**	**(e)**
Patients/Episodes with any SAE	6	(10)	10	(15)
Body as a Whole - General Disorders				
Respite care	3	(6)	3	(5)
Treatment-emergent surgery	0	(0)	2	(2)
Central and Peripheral Nervous System Disorders	**:**			
Dementia	0	(0)	1	(1)
Headache	0	(0)	1	(1)
Musculo-Skeletal System Disorders				
Fracture accidental	1	(1)	1	(1)
Neoplasm				
GI Neoplasm malignant	0	(0)	1	(2)
Platelet, Bleeding & Clotting Disorders				
Embolism pulmonary (fatal)	1	(1)	0	(0)
Psychiatric Disorders				
Aggressive reaction	0	(0)	1	(1)
Respiratory System Disorders				
Sinusitis	0	(0)	1	(1)
Vascular (Extracardiac) Disorders	**:**			
Cerebral hemorrhage	1	(1)	1	(1)
Disorders, Male				
Prostatic disorder	1	(1)	0	(0)

Note: n (e) = number of patients (episodes) experiencing SAEs.

Rates of overall incidence of treatment-emergent AEs, SAEs, and AE-related withdrawals were similar in the two treatment groups (Included are AEs and SAEs, that occurred while patients were in the IQ5-97-02-001 study). None of the AEs was considered by the investigator to be related to study medication.

Changes in laboratory test values were expected in this population of patients over 58 years old with Alzheimer's Disease, and fluctuations were observed for patients in both treatment groups. Values for most patients either returned to within normal range or were not of sufficient magnitude to be considered an extreme change.

Conclusion(s): In conclusion, oral doses of celecoxib 200 mg BID were generally safe and well tolerated in this population of patients ≥59 years old with Alzheimer's Disease.