

TMT Review: Cardiovascular Safety of Celebrex

Overview	1
Recommendation	2
Pfizer Meta-analysis of Controlled Studies	2
Numbers of Patients	2
Definitions of Cardiovascular Event Rates	3
Duration of Therapy	3
Total Daily Dosage.....	5
General Comments on Meta-Analysis	5
Comments on Three Key Celebrex Studies	5
APC Trial.....	5
ADAPT Trial.....	8
Study IQ5-97-02-001	9
Extract from Pfizer Briefing Book.....	11
Study Report: Celebrex Study IQ5-97-02-001 (downloaded 1/31/05)	13

This review was prepared by TMT Inc., New York, NY (see www.masterdocs.com).

Overview

- As with most chronic-use drugs, most chronic pain drugs have not been subjected to the type of study (long-term, controlled evaluation of cardiovascular endpoints) necessary for adequate assessment of cardiovascular safety.
- An exception is aspirin which has been conclusively shown to reduce cardiovascular events. However, aspirin also increases the risk of GI hemorrhage, so that for many patients aspirin therapy is not suitable for the treatment of chronic pain.
- Since the introduction of selective COX-2 inhibitors, long-term controlled studies evaluating cardiovascular safety have been performed and there is now evidence that some COX-2 inhibitors as well as the conventional NSAID naproxen may increase cardiovascular risk (particularly heart attack, stroke and other thrombogenic events). Insufficient cardiovascular safety data are available for most NSAIDs.
- It is not yet clear whether increased cardiovascular risk is a class effect of COX-2 inhibitors, a class effect of non-aspirin drugs for chronic pain, or a drug-specific effect confined to certain drugs in the COX-2 or non-COX-2 NSAID drug classes.
- A unifying hypothesis based on the thromboxane/prostacyclin pathways has been proposed as a basis for a class effect of COX-2 inhibitors. However, this hypothesis has not been fully supported by the actual data.
- Significant differences in molecular structure and effects on blood pressure have been shown between different COX-2 inhibitors and there is some evidence that COX-2 inhibitors that increase blood pressure may be associated with greater cardiovascular risk.
- The limited evidence suggests that increasing doses of some COX-2 inhibitors are associated with progressive increase in cardiovascular risk.

Recommendation

- The following course of action seems prudent at this time:
 - Drugs for chronic pain should continue to be made available to patients with chronic arthritis or other causes of chronic pain.
 - Aspirin and acetaminophen may be excellent choices for many patients.
 - Dosage and duration of therapy of any drug for chronic pain should be limited to that necessary for adequate pain relief.
 - Particular caution in drug selection is necessary when treating patients who also have increased cardiovascular risk or an increased risk of a GI bleed.
 - Of the currently marketed COX-2 inhibitors in the United States, celecoxib (Celebrex) appears to have the most extensive safety evaluation and the most favorable safety profile. No evidence of increased cardiovascular risk has been shown at dosage of 200 mg/day or less.
 - The maximum Celebrex dosage should be restricted to 200 mg/day until additional safety data become available.
 - Direct marketing of Celebrex to the consumer should not be resumed, and should be discouraged for medications in general.
 - Celebrex should continue to be one of the options available for the treatment of chronic pain.

Pfizer Meta-analysis of Controlled Studies

In early February, 2005, Pfizer released a Briefing Book including a meta-analysis of safety data from Celebrex controlled trials ([Pfizer Briefing Book](#)). This large database of controlled studies does not appear to raise concern about the cardiovascular safety of Celebrex. However, the average duration of therapy in those receiving ≥ 200 mg/day was only 2 months and Celebrex dosage may not have exceeded 200 mg/day in most patients. Additional analyses should be provided to clarify the dose-response and time-response relationships for cardiovascular events. Indices of cardiovascular safety should include myocardial infarction and stroke event rates as well as the modified APTC composite index used in most of the analysis. The basis for the cardiovascular event rate definitions used should be given further clarification. It is not stated whether p values in the meta-analysis were based on one-sided or two-sided testing. To the extent possible from the data available to Pfizer, tabulations of cardiovascular safety should include both Pfizer-sponsored and non-Pfizer-sponsored studies.

Numbers of Patients

Over 44,000 patients were included (about 25,000 on Celebrex). Only studies for which Pfizer possessed the databases were included in the meta-analysis. Accordingly, the NCI-sponsored APC trial for prevention of sporadic colorectal adenomas was not included. This study is discussed separately.

Definitions of Cardiovascular Event Rates

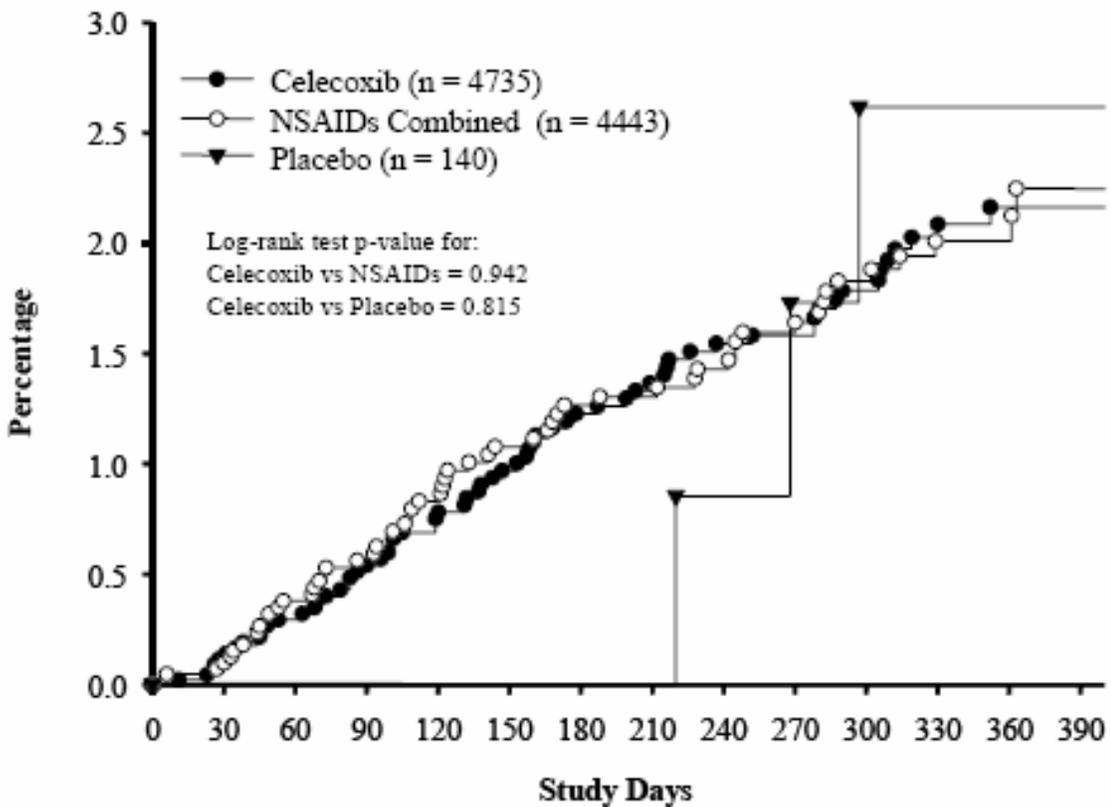
- The main index of cardiovascular safety was “Serious Cardiovascular Thromboembolic Adverse Events” and this was based on a modification of the APTC composite value.
- This index is defined in Table 2 of the Pfizer Briefing Book and includes 19 event types, some of which are debatable (e.g., all five peripheral vascular terms dealing with venous rather than arterial thrombosis, and inclusion of "cerebrovascular disorder" and "cerebral hemorrhage").
- A footnote to Table 2 states that "Stroke comprised the individual adverse events cerebrovascular accident, cerebrovascular disorder, and cerebral hemorrhage." Including "cerebrovascular disorder" as a "stroke" is debatable, particularly in patients with Alzheimer's disease. In addition, it would be useful to have event rates separately for cerebrovascular accident and cerebral hemorrhage, since the thromboxane/prostacyclin hypothesis would suggest that thrombotic cerebrovascular events might be increased with Celebrex whereas cerebral hemorrhage could be reduced.
- Assurance is required that inclusion of many terms in the APTC and stroke definitions did not dilute a true drug effect on events related purely to arterial thrombosis.
- Separate Kaplan-Meier plots for myocardial infarction and/or stroke, myocardial infarction alone, and stroke alone would be useful.
- It should also be stated whether the decision to use the modified APTC composite index was made before or after the safety results had been examined.

Duration of Therapy

- Planned duration of therapy was at least 2 weeks and patients received Celebrex therapy “for up to 1 year”.
- The average duration of therapy and the numbers of patients receiving at least one year of therapy were not clear from the initial review of the report. This information should be provided, together with the cardiovascular event rates by therapy duration.
- It was stated that 7462 patients were “exposed to celecoxib \geq 200 mg TDD for 1268 patient-years” which indicates an average duration of therapy for this subset of 2.0 months.
- Figure 1 in the Pfizer Briefing Book addresses the cardiovascular safety of long-term therapy.
- Figure 1 is a Kaplan-Meier plot of “Time to Serious Cardiovascular Thromboembolic Adverse Events” through 1 year of therapy shows no apparent difference in event rates between Celebrex (N=4735) and conventional NSAIDs (N=4443). However, the NSAID patients are plotted on top of the Celebrex patients and the Celebrex patients are represented by closed circles; for both these reasons it is possible that some Celebrex patients are obscured in the plot. Performing a manual estimate of the number of APTC events in the 6-12 month period gave 21 Celebrex and 17 NSAID patients (0.44% and 0.38% respectively, for a relative risk of 1.16 during this period). There were too few placebo patients (N=140) receiving long-term therapy to allow a meaningful comparison of the time course of these events on placebo.

- If the data can be made available, it would be important to include data from non-Pfizer-sponsored studies in the Kaplan-Meier plots. If this is not possible, a tabulation of cardiovascular event rates should be provided including both Pfizer-sponsored and non-Pfizer-sponsored long-term studies.
- It should be noted that the greatest cardiovascular risk with Vioxx was reported as having been seen with duration of therapy of 18 months or more.

Figure 1. Kaplan-Meier Plot of Time to Serious Cardiovascular Thromboembolic Adverse Events in CLASS, CAESAR, and Alzheimer’s Disease Study IQ5-97-02-001: Celecoxib (Any Dose) Versus Nonselective NSAIDs and Versus Placebo



Celecoxib doses were 400 mg BID in CLASS (Study N49-98-02-035/102), 200 mg QD in CAESAR (Study A3191006), and 200 mg BID in Alzheimer’s Disease Study IQ5-97-02-001. Doses of nonselective NSAIDs were diclofenac 50 mg BID in CAESAR, diclofenac 75 mg BID and ibuprofen 800 mg TID in CLASS. Event rates are based on Kaplan-Meier estimates.

Total Daily Dosage

Celebrex total daily dosage varied from 50-800 mg/day and “the predominant exposure to celecoxib was in the range of 200 to 400 mg TDD...” (TDD = Total Daily Dose). The average total daily dose and the numbers of patients receiving >200 mg/day and ≥400 mg/day were not clear from the initial review of the report. Data on cardiovascular safety as a function of dosage should be provided. (It should be noted that in the NCI APC polyp study (IQ4-99-02-005), a study not included in the Pfizer meta-analysis, a preliminary report found a statistically significant increase versus placebo in relative risk of a composite cardiovascular endpoint of 2.5 at the 200mg bid Celebrex dose and of 3.4 at the 400 mg bid dose.).

General Comments on Meta-Analysis

- Celebrex, in comparison with conventional NSAIDs, was associated with a significant reduction in the risk of "stroke" ($p < .001$; relative risk 0.31), and non-significant differences for cardiovascular risk: relative risks (and p-values) for “Any Cardiovascular Thromboembolic”, “Any Myocardial Thromboembolic” and “Myocardial Infarction” were 0.88 (0.40), 1.31 (0.213) and 1.58 (0.096) respectively. Thus, there was a trend towards an increased risk of myocardial infarction versus conventional NSAIDs.
- Celebrex, conventional NSAIDs and placebo were comparable with regard to overall risk of serious cardiovascular/thromboembolic/cerebrovascular events.
- Percentages of patients with "cardiorenal adverse events" (serious or non-serious) were comparable with Celebrex and conventional NSAIDs but higher than with placebo. Three individual categories (hypertension/aggravated hypertension, edema/edema generalized/edema peripheral, and cardiac failure/cardiac failure left/cardiac failure right) were associated with increased risk with Celebrex and conventional NSAID therapy compared with placebo. This is “consistent with published reports in the medical literature” indicating that NSAIDs (conventional and COX-2 inhibitors) “can be associated with cardiorenal effects”.

Comments on Three Key Celebrex Studies

The Pfizer Briefing Book discusses three key Celebrex studies (APC trial, ADAPT trial, and Study IQ5-97-02-001) that relate to cardiovascular safety:

APC Trial

- A recent analysis of the APC trial for prevention of sporadic colorectal adenomas identified a “statistically significant increase in cardiovascular events for patients treated with celecoxib 200 mg bid or 400 mg bid compared to patients treated with placebo.”
- There was evidence of a dose-response relationship for this effect (relative risk 2.5 for 200 mg bid and 3.4 for 400 mg bid).

- It is probable that most patients receiving Celebrex have effective pain relief at total daily dosage of 200 mg or less, and the US labeling for osteoarthritis restricts maximum dosage to 200 mg/day.

2.3.1. Sporadic Adenomatous Polyposis Prevention Trials: PreSAP and APC

In both the PreSAP trial (Protocol EQ4-00-02-018, sponsored by Pfizer) and the APC trial (Protocol IQ4-99-02-005, sponsored by the Division of Cancer Prevention at the National Cancer Institute [NCI] with the support of Pfizer [NCI Contract N01-CN-95014]), patients who had undergone colonoscopic resection of all evident polyps were randomized in double-blind fashion to receive celecoxib or placebo for 3 years. Repeat colonoscopic surveillance is performed at Year 1 and Year 3 after randomization with the intent of assessing the cumulative proportion of patients who are polyp free at 3 years. Both protocols were powered to be able to detect a 35% reduction in the recurrence of colon polyps on active treatment, and each was amended to add a 2-year extension to provide additional placebo-controlled information on the durability of adenoma prevention and the safety of celecoxib. These extensions allow patients who are adenoma-free at the completion of the initial 3-year treatment period to continue their current blinded treatment for an additional 2 years, at which time an end-of-study colonoscopy will be performed. Patients who are not eligible to continue on study drug into the 2-year extension, either because they have adenomas at Year 3 colonoscopy or because they refuse further therapy, will be offered an end-of-study colonoscopy 2 years after stopping study medication.

In the PreSAP trial as of October 2004, a total of 1561 patients had been randomized in a 2:3 ratio to either placebo or celecoxib 400 mg QD; in the APC trial, a total of 2035 patients have been randomized in a 1:1:1 ratio to celecoxib 200 mg BID, celecoxib 400 mg BID, or placebo. The initial 3-year treatment periods of both the PreSAP trial and the APC trial were due to be completed during 2005 (see Table 11 for disposition of PreSAP and APC patients as of early October 2004), after which Pfizer has proposed that 3-year efficacy and safety data should be analyzed for the purpose of publication and possible registration.

Table 11. Disposition of Patients in Celecoxib Long-Term Sporadic Adenomatous Polyposis Trials as of October 2004

	PreSAP ^a	APC ^b
First Patient Enrolled	March 2001	November 1999
Enrollment Complete	March 2002	March 2002
Number of Patients Randomized	1561	2035
Number of Patients Withdrawn During 3-Year Study	331	617
Number of Patients Completed Month 24 Visit	786	1687
Number of Patients Completed Month 36 Visit	325	1022
Number of Patients Enrolled in 2-Year Blinded Extension	242	246

^a Prevention of Colorectal Sporadic Adenomatous Polyps trial (Study EQ4-00-02-018); enrollments were as of 1 October 2004.

^b Prevention of Sporadic Colorectal Adenomas with Celecoxib trial (Study IQ4-99-02-005); enrollments were as of 5 October 2004.

Patient safety in both the PreSAP trial and the APC trial has been carefully monitored, and efficacy and safety data were reviewed twice yearly in both studies by independent data safety monitoring boards (DSMBs; reports of unblinded data are prepared for DSMBs by independent statisticians, in order to protect the integrity of the respective studies; only these independent statisticians and DSMB members have had access to unblinded data), paying particular attention to cardiovascular and gastrointestinal events (the DSMB for the APC trial also receives monthly reports of serious adverse events). At all interim reviews of safety and efficacy data prior to 16 December 2004, the respective DSMBs found no reason to stop either trial, and following the September 30th withdrawal of rofecoxib, each of the DSMBs restated that their safety reviews to date had identified no basis for altering the progress of these studies.

In response to the withdrawal of rofecoxib from the worldwide market, the NCI requested the formation of an expert Cardiovascular Safety Committee (CSC) to review cardiovascular safety data from the APC trial. At the request of Pfizer, this same CSC was asked to review also cardiovascular safety data from the PreSAP trial. Members of the CSC, all of whom were experienced in the evaluation of cardiovascular endpoints, reevaluated and adjudicated all potential cardiovascular events from both trials without knowledge of study treatment according to endpoint definitions established 3 December 2004. A statistician member of the CSC then analyzed these adjudicated events with respect to the frequency of occurrence in each treatment arm. On 16 December 2004, the CSC concluded the following based on preliminary evaluation of interim safety data (no data regarding patient medical history or baseline characteristics are currently available):

- At 33 months of treatment, the incidence rates for the APTC composite endpoint were 6/679 patients for placebo, 0.9%; 15/685 patients for celecoxib 200 mg BID, 2.2%; and 20/671 patients for celecoxib 400 mg BID, 3.0%. Patients in the celecoxib 200 mg BID treatment group had a relative risk of 2.5 (95% CI: 1.0 to 6.3) and patients in the celecoxib 400 mg BID treatment group had a relative risk of 3.4 (95% CI: 1.4 to 8.3) compared to placebo; both of these increases in risk were statistically significant.
- At 33 months of treatment, the incidence rates for the APTC composite endpoint in the PreSAP trial were 11/628 patients for placebo, 1.8%; and 16/933 patients for celecoxib 400 mg QD, 1.7%. The relative risk was 1.0 (95% CI: 0.5 to 2.1) for celecoxib compared to placebo.
- In the opinion of the CSC, continued exposure to celecoxib placed patients in both trials at increased risk for serious adverse events compared to the as yet unproven benefit; as a result, the respective DSMBs recommended that treatment with study medication in both SAP prevention trials should be suspended.

Because treatment with study medication in the APC trial and the PreSAP trial was suspended very recently (17 December 2004), only a preliminary DSMB report (ie, results for the interim cardiovascular safety reviews described above) is currently available; both studies remain ongoing for the purpose of collecting further efficacy and safety data. Pfizer and the NCI are currently working with the investigators and sponsors of the PreSAP and APC trials to make full study reports including comprehensive safety data available as quickly as possible after study completion, and also to make available when possible specific analyses requested by regulatory authorities. However, Pfizer is not the sponsor of the APC trial and does not control access to either individual patient data or any reports summarizing results.

ADAPT Trial

- Preliminary results from the ADAPT Alzheimer's prevention trial comparing celecoxib 200 mg bid, naproxen 220 mg bid (a fairly low dose of naproxen) and placebo "indicate significantly increased risk for gastrointestinal bleeding and for cardiovascular and cerebrovascular events in patients treated with low dose naproxen compared to patients treated with placebo at 18 months, but no increase in risk for these events in patients treated with celecoxib compared to patients treated with placebo...".

2.3.2. The Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT)

The ADAPT trial, sponsored by the National Institute of Aging (NIA) branch of the US National Institutes of Health and administered through the University of Washington and Johns Hopkins University, is a US, multicenter, double-blind, placebo-controlled trial of naproxen 220 mg BID or celecoxib 200 mg BID versus placebo to test the hypothesis that long-term use of a nonselective NSAID (naproxen) or selective COX-2 inhibitor (celecoxib) will reduce the incidence of Alzheimer's Disease (AD) in dementia-free, elderly subjects at risk for AD. As of 27 September 2004, the trial had been ongoing for 3.5 years, with a total of 2,450 subjects randomized (the enrollment target was 4500 subjects total). The majority of randomized subjects are between 70 and 74 years (56.2%), white (97%), and male (53.8%). In approximately 3900 patient-years of follow-up (including >1100 patient-years for patients treated with celecoxib), the rate of mortality in ADAPT has been low.

The ADAPT trial's safety monitoring group, the Treatment Effects Monitoring Committee (TEMC), has met twice yearly since the start of the trial to scrutinize closely all safety data, assess the risk/benefit ratio for subjects, and make recommendations regarding the conduct of the trial. At its most recent meeting (10 December 2004), the TEMC analyzed safety data collected up to a cutoff date of 1 October 2004, representing approximately 750 patients with exposure to celecoxib for >1.5 years, and found no reason to stop the ADAPT trial. However, on 17 December 2004, in response to the suspension of treatment with study medication in the PreSAP and APC trials, the executive board of the ADAPT trial suspended enrollment and treatment with study medication for ADAPT patients. The TEMC for the ADAPT trial has released top-line results of the safety analysis prepared for its 10 December 2004 meeting. These preliminary results indicate significantly increased risks for gastrointestinal bleeding and for cardiovascular and cerebrovascular events in patients treated with low dose naproxen compared to patients treated with placebo at 18 months, but no increase in risk for these events in patients treated with celecoxib compared to patients treated with placebo (no data regarding patient medical history or baseline characteristics are currently available). Conclusions from this report are only preliminary, based upon only very limited information available concerning the study population, its risk factors, and any methods used to adjudicate or determine events. The sponsors of the ADAPT trial are currently working to prepare a complete report for publication.

Study IQ5-97-02-001

- It has been suggested that a recent reanalysis of Celebrex study IQ5-97-02-001 in Alzheimer's disease patients raises concerns about cardiovascular safety. However, the evidence is not at all convincing.
- Dr. Sidney Wolfe of Public Citizen wrote a January 31, 2005 letter to FDA in which he described this study as “an unpublished randomized placebo-controlled study by Pfizer, finished more than four years ago, that showed a significantly increased rate (3.6-fold) of serious cardiovascular adverse events and more than a doubling in the rate of cardiovascular deaths in people using celecoxib compared to those using a placebo in a study concerning Alzheimer's disease.”
 - However, detailed review shows that Dr. Wolfe's analysis is clearly flawed.
 - The Pfizer study report is provided at http://www.clinicalstudyresults.org/documents/company-study_76_0.pdf as a PDF file apparently prepared on January 24, 2005 by a Manhattan company called Global Document Solutions. It is not clear who performed the statistical analysis and who wrote the report.
 - Dr. Wolfe apparently derived his conclusions of increased cardiovascular risk by selecting an arbitrary set of serious cardiac event types and stroke and adding up the numbers of occurrences on Celebrex and placebo. This subset of the data gave a count of 3 (2.1%) in the 140 placebo patients and 22 (7.7%) in the 285 Celebrex patients from which he concluded that “there was a statistically significant increase in the composite of all serious cardiovascular events in patients getting Celebrex compared to patients getting placebo”.
 - Dr Wolfe appears to have made the elementary error of summing the number of episodes in this subset, rather than the number of patients who had one or more of these types of event. As an example, there were 5 Celebrex patients with “Cardiac Failure” and 2 Celebrex patients with “Pulmonary Edema”. Pulmonary Edema is a type of Cardiac Failure and it is likely that this resulted in double counting of 2 patients who had Cardiac Failure as manifested by Pulmonary Edema. The limited data provided in the Pfizer report do not allow correction for this potential problem. Thus, Dr. Wolfe's statistical analysis is not valid.
 - Dr. Wolfe also reported “There were two deaths (out of 140 patients) in which cardiovascular diagnoses were mentioned in the placebo group and nine deaths (out of 285 patients) in which cardiovascular diagnoses were mentioned in the group getting celecoxib. This also represents a statistically significant ($p=.04$, more than 2-fold) increase in the rate of cardiovascular deaths in people getting celecoxib compared to those getting a placebo (from table on page 7 of the Pfizer results).”
 - However, examination of the table on page 7 shows that Dr. Wolfe “cherry picked” the deaths in the table to make his point. There were 4 deaths on placebo (2.9%) and 13 deaths (4.6%) on Celebrex (with all deaths occurring between December 1997 and January 1999). Since the current concern about Cox-2 drugs is an increased risk of heart attack or stroke, this is the most relevant subset of deaths to examine – 3 deaths on

Celebrex (1.1%) and 1 death on placebo (0.7%). The other “cardiovascular deaths” included by Dr. Wolfe were “cerebrovascular disorder” (rather than cerebrovascular accident, i.e., stroke), ruptured aortic aneurysm, pulmonary embolism, atrial fibrillation, subdural hematoma, and one patient in whom 5 causes of death were listed, the first two being “emphysema” and “respiratory insufficiency” (with none of the other causes including heart attack or stroke). One could make an argument for including pulmonary embolism in this analysis (since it is normally a thrombus-induced event) but none of the other conditions have been linked to Cox-2 drugs and they should not have been included in Dr. Wolfe’s analysis.

- The Pfizer report states “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.”
 - This statement is puzzling.
 - It is not appropriate to cherry pick the types of events to group together and then apply a statistical significance test to this highly selective dataset. More details are required on the data supporting the statement and on the data underlying the statement.
 - In any case, it is traditional to specify in the protocol the hypotheses for which statistical significance testing will be performed; if not, the results should be described as hypothesis generation rather than hypothesis testing, with appropriately conservative conclusions.
 - The Pfizer report also states that baseline imbalances existed between treatment groups for certain cardiovascular risk factors. This is an important observation but additional information on this is required and the analysis should be adjusted for the effects of these baseline imbalances.
 - It is also worth noting that two interim analyses were performed during this study, so that the statistical significance testing should also be adjusted for this multiple testing.
 - A safety monitoring board independent of Pfizer was responsible for assessing Celebrex safety in this study and apparently did not express concerns during or after the study.

It is TMT's view that there will be continuing concern about the safety of Celebrex until additional long-term controlled data are available. In the meantime, responsible physicians should not cherry pick from the available data so as to generate conclusions for or against the drug.

A TMT tabulation of key results from Pfizer Study IQ5-97-02-001 is shown below:

Pfizer Study IQ5-97-02-001				
	Numbers of Patients		% of Patients	
	Celebrex	Placebo	Celebrex	Placebo
Dose (mg/day)	400	0	-	-
Number of Patients	285	140	-	-
Any AE (Adverse Event)	229	105	80.4	75.0
Discontinued because of AE	34	14	11.9	10.0
Serious AE	73	32	25.6	22.9
Death	13	4	4.6	2.9
Death from Heart Attack or Stroke	3	1	1.1	0.7

Extract from Pfizer Briefing Book

2.2.3.3.4. Study IQ5-97-02-001: Treatment With Celecoxib for Up To 12 Months in Patients With Alzheimer's Disease

In Study IQ5-97-02-001, patients ≥ 50 years of age with mild to moderate Alzheimer's disease were treated with placebo (140 patients) or celecoxib 200 mg BID (285 patients) for up to 52 weeks, to assess whether treatment with celecoxib would limit or attenuate the progression of Alzheimer's disease and to evaluate the safety of celecoxib 200 mg BID in elderly patients suffering from mild to moderate Alzheimer's disease during 1 year of treatment. Results of the study showed that celecoxib did not significantly affect the symptomatic progression of Alzheimer's disease in this population.

Larger percentages of patients treated with celecoxib 200 mg BID had serious cardiovascular thromboembolic adverse events compared to patients treated with placebo in Study IQ5-97-02-001 (Table 10), although comparisons between treatment groups in this study are of limited value for the evaluation of cardiovascular safety because limited total exposure to the study medication, and small numbers of events. Moreover, interpretation of cardiovascular safety results are complicated by imbalances between treatment groups in baseline medical history (e.g., hypertension for 22% of patients treated with placebo versus 32% 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) and the complex medical condition of many of these patients. There were 17 deaths during the study, with an imbalance in deaths between treatment groups (4/140 patients treated with placebo, 2.9%; 13/285 patients treated with celecoxib, 4.6%). The deaths were attributed to causes not atypical of those expected in this patient population: for example, 5 pneumonia-related deaths out of 13 deaths total in the celecoxib treatment group. A review by an independent DSMB was conducted after all patients completed the Week 26 visit, and an interim analysis considered all adverse events in February 1999; celecoxib treatment was considered generally safe and well tolerated in the study population in both of these evaluations, the latter of which was published in

connection with the 6th International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy – 2000.

In the meta-analysis described in Section 2.2.3, Study IQ5-97-02-001 contributed 285 out of the 7444 patients from placebo-controlled studies in the celecoxib ≥ 200 mg TDD treatment group (250 patient-years of exposure), and accounted for 11 of the 23 patients in the celecoxib treatment group with serious cardiovascular thromboembolic adverse events. For comparison, the study contributed 140 of the 4057 patients in the placebo treatment group (120 patient-years of exposure) and accounted for 3 of the 10 patients in the celecoxib treatment group with serious cardiovascular thromboembolic adverse events.

**Table 10. Serious Cardiovascular Thromboembolic Adverse Events:
 Alzheimer’s Disease Study IQ5-97-02-001**
 (Number of Patients)

Adverse Event Category Adverse Event	Placebo N = 140 120 pt-yrs	Celecoxib 200 mg BID N = 285 250 pt-yrs
Any Cardiovascular Thromboembolic	3 (2.1)	11 (3.8)
Any Myocardial Thromboembolic	0 (0.0)	4 (1.4)
Myocardial Infarction	0 (0.0)	2 (0.7)
Any Cerebrovascular	3 (2.1)	7 (2.5)
Stroke	2 (1.4)	6 (2.1)
Any Peripheral Vascular	0 (0.0)	1 (0.4)

Note: Results of this study have been published or otherwise addressed as part of the Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical Study Results Database, available at www.clinicalstudyresults.org.

N = Number of patients; BID = Twice daily; pt-yrs = patient years.

Study Report: Celebrex Study IQ5-97-02-001 (downloaded 1/31/05)

Celecoxib PhRMA IQ5-97-02-001 final 012405

PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

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-

CLINICAL STUDY SYNOPSIS

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 Behavior-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 $\alpha=0.05$. 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

CLINICAL STUDY SYNOPSIS

(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.

CLINICAL STUDY SYNOPSIS

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						
Mean (n)	ADAS-Cog Change From Baseline			CIBIC-Plus		
	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)
<i>P</i> _{ANCOVA}	0.897	0.461	0.541	0.571	0.277	0.446
<i>P</i> _{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									
Mean (n)	Behave-ADI			Behave-AD2			NOSGER		
	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)
<i>P</i> _{ANCOVA}	0.897	0.122	0.655				0.915	0.633	0.348
<i>P</i> _{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

CLINICAL STUDY SYNOPSIS

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 $\geq 5\%$ of patients in either treatment group are shown below.

Adverse Events Reported for $\geq 5\%$ 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%)

CLINICAL STUDY SYNOPSIS

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)

CLINICAL STUDY SYNOPSIS

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 (3 rd 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)

CLINICAL STUDY SYNOPSIS

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